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Autosomal Dominant Tubulointerstitial Kidney Disease – *REN*

Synonyms: ADTKD-*REN*, Familial Juvenile Hyperuricemic Nephropathy Type 2 (FJHN2)

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Summary

Clinical characteristics

The two clinical presentations observed in autosomal dominant tubulointerstitial kidney disease – *REN* (ADTKD-*REN*) correlate with the renin protein domains affected by the causative *REN* variants.

- Childhood/adolescent onset, the more common presentation (caused by *REN* variants encoding the signal peptide or prosegment domains), is characterized by decreased estimated glomerular filtration rate, acidosis, hyperkalemia, and anemia early in life, followed by slowly progressive chronic kidney disease (CKD) and gout.
- Adult onset, the less common presentation (caused by *REN* variants encoding the mature renin peptide), is characterized by gout or mild slowly progressive CKD, beginning in the third decade. Anemia, hyperkalemia, and acidemia do not occur.

Diagnosis/testing

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

Management

Treatment of manifestations: Care by a nephrologist as soon as ADTKD-*REN* is diagnosed. In persons with childhood/adolescent-onset disease, anemia may be treated with erythropoietin. Fludrocortisone (a pharmacologic analog of aldosterone) corrects aldosterone deficiency (and associated mild hypotension), hyperkalemia, and acidemia. Treatment with fludrocortisone prior to the development of Stage 3 CKD may be indicated.

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In all persons with ADTKD-*REN*, lifelong treatment of hyperuricemia with allopurinol prevents gout. Renal replacement therapies (such as hemodialysis and peritoneal dialysis) can replace renal function, but are associated with potential complications. Kidney transplantation is curative, as the transplanted kidney does not develop the disease.

Surveillance: Childhood/adolescent-onset disease: measurement of hemoglobin concentration and serum concentration of uric acid, bicarbonate, and creatinine at least every six months starting at the time of diagnosis. Adult-onset disease: similar laboratory testing every six to 12 months, depending on the level of kidney function.

Agents/circumstances to avoid: Nonsteroidal anti-inflammatory drugs, especially in persons who are dehydrated. Angiotensin-converting enzyme inhibitors could aggravate the underlying relative renin deficit. Volume depletion and dehydration as well as high meat and seafood intake may worsen hyperuricemia and exacerbate gout. Affected individuals should not be on the low-sodium diet typically used in the treatment of CKD.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status (by molecular genetic testing for the familial *REN* pathogenic variant) of apparently asymptomatic at-risk relatives, as CKD – one of the primary manifestations of this disorder – is often asymptomatic. Diagnosis of an affected individual as early as possible allows prompt initiation of treatment and awareness of agents/circumstances to avoid. Particularly important are: (1) children and adolescents because of their increased risk for acute kidney injury, anemia, acidemia, and hyperuricemia and gout; and (2) relatives interested in donating a kidney to an affected family member.

Genetic counseling

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

Diagnosis

Consensus clinical diagnostic criteria for autosomal dominant tubulointerstitial kidney disease due to *REN* pathogenic variants (ADTKD-*REN*) have been published [Eckardt et al 2015] (full text).

Suggestive Findings

ADTKD-*REN* **should be suspected** in individuals with the following clinical findings (grouped by age) and a family history consistent with autosomal dominant inheritance [Živná et al 2020].

Clinical Findings – Childhood/Adolescent-Onset Disease

Low renin production (low to low-normal plasma renin and aldosterone levels associated with the following in most, but not all, individuals) manifesting as:

- Blood pressure that is often borderline low, but usually asymptomatic
- Hyperkalemia (serum potassium levels >5 mEq/L, sometimes as high as 6.5 mEq/L) in about 50% of individuals, often present from birth
- Acidosis (serum bicarbonate levels between 15 and 24 mEq/L), often present from birth

Hypoproliferative anemia in most affected children by age one year characterized by:

- Low erythropoietin concentration
- Low hemoglobin concentrations (usually 9-11 g/dL)
- Low reticulocyte count relative to the hemoglobin concentration
- Otherwise normal hematologic findings

Hyperuricemia resulting from decreased renal excretion of uric acid:

- Hyperuricemia (serum uric acid concentration >6 mg/dL) is present in 80% of affected individuals beginning in childhood.

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

- Decreased fractional excretion of urinary uric acid in the vast majority of individuals with ADTKD-*REN*. See Table 2 for reference ranges by age in individuals with normal kidney function.

  The fractional excretion of uric acid is usually <5% in adult men and <6% in adult women. The reduction of urate excretion can be detected in affected children with preserved renal function [Moro et al 1991, McBride et al 1998].

  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 who have an eGFR <70 mL/min.

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

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

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

Table 2. Fractional Excretion of Urinary Uric Acid in Individuals with Normal Renal Function

Age		Mean	Standard Deviation [1]
0-6 wks		29.1%	11.7
6 wks-1 yr		23.9%	10.4
1-3 yrs		15.2%	6.2
3-13 yrs		12.2%	5.5
>13 yrs	Female	8.0%	3.7
	Male	10.3%	4.2

Stibůrková et al [2006]
The fractional excretion of urinary uric acid can be calculated as follows: urine uric acid concentration x serum creatinine concentration ÷ serum uric acid concentration x urine creatinine concentration
1. A fractional excretion of urate >1 SD below the mean suggests reduced urate excretion.

Gout (due to hyperuricemia) may first appear in the early teen years, but has been described in some younger children.

Kidney

- Estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 was seen at earliest clinical presentation in most children.
  - Bland urinary sediment (i.e., little blood or protein). Hematuria is generally not present, and excretion of protein is <1 g per 24 hours except when CKD is advanced.
  - Kidney ultrasound examination shows normal-to-small kidney size without cysts.
- Predisposition to acute, but reversible, kidney injury in the setting of dehydration or viral illness, especially if there has been concomitant treatment with a nonsteroidal anti-inflammatory drug [Bleyer et al 2010b]

Clinical Findings – Adult-Onset Disease (from 3rd decade)

Slowly progressive chronic tubulointerstitial kidney disease evident as a slowly rising serum creatinine in the absence of hematuria and proteinuria

Hyperuricemia (serum urate level >6 mg/dL in adults) and **gout**, resulting from decreased renal excretion of uric acid

Family History

Family history consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). 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 pathologic findings are too nonspecific to reliably identify the causative disorder (see Clinical Description). Molecular genetic testing, the gold standard for diagnosis, is safer and less expensive than kidney biopsy.

The diagnosis of ADTKD-*REN* **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *REN* identified by molecular genetic testing (see Table 3).

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 *REN* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of ADTKD-*REN* has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *REN* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Typically, if no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder, and thus are unlikely to cause this disorder.

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

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

Option 2

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

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

Table 3. Molecular Genetic Testing Used in ADTKD-*REN*

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
REN	Sequence analysis [3]	All variants reported to date [4]
	Gene-targeted deletion/duplication analysis [5]	None reported

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Živná et al [2020] and references therein
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

In the most comprehensive report of autosomal dominant tubulointerstitial kidney disease due to *REN* pathogenic variants (ADTKD-*REN*) to date, comprising 111 individuals from 30 families, Živná et al [2020] observed two clinical presentations, childhood/adolescent onset and adult onset, which correlate with the protein domains encoded by *REN* variants (see Table 4).

Childhood/adolescent onset, the more common presentation, is caused by *REN* variants encoding the signal peptide or prosegment domains. It is characterized by decreased estimated glomerular filtration rate (eGFR), acidosis, hyperkalemia, and anemia early in life, followed by slowly progressive chronic kidney disease and gout. Some children also experience polyuria.

Adult onset, the less common presentation, is caused by *REN* variants encoding the mature renin peptide. It is characterized by gout or mild, slowly progressive CKD, beginning in the third decade. Anemia, hyperkalemia, and acidemia do not occur.

Table 4. ADTKD-*REN*: Comparison of Phenotypes by Genotype and Select Features

Features		Childhood/Adolescent Onset		Adult Onset
		Signal peptide [1]	Prosegment [1]	Mature peptide [2]
# of families/persons		21/69	4/27	5/15
Mean age at presentation ± SD		19.7±15.7 yrs	22.4±20.2 yrs	37.0±12.4 yrs
Age at presentation	<10 yrs	39%	61%	0
	10-20 yrs	32%	11%	0
	>20 yrs	29%	28%	100%
Presented with:	AKI	10%	0	0
	Anemia, acidosis, CKD	13%	0	0
	Anemia	31%	50%	0
	CKD	22%	14%	25%
	Gout	25%	36%	75%
Anemia as child		91%	69%	0
Gout		56%	65%	54%
Age of first gout attack ± SD		29.7±9.9 yrs	25.7±8.2 yrs	32.9±11.2 yrs
Age of ESKD ± SD		53.1±10.6 yrs	50.8±17.6 yrs	63.6±7.6 yrs

Adapted from Živná et al [2020]
AKI = acute kidney injury; CKD = chronic kidney disease; ESKD = end-stage kidney disease; SD = standard deviation(s)
1. Correlated with *REN* variants encoding the signal peptide and prosegment (See Genotype-Phenotype Correlations.)
2. Correlated with *REN* variants encoding the mature peptide (See Genotype-Phenotype Correlations.)

Childhood/Adolescent Onset

Individuals often present between birth and age ten years with manifestations related to renin deficiency. As renin is important in prenatal kidney development, the eGFR is low (usually <60 mL/min/1.73 m^2) from early in life. These individuals frequently have mildly low blood pressure, hyperkalemia, acidosis, and hyperkalemia. They often first come to medical attention with acute kidney injury during a viral infection [Bleyer et al 2010a]. Although acute kidney failure usually resolves if treated appropriately, chronic kidney disease remains, and the associated findings of hyperkalemia, anemia, and acidemia are first noted.

Chronic kidney disease may slowly worsen in the second decade; acidemia and hyperkalemia persist. Gout may develop at this time due to decreased renal excretion of uric acid.

Despite low eGFR at presentation, only one child required renal replacement therapy at age 15 years; others did not reach end-stage kidney disease (ESKD) until after age 30 years (mean age ~52 years). For these individuals, kidney function continues to worsen very slowly over time, with a mean age of ESKD of 53 in the signal peptide group and 51 in the prosegment group (see Table 4).

Adult Onset

Individuals present in their twenties with gout and chronic kidney disease. Gout is easily controlled with allopurinol. The serum creatinine slowly rises with slow progression to ESKD at a mean age of 64 years [Živná et

al 2020]. Although CKD occurs in all individuals with adult-onset disease, progression may be very slow, with ESKD occurring as late as the seventh decade in some individuals.

Kidney Biopsy

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

Histologic examination reveals focal tubular atrophy, secondary glomerular scarring, and interstitial fibrosis [Zivná et al 2009]. Early in the disease course immunostaining for renin and prorenin is markedly decreased (compared to control tissues) in the granular cells of the juxtaglomerular apparatus and undetectable in the tubular epithelium. In advanced stages, neither the granular cells of the juxtaglomerular apparatus or the tubular epithelium stain for renin or prorenin.

Genotype-Phenotype Correlations

The following phenotype-genotype correlations have been identified based on the *REN* variants encoding the signal peptide and prosegment protein domains [Živná et al 2020, Table 4]. See Table 7 for details about specific *REN* pathogenic variants.

Childhood/adolescent-onset disease with a more severe disease course is associated with the following:

- *REN* variants involving nucleotides c.45-113 in exon 1, which encode the signal peptide domain (i.e., the first 23 amino acids of preprorenin)
- *REN* variants involving nucleotides c.114-242 in exon 1 and exon 2, which encode the prosegment protein domain (i.e., amino acids 24-66 of preprorenin)

Adult-onset and milder disease course is associated with *REN* variants involving nucleotides c.243-1262 in exons 2 to 10, which encode the mature renin peptide segment of preprorenin (i.e., amino acids 67-406).

Penetrance

Penetrance is age related. Thus, in individuals with childhood-onset disease, manifestations of ADTKD-*REN*, especially anemia, are evident early in life; and in individuals with adult-onset disease, manifestations (gout and chronic kidney disease) do not become evident until adulthood.

Nomenclature

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

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

Prevalence

ADTKD-*REN* is extremely rare, with approximately 30 families reported worldwide [Živná et al 2020 and references therein].

The prevalence of disease is expected to be similar in all populations.

Genetically Related (Allelic) Disorders

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

Homozygosity or compound heterozygosity for loss-of-function (null) *REN* variants results in grossly normal kidneys that show loss of proximal tubular differentiation (OMIM 267430). Autosomal recessive renal tubular dysgenesis is lethal in the perinatal period.

Differential Diagnosis

See Figure 1 for a diagnostic algorithm for inherited kidney disease.

Table 5. Monogenic Kidney Diseases in the Differential Diagnosis of ADTKD-*REN*

Gene(s)	Disorder	MOI	Renal Phenotype	Distinguishing Features of Disorder
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 • Anemia usually correlates w/level of kidney function (i.e., may not be present in childhood). • Severity of kidney failure is usually much greater (usually requiring dialysis in teens & early 20s). • Hyperkalemia & acidemia are not as pronounced.
COL4A3 *COL4A4* *COL4A5*	Alport syndrome (& other types of hereditary glomerulonephritis)	XL AR AD	Microscopic hematuria (microhematuria), proteinuria, progression to ESKD	• Frequent cochlear & ocular manifestations • Hematuria is present. • Much more severe in males than in females
DNAJB11 *GANAB* *PKD1* *PKD2*	Autosomal dominant polycystic kidney disease (ADPKD)	AD	Bland urinary sediment [2]; large # of cysts > 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 ESKD 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); vascular cutaneous lesions (angiokeratomas), hypohidrosis, & characteristic corneal & lenticular opacities.
MUC1	ADTKD-*MUC1*	AD	Minimal proteinuria; slowly progressive CKD	Only clinical findings are chronic kidney disease & its sequelae. [4]
UMOD	ADTKD-*UMOD*	AD	Proteinuria is rare; slowly progressive CKD	• Not assoc w/anemia in childhood or acidemia & hyperkalemia often seen in ADTKD-*REN* [4] • Phenotype is indistinguishable from adult-onset ADTKD-*REN*.
DNAJB11 [4]	Atypical ADPKD-ADTKD	AD	Slowly progressive CKD, multiple renal cysts	Numerous kidney cysts are common.

Table 5. continued from previous page.

Gene(s)	Disorder	MOI	Renal Phenotype	Distinguishing Features of Disorder
HNF1B	ADTKD-*HNF1B*	AD	Variable other manifestations incl maturity-onset diabetes of the young, hyperuricemia & gout, CKD, CAKUT, & unexplained liver function abnormalities	Incomplete penetrance for characteristic renal involvement & absence of other variable manifestations
mtDNA	m.547A>T [5]	Mat	Chronic tubulointerstitial kidney disease	Absence of childhood anemia, hyperkalemia, & acidemia
PAX2	*PAX2*-related disorder	AD	Glomerular proteinuria, hematuria, CKD, & ocular coloboma	Absence of hematuria, proteinuria, & coloboma
SEC61A1	ADTKD-*SEC61A1*	AD	Slowly progressive CKD, leukopenia, abscess formation, & intrauterine & postnatal growth restriction	Absence of leukopenia, abnormal growth

α-Gal A = alpha-galactosidase A; AD = autosomal dominant; AR = autosomal recessive; CAKUT = congenital anomalies of the kidneys and urinary tract; CKD = chronic kidney disease; ESKD = end-stage kidney disease; Mat = maternal; MOI = mode of inheritance; XL = X-linked

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

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

3. Males with >1% alpha-galactosidase 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 due to pathogenic variants in *REN* (ADTKD-*REN*) have been published [Eckardt et al 2015] (full text).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ADTKD-*REN*, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

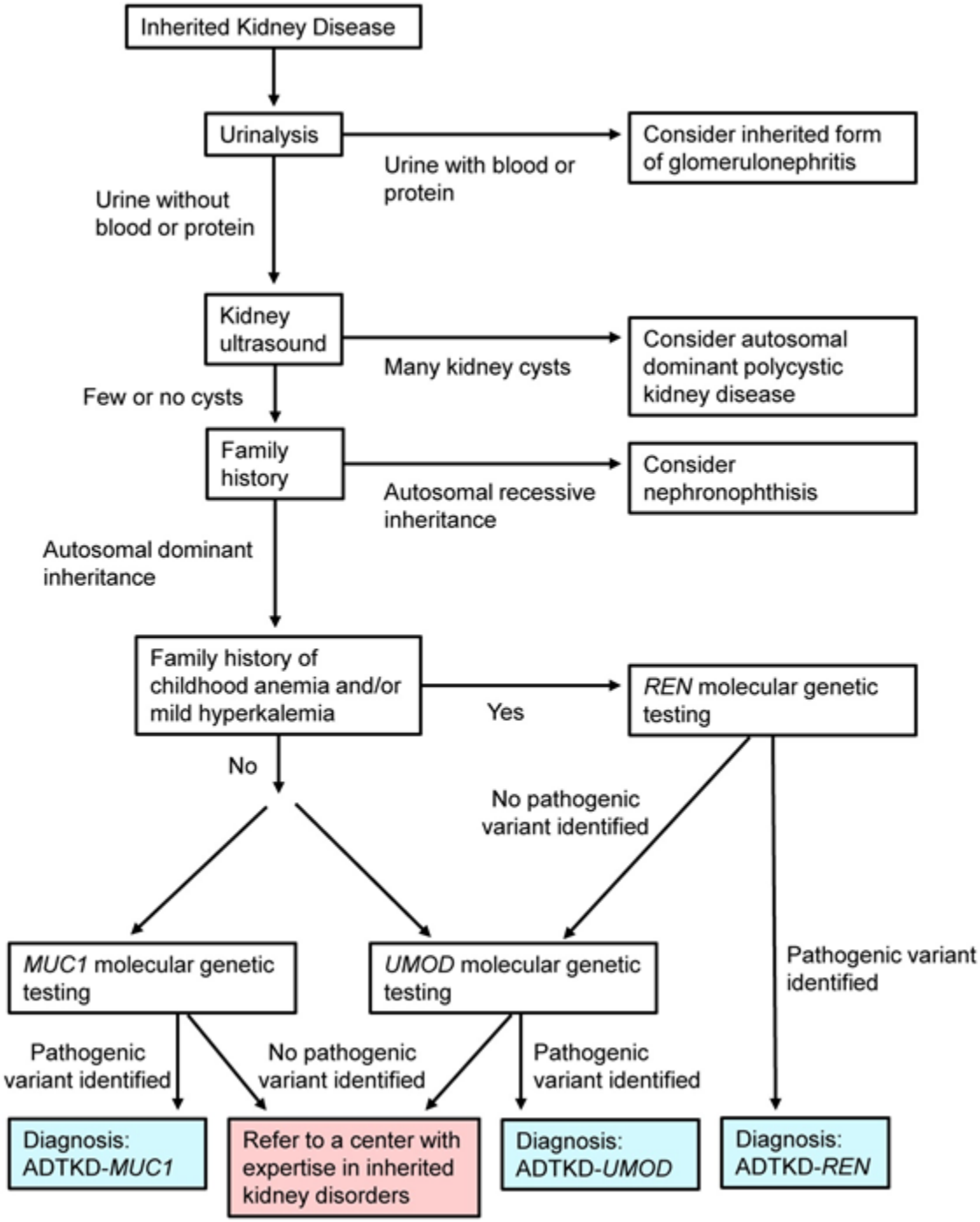

Figure 1. Testing strategy for inherited kidney disease

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with ADTKD-*REN*

System/Concern	Evaluation [1]
Anemia	• Hemoglobin level • In childhood/adolescent-onset ADTKD-*REN*: possibly erythropoietin level
Acidosis	Serum bicarbonate (part of basic metabolic panel)
Hyperkalemia	Serum potassium (part of basic metabolic panel)
Gout risk	Serum urate

Table 6. continued from previous page.

System/Concern	Evaluation [1]
Hypotension	In childhood/adolescent-onset ADTKD-*REN*: plasma renin/aldosterone level
Polyuria	In childhood/adolescent-onset ADTKD-*REN*: • Obtain history for enuresis & excessive thirst or urination. • 24-hr urine collection to quantify urine output
Kidney function	Serum creatinine (part of basic metabolic panel)
	Nephrology referral
Kidney structure	Eval by kidney ultrasound
Genetic counseling	Eval by genetics professionals [2] to inform affected persons re nature, MOI, & implications of ADTKD-*REN* to facilitate medical & personal decision making

MOI = mode of inheritance
1. Applies to both presentations of ADTKD-*REN* except where indicated
2. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Care by a nephrologist is recommended.

Childhood/Adolescent-Onset Disease Only

Anemia may be reversed by treatment with erythropoietin [Zivná et al 2009], a medication that is given subcutaneously and managed by hematologists or pediatric nephrologists. Dose is based on response to therapy. No clear target dose has been established to date; dosage is left to the discretion of the hematologist or nephrologist.

Many children have relatively mild anemia with hemoglobin levels of 10-11 g/dL, and can be safely followed off erythropoietin.

Note: The dose of erythropoietin will need to be reduced as hemoglobin concentration increases during adolescence.

Iron stores should be replenished as needed to treat iron deficiency (an unrelated condition) if it is present.

Mild hypotension, hyperkalemia, and acidemia. Fludrocortisone, a synthetic analog of aldosterone, has been used for many years as a form of aldosterone replacement. In individuals with childhood/adolescent-onset ADTKD-*REN*, fludrocortisone corrects aldosterone deficiency and associated mild hypotension, as well as serum levels of urate, potassium, and bicarbonate.

In a retrospective cohort study [Živná et al 2020], treatment of acidosis with sodium bicarbonate was often suboptimal (i.e., treated serum bicarbonate levels <24 mEq/L); whereas individuals receiving fludrocortisone were more likely to have a serum bicarbonate level >24 mEq/L. Another consideration is that the small dose of the fludrocortisone pill (0.1 mg) vs the higher dose required for sodium bicarbonate (often >1300 mg/day) is favorable, especially for children.

Because fludrocortisone increases estimated glomerular filtration rate (eGFR), fludrocortisone treatment should be started prior to chronic kidney disease (CKD) Stage 3 (eGFR >60 mL/min/1.73 m^2). Note: When eGFR is <60 mL/min/1.73 m^2, fluid retention and hypertension may develop from fludrocortisone [Author, personal observation].

Hypotension is usually asymptomatic but will respond to a dietary sodium intake of 3-4 g/day, administration of sodium bicarbonate tablets, or the use of fludrocortisone.

Acidosis can be treated with sodium bicarbonate tablets or sodium citrate in a liquid formulation, dosed based on body size and degree of acidemia; however, Živná et al [2020] found that treatment of acidemia with sodium bicarbonate was often suboptimal.

Hyperkalemia responds to dietary potassium restriction; administration of sodium bicarbonate will also lower serum potassium.

Risk of acute kidney injury. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in a febrile child with ADTKD-*REN* precipitated acute renal failure [Bleyer et al 2010b]. The use of other analgesics/antipyretics should be considered.

Both Childhood/Adolescent-Onset and Adult-Onset Disease

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

Acute gout typically responds well to prednisone or colchicine. Prednisone is preferred to nonsteroidal anti-inflammatory drugs because the combination of NSAIDs and the low renin state in individuals with ADTKD-*REN* can lead to acute kidney injury.

For individuals with allergies or intolerance to allopurinol, febuxostat may be considered.

Kidney disease. Refer to a nephrologist to monitor kidney function, evaluate for manifestations of chronic kidney disease, and prepare for renal replacement therapy when ESKD occurs. Note: Affected individuals should not be on the low-sodium diet typically used in the treatment of CKD.

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

Kidney transplantation cures ADTKD-*REN,* as the transplanted kidney does not develop the disease.

Surveillance

Childhood/adolescent-onset disease. Monitor blood pressure, serum potassium, bicarbonate, creatinine, and hemoglobin at least every six months.

Adult-onset disease. Monitor blood pressure, serum potassium, bicarbonate, creatinine, and hemoglobin every six to 12 months, depending on the level of kidney function.

Agents/Circumstances to Avoid

Avoid use of the following:

- NSAIDs, especially in a person who is dehydrated or in a febrile child, as they can precipitate acute renal failure [Bleyer et al 2010b]. The use of other analgesics/antipyretics should be considered.
- Angiotensin-converting enzyme inhibitors, which may not be beneficial in the treatment of CKD and could aggravate the underlying relative renin deficit
- Drugs known to be nephrotoxic
- The low-sodium diet typically prescribed in the treatment of CKD

Avoid the following, which may worsen hyperuricemia, leading to more frequent attacks of gout:

- Volume depletion, dehydration, and physical exertion under extreme conditions (e.g., when it is hot)
- High meat and seafood intake

Evaluation of Relatives at Risk

For early diagnosis and treatment. It is appropriate to clarify the genetic status of apparently asymptomatic* at-risk relatives (by molecular genetic testing for the familial *REN* pathogenic variant) to identify individuals with the familial *REN* variant as early as possible in order to monitor their serum creatinine levels, and promptly initiate treatment and awareness of agents/circumstances to avoid. Early evaluation of children and adolescents is particularly important because of their increased risk for acute kidney injury, anemia, acidemia, and hyperuricemia.

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

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

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

Pregnancy Management

Successful pregnancies have been documented in women with ADTKD-*REN*. The rate of miscarriages or other adverse outcomes was not increased.

Allopurinol. Published data on the fetal risk associated with use of allopurinol during pregnancy is limited. While a number of pregnancies in which allopurinol use resulted in the birth of healthy infants, the rare occurrence of a pattern of malformations similar to that observed in women who took 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).

In the authors' experience, in ADTKD-*REN*, most women complete pregnancy without developing gout while not on allopurinol; therefore, the authors recommend discontinuing use of allopurinol during pregnancy.

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

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

Erythropoietin use during pregnancy is unlikely to lead to congenital anomalies in the fetus [Cyganek et al 2011].

Fludrocortisone. Women who use high doses of fludrocortisone during pregnancy may be at increased risk of having an infant who has clinical hyperaldosteronism (see Prescribing Information).

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

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

Genetic Counseling

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

Mode of Inheritance

By definition, autosomal dominant tubulointerstitial kidney disease due to pathogenic variants in *REN* (ADTKD-*REN*) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with ADTKD-*REN* have an affected parent.
- A proband with ADTKD-*REN* may have the disorder as the result of a *de novo REN* pathogenic variant; the proportion of probands who have 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, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism (although no instances of germline mosaicism have been reported, it remains a possibility). Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.
- An apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the *REN* pathogenic variant identified in the proband.
  - Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the disorder and/or a milder phenotypic presentation.
  - Parents will usually have had anemia in childhood, but they may not recall this from their childhood, or the diagnosis of anemia may have been missed at that time.

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 *REN* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. ADKTD-*REN* is associated with biochemical abnormalities from birth in all heterozygous individuals, although some individuals may be clinically asymptomatic.
- If the proband has a known *REN* 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 *REN* pathogenic variant but are clinically asymptomatic, sibs are still presumed to be at increased risk for ADTKD-*REN* because of the possibility of asymptomatic chronic kidney disease or age-related penetrance (see Penetrance) in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with ADTKD-*REN* has a 50% chance of inheriting the *REN* 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 *REN* 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 relatives for the purpose of early diagnosis and treatment.

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

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *REN* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for ADTKD-*REN* are possible.

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

Resources

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

- **Medline Plus**

  Autosomal dominant tubulointerstitial kidney disease

- **REN-Related Kidney Disease Registry**

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

Email: ableyer@wakehealth.edu

Molecular Genetics

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

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

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
REN	1q32.1	Renin	REN database	REN	REN

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 -- REN (View All in OMIM)

179820	RENIN; REN
613092	TUBULOINTERSTITIAL KIDNEY DISEASE, AUTOSOMAL DOMINANT, 4; ADTKD4

Molecular Pathogenesis

Renin is an aspartyl protease synthesized as preprorenin, which contains a signal sequence that directs endoplasmic reticulum (ER) targeting, glycosylation, and proteolytic processing [Imai et al 1983]. Renin cleaves angiotensinogen to angiotensin, with the subsequent stimulation of aldosterone production. The renin angiotensin system (RAS) has been found to have widespread and diverse roles, including modulation of vascular tone, renal sodium and potassium handling, erythropoiesis, thirst, cardiac hypertrophy, and functioning through local RAS systems in many organs [Paul et al 2006].

In vitro studies have shown that the presence of the mutated signal peptide affects renin targeting and cotranslational translocation of preprorenin into the ER, and thus proper biosynthesis and intracellular trafficking of prorenin. This results in ER stress, cytosolic accumulation of abnormal non-glycosylated preprorenin, accelerated autophagocytosis, and reduced growth rate. In vivo this gradually reduces viability of renin-producing juxtaglomerular cells, and results – by as-yet undefined mechanism(s) – in tubular atrophy, nephron loss, and chronic kidney failure, similar to that observed in mice with ablated juxtaglomerular cells [Pentz et al 2004].

REN pathogenic variants also result in decreased renin production, a goal of therapy for many chronic kidney diseases. Thus, the disease becomes its own treatment.

Mechanism of disease causation. Autosomal dominant tubulointerstitial kidney disease due to pathogenic variants in *REN* (ADTKD-*REN*) is caused by pathogenic variants in the REN signal peptide, prosegment, and mature renin peptide [Zivná et al 2009, Schaeffer et al 2019, Živná et al 2020].

- Mutated signal peptide cannot enter the ER for transcription. Mutated prosegment prevents proper folding of the renin peptide. In both instances, mutated renin is deposited within the cell, leading to cell stress, premature cell death, and subsequent tubular cell dropout, interstitial scarring, and chronic kidney

disease. Individuals with childhood/adolescent-onset disease, caused by *REN* pathogenic variants encoding the signal peptide and prosegment, have more severe disease that presents in childhood.
- Mutated mature renin peptide is deposited in the endoplasmic reticulum. Individuals with adult-onset disease, caused by *REN* pathogenic variants encoding the mature renin peptide, have milder manifestations (presenting with gout in the third decade) and slower progression to end-stage kidney disease.

***REN*-specific laboratory technical considerations.** Only pathogenic missense variants and/or small insertions/deletions affecting renin biosynthesis and trafficking are expected to cause ADTKD-*REN*.

REN pathogenic variants occur in exons 1, 2, 8, 9, and 10.

- 62% occur in exon 1 encoding the signal peptide of preprorenin, and 27% in the part encoding the prosegment of prorenin.
- 15% occur in exons 2, 8, 9, and 10 encoding the mature renin peptide.

Table 7. Notable *REN* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Exon)	Predicted Protein Change	Affected Protein Domain	Comment [Reference]
NM_000537.3 NP_000528.1	c. 28T>C (Ex1)	p.Trp10Arg	Signal peptide	The only recurrent variant (1/21 families) affecting this protein domain [1, 2]
	c.35T>C (Ex1)	p.Leu12Pro	Signal peptide	The only recurrent variant (1/21 families) affecting this protein domain [2]
	c. 38T>A (Ex1)	p.Leu13Gln	Signal peptide	The only recurrent variant (1/21 families) affecting this protein domain [2]
	c.45_47del (Ex1)	p.delLeu16	Signal peptide	Most common recurrent variant (6/21 families) affecting this protein domain [2]
	c. 47T>C (Ex1)	p.Leu16Pro	Signal peptide	The only recurrent variant (3/21 families) affecting this protein domain [2]
	c. 47T>G (Ex1)	p.Leu16Arg	Signal peptide	The only recurrent variant (2/21 families) affecting this protein domain [2, 3]
	c. 49T>C (Ex1)	p.Trp17Arg	Signal peptide	The 2nd most common recurrent variant (4/21 families) affecting this protein domain [2, 4]
	c. 58T>C (Ex1)	p.Cys20Arg	Signal peptide	The only recurrent variant (3/21 families) affecting this protein domain [2, 5]
	c.77C>T (Ex1)	p.Thr26Ile	Prosegment	The only recurrent variant (2/4 families) affecting this protein domain [2]
	c. 116T>A (Ex1)	p.Met39Lys	Prosegment	The only recurrent variant (1/4 families) affecting this protein domain [2]

Table 7. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Exon)	Predicted Protein Change	Affected Protein Domain	Comment [Reference]
	c.142G>A (Ex1)	p.Glu48Lys	Prosegment	The only recurrent variant (1/4 families) affecting this protein domain [2]
	c. 973T>C (Ex8)	p.Cys325Arg	Mature	The only recurrent variant (1/5 families) affecting this protein domain [2]
	c. 1097T>A (Ex9)	p.Ile366Asn	Mature	The only recurrent variant (1/5 families) affecting this protein domain [2]
	c. 1142T>C (Ex10)	p.Leu381Pro	Mature	The only recurrent variant (1/5 families) affecting this protein domain [2, 6]
	c. 1172C>G (Ex10)	p.Thr391Arg	Mature	The only recurrent variant (1/5 families) affecting this protein domain [2, 7]
	c. 255G>C (Ex2)	p.Gln85His	Mature	The only recurrent variant (1/5 families) affecting this protein domain [2, 8]

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

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

1. Beck et al [2011]
2. Živná et al [2020]
3. Zivná et al [2009]
4. Clissold et al [2017]
5. Bleyer et al [2010b]
6. Schaeffer et al [2019]
7. Abdelwahed et al [2019]
8. Petrijan & Menih [2019]

Chapter Notes

Author Notes

Martina Živná, PhD (mzivna@lf1.cuni.cz) and Stanislav Kmoch, PhD (skmoch@lf1.cuni.cz) are actively involved in basic research on ADTKD-*REN*. Anthony Bleyer, MD (ableyer@wakehealth.edu) is actively involved in clinical research concerning individuals with *REN* pathogenic variants and other forms of inherited kidney disease; all the authors would be happy to communicate with individuals who have any questions regarding diagnosis or other considerations.

Related website: www.wakehealth.edu/condition/i/inherited-kidney-disease

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