GENEReviews

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Collagen IV-Related Nephropathies (Alport Syndrome and Thin Basement Membrane Nephropathy)

[*Collagen IV-Related Alport Syndrome and Benign Familial Hematuria, Collagen IV-Related Alport Syndrome and Thin Basement Membrane Disease. Includes: COL4A3 Alport Syndrome and Thin Basement Membrane Nephropathy, COL4A4 Alport Syndrome and Thin Basement Membrane Nephropathy, COL4A5 Alport Syndrome*]

Clifford E Kashtan, MD
Department of Pediatrics
University of Minnesota
Minneapolis
kasht001@tc.umn.edu

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Summary

Disease characteristics. Collagen IV-related nephropathies comprise a spectrum of phenotypes from Alport syndrome to thin basement membrane nephropathy (TBMN). Subtypes of collagen IV-realted nephropathies are X-linked Alport syndrome (XLAS), autosomal recessive Alport syndrome (ARAS), and autosomal dominant Alport syndrome (ADAS) and TBMN. Alport syndrome is characterized by renal, cochlear, and ocular involvement. Renal disease progresses from microscopic hematuria to proteinuria, progressive renal insufficiency, and end-stage renal disease (ESRD) in all males with XLAS, and in all males and females with ARAS. Progressive sensorineural hearing loss (SNHL) is usually present by late childhood or early adolescence. Ocular findings include anterior lenticonus (which is virtually pathognomonic), maculopathy (whitish or yellowish flecks or granulations in the perimacular region), corneal endothelial vesicles (posterior polymorphous dystrophy), and recurrent corneal erosion. TBMN is characterized by persistent microscopic hematuria often first observed in childhood; progressive renal involvement and extrarenal abnormalities are rare.

Diagnosis/testing. The diagnosis of collagen IV-related nephropathies rests on (1) history and physical examination, which may include audiologic and ophthalmic evaluation; (2) detailed family history and possibly urinalyses on first- and second-degree relatives; (3) immunohistochemical analysis of basement membrane type IV collagen expression, using skin and/or renal biopsy specimens; and (4) examination of renal biopsy specimens by electron microscopy. With these tools, the diagnosis can be confirmed in most cases. Molecular genetic testing of the type IV collagen genes *COL4A3*, *COL4A4*, and *COL4A5* is available on a clinical basis.

Management. *Treatment of manifestations:* Alport syndrome: routine treatment of hypertension; renal transplantation for ESRD; routine treatment of SNHL and cataracts; surgical intervention for symptomatic leiomyomas. *Prevention of secondary complications:* Protect corneas of those with recurrent corneal erosions from minor trauma. *Surveillance:* follow-up of all individuals with a collagen IV-related nephropathy with a nephrologist; monitor females with XLAS with measurement of blood pressure and renal function; audiologic evaluation of children with Alport syndrome every one to two years beginning at age six to seven years. *Testing of relatives at risk:* Evaluate at-risk family members either by urinalysis or molecular genetic testing if the disease-causing mutation(s) in the family is/are

known. *Other:* Potential living related donors must be evaluated carefully to avoid nephrectomy in an affected individual.

Genetic counseling. The mode of inheritance for collagen IV-related nephropathies is X-linked, autosomal recessive, or autosomal dominant. In XLAS, carrier mothers have a 50% chance of transmitting the disease-causing mutation in each pregnancy; sons who inherit the mutation will be affected and will eventually develop ESRD and, in most cases, deafness; daughters who inherit the mutation will be carriers and will typically have asymptomatic hematuria but may have more severe renal disease. Affected males will pass the disease-causing mutation to all of their daughters and to none of their sons. In ARAS, the parents of an affected child are obligate heterozygotes and carry one mutant allele; at conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier who may or may not be symptomatic, and a 25% chance of being unaffected and not a carrier. In autosomal dominant collagen IV disorders (ADAS and TBMN), each child of an affected individual has a 50% chance of inheriting the mutation. Carrier testing and prenatal testing are possible if the disease-causing mutation(s) in the family are known.

Diagnosis

Clinical Diagnosis

Collagen IV-related nephropathies, caused by mutations in the three genes encoding collagen type IV, represent a spectrum of phenotypes from Alport syndrome to thin basement membrane nephropathy (TBMN) [Longo et al 2002]. Subtypes of collagen IV-related nephropathies are X-linked Alport syndrome (XLAS), autosomal recessive Alport syndrome (ARAS), or autosomal dominant collagen IV disorders (autosomal dominant Alport syndrome [ADAS] and TBMN).

Diagnostic criteria for Alport syndrome [Kashtan 2004]

- **Renal**
  - Hematuria. In XLAS, 100% of affected males and more than 90% of affected females have microhematuria. One hundred percent of males and females with ARAS have hematuria. Episodic gross hematuria is not unusual.
  - Proteinuria, hypertension, and renal insufficiency develop with advancing age in all males with XLAS, and in all males and females with ARAS.
- **Cochlear**
  - Bilateral high-frequency sensorineural hearing loss (SNHL) typically becomes apparent by audiometry in late childhood or early adolescence in males with XLAS and in males and females with ARAS.
  - In XLAS, SNHL eventually develops in 80%-90% of affected males as well as in some affected females; the incidence of SNHL in males and females with ARAS is probably similar to the incidence in males with XLAS.
  - In some families with XLAS and in ADAS, SNHL may not be detectable until well into adulthood.
- **Ocular**
  - Anterior lenticonus is pathognomonic of Alport syndrome. It occurs in 15%-20% of those with XLAS or ARAS and typically becomes apparent in late adolescence or early adulthood.

  - Perimacular flecks occur in approximately 30% of individuals with Alport syndrome.

- **Family history.** Family history of hematuria or renal failure may be negative because 10%-15% of males with XLAS represent *de novo* mutations and approximately 15% of affected individuals have ARAS.

Diagnostic criteria for TBMN

- Persistent hematuria without proteinuria
- Thin glomerular basement membrane (GBM) by electron microscopy
- Normal GBM staining for the α3, α4, and α5 chains of type IV collagen by immunohistochemistry
- Family history:
  - Negative for renal failure
  - Positive for hematuria (Criterion may not be reliable because individuals eventually diagnosed as having TBMN are frequently unaware that they have relatives with hematuria.)

Note: An individual suspected of having Alport syndrome or TBMN should be evaluated by either a pediatric or adult nephrologist (depending on age).

Testing

Urinalysis

- **Males with XLAS; males and females with ARAS.** Urinalysis typically shows hematuria (dozens to hundreds of erythrocytes per high-power microscope field). Overlap with normal results is minimal.
- **Female heterozygotes for XLAS.** Approximately 90% of carriers exhibit persistent or intermittent microhematuria (blood in the urine detectable only by microscope).
- **Heterozygotes for ARAS.** Approximately 50% of carriers of ARAS exhibit persistent or intermittent microhematuria.
- **Individuals with TBMD.** Urinalysis shows microscopic hematuria.

Immunohistochemical Analysis of Basement Membrane Type IV Collagen Expression —Skin biopsy

- **Males with XLAS.** In 80% of males, incubation of a skin biopsy specimen with a monoclonal antibody directed against the collagen α5(IV) chain shows complete absence of staining of epidermal basement membranes. Approximately 20% of males show normal staining.
- **Females heterozygous for XLAS.** Approximately 60%-70% of heterozygous females exhibit discontinuous staining of the collagen α5(IV) chain [van der Loop et al 1999]. This is attributed to lyonization, by which it would be expected that one-half of the basilar keratinocytes would express a normal collagenα5(IV) chain.
- **Individuals with ARAS.** All individuals have normal skin reactivity for the collagen α5 (IV) chain.
- **Individuals with TBMD.** All individuals have normal skin reactivity for the collagen α5(IV) chain.

Renal biopsy

- **Males with XLAS.** Males with XLAS typically show complete absence of immunostaining for the collagen α3(IV) chain, α4(IV) chain, and α5(IV) chain on renal biopsy. Approximately 20% of males with XLAS show normal staining of renal basement membranes for the collagenα3(IV) chain, α4(IV) chain, and α5(IV) chain.
- **Females heterozygous for XLAS.** Females typically exhibit patchy loss of staining for the collagen α3, α4, and α5(IV) chains in GBMs and tubular basement membranes [Kashtan et al 1996]. Some heterozygous females exhibit normal staining for the collagen α3, α4, and α5(IV) chains in their renal basement membranes.
- **Individuals with ARAS** show abnormalities of renal type IV collagen expression that differ from those of individuals with X-linked disease. Individuals with ARAS typically exhibit complete absence of staining for the collagenα3(IV) chain and α4 (IV) chain. However, whereas their GBMs show no staining for the collagen α5(IV) chain, staining of Bowman's capsules and tubular basement membranes for the collagen α5(IV) chain is positive [Gubler et al 1995]. Some individuals with ARAS exhibit normal renal basement membrane staining for the collagen α3(IV) chain, α4 (IV) chain, and α5(IV) chain.
- **Individuals with TBMN** exhibit normal GBM staining for the collagen α3(IV) chain, α4(IV) chain, and α5(IV) chain.

Electron microscopy (EM)

- **Normal.** The normal glomerular capillary wall has a trilaminar appearance consisting of a homogeneous electron-dense layer (lamina densa) sandwiched between two electron-lucent layers (the laminae rara interna and externa).

  The outer (subepithelial) aspect of the glomerular capillary wall, where it abuts the foot processes of the glomerular visceral epithelial cells, is smooth and regular.

  A variety of techniques have been used to measure GBM width. The cut-off value in adults ranges from 250 nm to 330 nm, depending on technique. The cut-off value in children ranges from 200 nm to 250 nm, depending on technique (250 nm is within 2 SD of the mean at age 11 years).
- **Alport syndrome.** When diffusely present, the following three alterations are pathognomonic of Alport syndrome:
  - The lamina densa appears to be split into multiple interlacing strands of electron-dense material, resembling basket-weaving.
  - The lacunae between these strands are frequently occupied by round, electron-dense bodies (possibly entrapped cytoplasm).
  - The glomerular capillary wall is diffusely thickened and its epithelial aspect is scalloped.

However, the earliest change in Alport syndrome is diffuse thinning of the glomerular capillary wall; thus, electron microscopy alone may not always be sufficient to differentiate Alport syndrome from thin basement membrane disease. (Marked variability in GBM width within a glomerulus in an individual with persistent microhematuria should raise suspicion of Alport syndrome.)

TBMN. Most individuals with TBMN exhibit diffuse thinning of the lamina densa and of the GBM as a whole. The intraglomerular variability in GBM width is small in individuals with TBMN [Tiebosch et al 1989] and the GBM of individuals with TBMN remains attenuated over

time, rather than undergoing the progressive thickening and multilamellation that is pathognomonic of Alport syndrome.

Light and immunofluorescence microscopy are unremarkable in individuals with typical TBMN.

Molecular Genetic Testing

Molecular Genetic Testing —Genes. Three genes, *COL4A3*, *COL4A4*, and *COL4A5*, have been associated with fcollagen IV-related nephropathies.

- Approximately 80% of Alport syndrome is caused by mutations in *COL4A5*, inherited in an X-linked manner.
- Approximately 15% of Alport syndrome is caused by mutations in *COL4A3* and *COL4A4*, inherited in an autosomal recessive manner.
- Approximately 5% of Alport syndrome is caused by mutations in *COL4A3* and *COL4A4*, inherited in an autosomal dominant manner.
- Many individuals with autosomal dominant TBMN(precise percentage unknown) have heterozygous mutations in *COL4A3* or *COL4A4* [Lemmink et al 1996, Boye et al 1998, Heidet et al 2001, Badenas et al 2002, Buzza et al 2003].

Other loci. Linkage to *COL4A3* and *COL4A4* has been excluded in some families with TBMD, indicating that TBMD is a genetically heterogeneous condition [Piccini et al 1999].

Clinical testing

COL4A5 Alport syndrome (XLAS)

- **Sequence analysis** of *COL4A5* identifies mutations in approximately 80% of affected individuals whose family history is consistent with X-linked inheritance [Martin et al 1998].

  Note: Sequence analysis does not detect exonic or whole gene deletions in females with a COL4A5 mutation.
- **Mutation scanning** identifies mutations in approximately 50% of individuals who demonstrate clear X-linked inheritance or linkage to the COL4A5 locus [Plant et al 1999].
- **Deletion analysis.** COL4A5 deletion/duplication analysis identifies deletions (typically multiexonic) in approximately 10% of females whose family history is consistent with X-linked inheritance [Jais et al 2003, King et al 2006].

  Note: In males, sequence analysis identifies exonic or whole gene deletions and, thus, deletion analysis is not necessary.

COL4A3 and *COL4A4* Alport syndrome (ARAS)

- **Sequence analysis** of *COL4A3* and *COL4A4* has been used to identify mutations in affected individuals with proven autosomal recessive inheritance; both mutations have been identified in all individuals tested to date with typical clinical findings of ARAS and consanguineous parents [Nagel et al 2005].

Research testing

- ***COL4A3* and *COL4A4* Alport syndrome (ARAS).** The detection rate of *COL4A3* and *COL4A4* mutations by polymerase chain reaction-single strand conformation

polymorphism (PCR-SSCP) is approximately 50% [Boye et al 1998, Heidet et al 2001].

Table 1 summarizes molecular genetic testing for collagen IV-related nephropathies.

Table 1. Molecular Genetic Testing Used in Collagen IV-Related Nephropathies

Test Method	Mutations Detected	Proportion of Collagen IV-related Nephropathies Attributed to Mutations in This Gene	Mutation Detection Frequency by Test Method	Test Availability
Sequence analysis	*COL4A5* sequence variations	80%	>80% [1]	Clinical Testing
Deletion analysis			~10% [2]	
Mutation scanning			~50%	
Sequence analysis	*COL4A3* or *COL4A4* sequence variants	20%	100% [3]	Clinical Testing
Mutation scanning			~50% [4]	Research only

1. Males with XLAS [Martin et al 1998, Plant et al 1999]
2. Used to identify (typically multiexonic) deletions that occur in approximately 10% of females whose family history is consistent with X-linked inheritance [Jais et al 2003, King et al 2006]
3. Individuals with ARAS with typical clinical findings and consanguineous parents [Nagel et al 2005]
4. In individuals with ARAS [Boye et al 1998, Heidet et al 2001]

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

Testing Strategy

To confirm the diagnosis in a proband with suspected collagen IV-related nephropathy:

- Clinical assessment should include urinalysis, renal function studies, family history, testing of relatives for hematuria and, where appropriate, audiometry and expert ophthalmic evaluation.
- Skin and/or kidney biopsy results, combined with the aforementioned studies, usually allow confirmation of a suspected diagnosis of collagen IV-related nephropathy and establish the mode of inheritance.
- Where available, molecular genetic testing by direct sequencing may supersede tissue studies. The choice of which gene to test first is based on family history, clinical findings, histopathology, and frequencies of collagen IV-related nephropathies.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutation(s) in the family.

Note: Carriers are heterozygotes for either ARAS or XLAS.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation(s) in the family.

Genetically Related (Allelic) Disorders

Alport syndrome with diffuse leiomyomatosis results from large deletions that span the adjacent 5' ends of *COL4A5* and *COL4A6* [Zhou et al 1993] (see Genotype-Phenotype Correlations). The association of Alport syndrome with diffuse leiomyomatosis of the esophagus and tracheobronchial tree has been reported in several dozen families [Antignac & Heidet 1996, Mothes et al 2002]. Symptoms usually appear in late childhood and include dysphagia, postprandial vomiting, retrosternal or epigastric pain, recurrent bronchitis, dyspnea,

cough, and stridor. Affected females in these kindreds typically exhibit genital leiomyomas as well, causing clitoral hypertrophy with variable involvement of the labia majora and uterus. Bilateral posterior subcapsular cataracts also occur frequently in affected individuals.

AMME complex (Alport syndrome, **m**ental retardation, **m**idface hypoplasia, and **e**lliptocytosis) was described in two brothers who were shown to have a microdeletion involving the entire *COL4A5* gene and extending beyond its 3' end [Jonsson et al 1998, Meloni et al 2002].

Clinical Description

Natural History

In collagen IV-related nephropathies, a spectrum of phenotypes from progressive renal disease with extrarenal abnormalities (Alport syndrome) to isolated hematuria with a typically benign course (thin basement membrane nephropathy [TBMN]) is observed.

Alport syndrome. Alport syndrome has renal, cochlear, and ocular manifestations. Approximately 80% of Alport syndrome is X-linked; approximately 15% is autosomal recessive, and approximately 5% is autosomal dominant. Because Alport syndrome is predominantly an X-linked disorder, these manifestations are typically more severe in affected males. However, affected females with either XLAS or ARAS may have severe involvement as well. ADAS is typically a slowly progressive disorder; renal insufficiency and sensorineural hearing loss (SNHL) may not develop until relatively late in life.

- **Renal.** The hallmark of Alport syndrome is microscopic hematuria (microhematuria). Males with XLAS have persistent microhematuria from early in life. Episodic gross hematuria can occur, especially during childhood. More than 90% of females with XLAS have microscopic hematuria, although it may be intermittent. Individuals with ARAS have persistent microhematuria, with no gender difference; heterozygous carriers of a *COL4A3* or *COL4A4* mutation have an estimated 50% incidence of persistent or intermittent microhematuria.

  All males with XLAS develop proteinuria and, eventually, progressive renal insufficiency, which leads to end-stage renal disease (ESRD). Overall, an estimated 60% reach ESRD by age 30 years, and 90% by age 40 years [Jais et al 2000]. The rate of progression to ESRD is influenced by the nature of the *COL4A5* mutation (see Genotype-Phenotype Correlations).

  Approximately 12% of females with XLAS develop ESRD before age 40 years, increasing to 30% by age 60 years and 40% by age 80 years [Jais et al 2003].

  Most individuals with ARAS develop significant proteinuria in late childhood or early adolescence and ESRD before age 30 years. Progression to ESRD occurs at a slower pace in individuals with ADAS than in those with XLAS or ARAS.

- **Cochlear.** Hearing loss in Alport syndrome is never congenital. Diminished hearing is usually detectable by late childhood or early adolescence in boys with XLAS. In its early stages, the hearing deficit is detectable only by audiometry, with bilateral reduction in sensitivity to tones in the 2000- to 8000-Hz range. In affected males, the hearing loss is progressive and eventually extends to other frequencies, including those of conversational speech. Hearing loss is frequently identifiable by formal assessment of hearing in late childhood, but in some families it is not detectable until relatively late in life.

  SNHL develops in 80%-90% of males with XLAS by age 40 years [Jais et al 2000]. The course of the hearing loss depends on the causative mutation (see Genotype-

Phenotype Correlations). Hearing impairment in members of families with Alport syndrome is always accompanied by evidence of renal involvement; no convincing evidence that deaf males lacking renal disease can transmit Alport syndrome to their offspring has been reported. In females with XLAS, hearing loss is less frequent and tends to occur later in life.

There do not appear to be gender differences in the incidence or course of hearing loss in ARAS. Individuals with ARAS typically exhibit juvenile onset of hearing loss. Hearing loss may be a very late development in individuals with ADAS.

A recent histologic study of cochleas in individuals with Alport syndrome suggests that defective adhesion of the organ of Corti to the basilar membrane may underlie the hearing deficit [Merchant et al 2004].

- **Ocular.** Ocular lesions are common in individuals with Alport syndrome, occurring in 30%-40% of individuals with XLAS. The spectrum of ocular lesions appears to be similar in XLAS and ARAS. Ocular lesions seem to be relatively uncommon in those with ADAS.
  - **Anterior lenticonus,** in which the central portion of the lens protrudes into the anterior chamber, is virtually pathognomonic of Alport syndrome. When present, anterior lenticonus is bilateral in approximately 75% of individuals. It is absent at birth, usually appearing during the second to third decade of life. Progressive distortion of the lens may occur, accompanied by increasing myopia. Lens opacities may be seen in conjunction with lenticonus, occasionally resulting from rupture of the anterior lens capsule.

    All reported individuals with anterior lenticonus who have been adequately examined have exhibited evidence of chronic nephritis and sensorineural hearing loss. It is far more common in affected males but can occur in females. The frequency of lenticonus in males with XLAS was 13% in one large series; its occurrence is related to the causative mutation (see Genotype-Phenotype Correlations).
  - **Maculopathy** consisting of whitish or yellowish flecks or granulations in the perimacular region was found in approximately 14% of males with XLAS in a large series. The maculopathy does not appear to be associated with any visual abnormalities.
  - **Corneal endothelial vesicles (posterior polymorphous dystrophy)** and **recurrent corneal erosion** may also be seen in individuals with Alport syndrome.

TBMN. Like Alport syndrome, TBMN is characterized clinically by persistent microscopic hematuria often first observed in childhood. In some individuals, microhematuria is intermittent and may not be detected until adulthood. Episodic gross hematuria, frequently in association with upper respiratory infections, is not unusual. The hematuria of TBMN appears to be lifelong.

TBMN differs clinically from Alport syndrome in the following important respects:

- It is only rarely associated with extrarenal abnormalities.
- Proteinuria and hypertension and progression to ESRD are unusual.
- Gender differences in expression of TBMN are not apparent.

Although overt proteinuria and hypertension are unusual in TBMN, they have been described [van Paassen et al 2004]. Some of these cases may represent individuals who actually have

Alport syndrome, and in whom the predominant abnormality of GBM is attenuation, rather than thickening and multilamellation.

Genotype-Phenotype Correlations

XLAS—Risk for renal disease

- Large rearrangements, nonsense mutations, and frameshift mutations confer a 90% probability of ESRD before age 30 years, with 50% reaching ESRD by age 20 years [Jais et al 2000].
- In affected individuals with splice-site mutations, the probability of ESRD before age 30 years is 70%, with 50% reaching ESRD by age 25 years.
- Missense mutations are associated with only a 50% probability of ESRD before age 30 years and a renal half-life (the time it takes for 50% of the group to reach end stage, i.e., the need for dialysis or transplantation) of 32 years.
- Non-glycine missense mutations and glycine mutations in the 3' portion of *COL4A5* are associated with earlier development of ESRD, compared with glycine missense mutations in the 5' portion of the gene [Gross et al 2002].

Risk for deafness

- In individuals with large rearrangements of *COL4A5*, nonsense mutations, frameshift mutations, and splice site mutations, the risk for deafness is 50% at age ten years.
- In individuals with missense mutations, the risk for deafness does not reach 50% until age 20 years.

Risk for anterior lenticonus. Anterior lenticonus occurs in approximately 15% of males with XLAS. Anterior lenticonus is almost entirely restricted to families with Alport syndrome with hearing loss and progression to ESRD before age 30 years. This observation is explained by the finding that lenticonus is significantly more common in individuals with a *COL4A5* deletion or a small mutation resulting in a premature stop codon than in those with missense or splice-site mutations [Jais et al 2000].

Risk for diffuse leiomyomatosis

- All families in which XLAS cosegregates with diffuse leiomyomatosis exhibit large deletions that span the adjacent 5' ends of *COL4A5* and *COL4A6*. These deletions involve varying lengths of *COL4A5*, but the *COL4A6* breakpoint is always located in the second intron of the gene.
- Leiomyomatosis does not occur in individuals with deletions of *COL4A5* and *COL4A6* that extend beyond intron 2 of *COL4A6*.
- Mutations of *COL4A6* alone do not appear to cause Alport syndrome, a finding consistent with the absence of the α6(IV) chain from normal GBM.

Penetrance

See Genotype-Phenotype Correlations.

Anticipation

Anticipation is not observed in collagen IV-related nephropathies.

Nomenclature

The term "benign familial hematuria" is no longer used; it has been replaced with the term "thin basement membrane nephropathy," or thin basement membrane disease.

Prevalence

The prevalence of Alport syndrome has been estimated at approximately 1:50,000 live births [Levy & Feingold 2000]. Data from several series suggest that approximately one-fifth of children evaluated by pediatric nephrologists for isolated microhematuria receive a diagnosis of Alport syndrome. According to the United States Renal Data System (USRDS), approximately 0.2% of adults and 3% of children in the United States with ESRD carry a diagnosis of Alport syndrome.

TBMN of all causes is estimated to affect an estimated 1% of the population; the proportion caused by mutations in *COL4A3* and *COL4A4* is unknown.

Differential Diagnosis

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

Alport syndrome most often presents in childhood, and thus must be differentiated from other causes of persistent (more than six months in duration) microhematuria in children. The first step in the evaluation of hematuria in children is to attempt to establish the source of the hematuria (renal/glomerular, renal/post-glomerular, post-renal). This often involves evaluation of urinary erythrocyte morphology by phase contrast microscopy, urinary calcium measurement, and/or renal ultrasound examination. Family history is an important component of the initial evaluation of the child with hematuria. When possible, obtaining urinalyses on first-degree relatives can also be informative.

Once microhematuria is provisionally localized to the glomeruli, possible etiologies include a number of chronic glomerulopathies. In the child with no known family history of hematuria, the most likely diagnoses are IgA nephropathy, thin basement membrane nephropathy (TBMN), Alport syndrome, and membranoproliferative glomerulonephritis (see Dense Deposit Disease/Membranoproliferative Glomerulonephritis Type II). In the child with familial hematuria, the diagnostic possibilities narrow down to TBMN and Alport syndrome, although IgA nephropathy is occasionally familial.

Fechtner/Epstein syndrome. The eponym Fechtner syndrome refers to the association of hereditary nephritis, sensorineural deafness, cataracts, and the triad of the May-Hegglin anomaly (thrombocytopenia, large platelets, and characteristic leukocyte inclusions ["Döhle-like" bodies]). It is transmitted in an autosomal dominant manner. Until recently, Epstein syndrome (the combination of nephritis, deafness, thrombocytopenia, and large platelets) and Fechtner syndrome were considered possible genetic variants of Alport syndrome. Some individuals with these disorders exhibit ultrastructural changes of the glomerular capillary wall reminiscent of those seen in individuals with Alport syndrome. However, these syndromes have been determined to be genetically distinct from Alport syndrome as both result from mutations in *MYH9*, the gene encoding non-muscle myosin heavy chain 9 [Seri et al 2000, Ghiggeri et al 2003, Kunishima et al 2003].

TBMN. Other glomerular disorders including IgA nephropathy and focal segmental glomerulosclerosis may occur in individuals with TBMN [Norby & Corsio 2005]. (See also Genetically Related Disorders.)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with collagen IV-related nephropathies (Alport syndrome and thin basement membrane nephropathy [TBMN]), the following evaluations are recommended:

Evaluation of renal function

- Overt proteinuria (urine protein-creatinine ratio >0.2 or, in a child, 24-hour urine protein >4 mg/m^2/hr) is an important indicator of renal disease progression in individuals with collagen IV-related nephropathies. Urine protein excretion should be assessed at the time of diagnosis and at least annually thereafter.
- In collagen IV-related nephropathies, decreased glomerular filtration and hypertension rarely appear before overt proteinuria. Once overt proteinuria has developed, renal function should be assessed by serum creatinine concentration or other estimates of glomerular filtration rate (e.g., creatinine clearance or serum cystatin C levels) periodically and blood pressure should be monitored.

Hearing evaluation. High-frequency sensorineural deafness typically becomes detectable by audiogram in late childhood (age 6-10 years) in boys with XLAS and in boys and girls with ARAS.

Ophthalmologic evaluation. Assessment of ocular status is often unnecessary if the diagnosis of Alport syndrome is established by other means. The maculopathy is asymptomatic, and anterior lenticonus is also frequently asymptomatic. Individuals who experience acute corneal erosion should be seen by an ophthalmologist.

Treatment of Manifestations

Renal. Hypertensive individuals should receive appropriate management.

Controlled clinical trials of therapy for the Alport nephropathy have not been conducted. As no proven therapy specifically for Alport syndrome exists, affected individuals are frequently treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers once proteinuria appears. This form of therapy is rarely associated with significant adverse effects. However, there is no evidence that such treatment alters the natural history of Alport nephropathy in humans, although angiotensin blockade has been shown to delay progression to ESRD in transgenic mice with ARAS [Gross et al 2003, Gross et al 2004].

Renal transplantation. Renal transplantation is typically successful in individuals with Alport syndrome [Kashtan et al 1995, Byrne et al 2002]. Anti-GBM nephritis involving the renal allograft is a dramatic, but rare, complication occurring in an estimated 3% of males with Alport syndrome who have undergone transplantation [Kashtan et al 1999, Byrne et al 2002].

Special considerations apply to the selection of potential living related kidney donors for individuals with XLAS. The following discussion considers potential donors on the basis of gender and the presence or absence of hematuria:

- **Male relative without hematuria.** The optimal living related donor is a male who has a normal urinalysis and is therefore unaffected.
- **Male relative with hematuria.** A related male with hematuria probably has Alport syndrome, and cannot be a kidney donor.

- **Female relative without hematuria.** Female relatives who have normal urinalyses are probably unaffected, although approximately 5%-10% of carrier females for XLAS are asymptomatic. It is rare for asymptomatic females whose children are also asymptomatic to be carriers. Asymptomatic females can probably donate a kidney safely, but should be informed of their risk of having affected male children to whom they will not be able to donate a kidney. Carrier status can be confirmed or excluded by molecular genetic testing if the disease-causing mutation in the family is known.
- **Female relative with hematuria (i.e., carrier female).** Carrier females should only be considered as potential kidney donors if no asymptomatic living donors are available.
  - The presence of proteinuria or sensorineural deafness is an absolute contraindication to kidney donation as these are risk factors for progression to ESRD.
  - Carrier females younger than age 40 years should not be used as donors, even in the absence of proteinuria or deafness.
  - Carrier females age 40 years or older who have normal renal function, blood pressure, and hearing and no proteinuria can be considered as donors because the risk of late progression to ESRD appears to be low in such individuals. However, the donor should be informed of the risk (albeit low) of late progression to ESRD.

Cochlear. Hearing aids should be prescribed when appropriate.

Ocular. The ocular manifestations of Alport syndrome rarely require specific ophthalmologic intervention.

Some individuals develop cataracts that interfere with vision; these should be extracted when necessary.

Diffuse leiomyomatosis. Symptomatic leiomyomas may require surgical intervention.

Prevention of Secondary Complications

Individuals who suffer recurrent corneal erosions may need to take measures (e.g., wearing goggles when riding a bicycle) to protect their corneas from minor trauma.

Surveillance

Individuals with a diagnosis of a collagen IV-related nephropathy should be followed by a nephrologist in addition to a primary care physician. Once overt proteinuria has developed, renal function should be assessed by serum creatinine concentration or other estimates of glomerular filtration rate (e.g., creatinine clearance or serum cystatin C levels) periodically and blood pressure should be monitored.

Although most females with XLAS exhibit only asymptomatic microhematuria, recent data indicate a significant risk of progression to ESRD [Jais et al 2003]. For this reason, all women with a diagnosis of Alport syndrome need to be monitored regularly for the development of proteinuria and hypertension.

Children with Alport syndrome should have audiologic evaluation every one to two years beginning at age six to seven years (see Hereditary Hearing Loss and Deafness Overview).

Testing of Relatives at Risk

It is appropriate to evaluate family members at risk for a collagen IV-related disorder either by urinalysis or, if the disease-causing mutation in the family is known, by molecular genetic testing. A single urinalysis is sufficient in a male. Several urinalyses should be performed in females before concluding that hematuria is absent.

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

Therapies Under Investigation

The vasoactive hormone angiotensin II (AII) is thought to be a significant factor in the progression of chronic kidney disease to renal failure. The role of AII in collagen IV-related nephropathies is not well understood. Studies of AII inhibition in human Alport syndrome have involved small numbers of individuals with proteinuria who served as their own controls; follow-up was relatively short and results mixed [Proesmans et al 2000, Adler et al 2002, Proesmans & Van Dyke 2004, Kaito et al 2006].

In a murine model of ARAS, Gross et al (2003) and Gross et al (2004) found that ramipril therapy initiated prior to the development of proteinuria delayed the onset of proteinuria and renal failure and lengthened survival. In dogs with XLAS, early angiotensin-converting enzyme inhibition had no effect on the onset of proteinuria but did delay ESRD [Grodecki et al 1997]. These observations suggest that angiotensin blockade initiated early in the course of disease (i.e., Phase I or very early in Phase II) may be beneficial in human Alport syndrome.

Callis et al (1999) reported that chronic treatment with cyclosporine resulted in reduced proteinuria and stabilization of creatinine clearance in eight males with Alport syndrome without evidence of nephrotoxicity. This intriguing result should be viewed with caution given the small sample size, the lack of contemporaneous controls, and the absence of confirmatory studies from other investigators. A recent report suggested that cyclosporine treatment may accelerate the process of interstitial fibrosis in patients with Alport syndrome [Charbit et al 2007].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Screening of potential living related kidney donors. Most individuals with Alport syndrome who require kidney transplantation have X-linked disease. Both hemizygous males and heterozygous females with XLAS are at risk for end-stage kidney disease. Potential living related donors must be evaluated carefully to avoid nephrectomy in an affected individual. Kashtan (2006) discusses in detail the evaluation of potential donors.

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

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

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Alport syndrome can be inherited in an X-linked manner, an autosomal recessive manner, or an autosomal dominant manner. Thin basement membrane nephropathy (TBMN) has only been described as being inherited in an autosomal dominant manner.

Risk to Family Members — X-Linked Inheritance

Parents of a male proband

- The father of a male with XLAS will not have the disease nor will he be a carrier of the mutation.
- In a family with more than one affected male, the mother of an affected individual is an obligate carrier.
- If only one male in a family is affected, the likelihood that that individual's mother is a carrier is 85%-90%. Approximately 10%-15% of male probands have XLAS as the result of a *de novo* mutation.
- The mother of a male with a known XLAS should have a urinalysis. The presence of microhematuria indicates that she is likely to be heterozygous for XLAS. In the absence of proteinuria or hypertension, she should, at a minimum, have an annual urinalysis and measurement of blood pressure. If proteinuria or hypertension is present, she should be referred to a nephrologist for further evaluation.

Parents of a female proband

- The father or the mother of a female proband may have the gene mutation, or the proband may have a *de novo* mutation.
- Approximately 10%-15% of affected individuals have XLAS as the result of a *de novo* mutation.
- Evaluation of parents of a female proband with XLAS begins with urinalysis and proceeds as described for the mother of a male proband.

Sibs of a male proband

- The risk to the sibs of a male proband depends on the carrier status of the mother.
- If the mother is a carrier, each sib has a 50% chance of inheriting the mutation. Males who inherit the mutation will be affected; females who inherit the mutation will be carriers and may or may not be symptomatic.
- If the mother is not a carrier, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Sibs of a female proband

- The risk to the sibs of a female proband depends on the genetic status of the parents.

- If the mother is a carrier, each sib has a 50% chance of inheriting the mutation. Males who inherit the mutation will be affected; females who inherit the mutation will be carriers and may or may not be symptomatic.
- If the father has a disease-causing mutation, all of his daughters will inherit the mutation and may or may not have symptoms. None of his sons will inherit the mutation.
- If neither parent has a disease-causing mutation, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a male proband. Affected males transmit the disease-causing mutation to all of their daughters and to none of their sons.

Offspring of a female proband. Women with a disease-causing gene mutation have a 50% chance of transmitting the disease-causing mutation to each child: sons who inherit the mutation will be affected; daughters will have a range of possible phenotypic expression.

Other family members of a proband. The male proband's maternal aunts may be at risk of being carriers and the aunts' offspring, depending on their gender, may be at risk of being carriers or of being affected.

Carrier Detection

Carrier testing of at-risk female relatives is available on a clinical basis if the mutation has been identified in the family.

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Approximately 50% of carriers exhibit persistent or intermittent microhematuria. Carriers of ARAS rarely develop proteinuria, hypertension, or renal insufficiency.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Approximately 50% of carriers exhibit persistent or intermittent microhematuria. Carriers of ARAS rarely develop proteinuria, hypertension, or renal insufficiency.

Offspring of a proband. The offspring of an individual with ARAS are obligate heterozygotes (carriers) for a disease-causing mutation.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing of at-risk relatives is available on a clinical basis if the mutation has been identified in the family.

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- Most individuals diagnosed with an autosomal dominant collagen IV-related nephropathy (ADAS or TBMN) have an affected parent.
- A proband with an autosomal dominant collagen IV-related nephropathy may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* gene mutations is unknown.
- Urinalysis is recommended for the evaluation of parents of a proband with an apparent *de novo* mutation.

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

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic the status of the parents.
- If a parent of the proband is affected, the risk is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- No instances of germline mosaicism have been reported, although it remains a possibility.

Offspring of a proband. Each child of an individual with autosomal dominant collagen IV-related nephropathy has a 50% chance of inheriting the mutation.

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

Related Genetic Counseling Issues

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

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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 of being carriers.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal testing is possible for pregnancies of women who are carriers of XLAS. The usual procedure is to determine fetal sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation or by

amniocentesis usually performed at approximately 15-18 weeks' gestation. If the karyotype is 46,XY and the disease-causing mutation has been identified, DNA from fetal cells can be analyzed for the known disease-causing mutation.

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

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as Alport syndrome or TBMN that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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

Molecular Genetics

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

Table A. Molecular Genetics of Collagen IV-Related Nephropathies (Alport Syndrome and Thin Basement Membrane Nephropathy)

Gene Symbol	Chromosomal Locus	Protein Name
COL4A3	2q36-q37	Collagen alpha-3(IV) chain
COL4A4	2q36-q37	Collagen alpha-4(IV) chain
COL4A5	Xq22.3	Collagen alpha-5(IV) chain

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

Table B. OMIM Entries for Collagen IV-Related Nephropathies (Alport Syndrome and Thin Basement Membrane Nephropathy)

104200	ALPORT SYNDROME, AUTOSOMAL DOMINANT
120070	COLLAGEN, TYPE IV, ALPHA-3; COL4A3
120131	COLLAGEN, TYPE IV, ALPHA-4; COL4A4
203780	ALPORT SYNDROME, AUTOSOMAL RECESSIVE
301050	ALPORT SYNDROME, X-LINKED; ATS
303630	COLLAGEN, TYPE IV, ALPHA-5; COL4A5

Table C. Genomic Databases for Collagen IV-Related Nephropathies (Alport Syndrome and Thin Basement Membrane Nephropathy)

Gene Symbol	Entrez Gene	HGMD
COL4A3	1285 (MIM No. 120070)	COL4A3
COL4A4	1286 (MIM No. 120131)	COL4A4
COL4A5	1287 (MIM No. 303630)	COL4A5

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

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Basement membranes, the sheet-like structures that support epithelial and endothelial cells, display heterogeneity in protein composition, ultrastructural features, and function. Basement membranes are composed of several major and minor glycoprotein constituents. Type IV collagen is present ubiquitously in basement membranes, where it is the major collagenous component. Type IV collagen molecules secreted by endothelial and epithelial cells self-associate into polygonal networks, which interact with laminin networks, as well as with nidogen, proteoglycans, and other glycoproteins, to form basement membranes.

It is now clear that the tissue pathology and clinical features of Alport syndrome result from abnormalities of basement membrane expression of the collagenα3, α4, α5, and possibly α6 (IV) chains. These chains are usually absent from or under-expressed in the basement membranes of individuals with Alport syndrome, so that the networks that they form are absent or, if present, defective in structure and function.

In the normal developing kidney, collagen α1(IV) and collagen α2(IV) chains predominate in the primordial glomerular basement membrane (GBM) of immature glomeruli. The formation of capillary loops within the maturing glomeruli is associated with the appearance of collagenα3, α4, and α5(IV) chains in the GBM. As glomerular maturation progresses, the α3, α4, and α5(IV) chains become the predominant type IV collagen chains in GBM. This process has been referred to as "isotype switching." Although an isotype switch does not occur in most males with Alport syndrome, glomerular development otherwise proceeds normally and the GBM of young animals and children with Alport syndrome exhibits a normal trilaminar appearance by electron microscopy. These glomeruli exhibit normal capacities for filtration and for selective permeability, as demonstrated by the normal glomerular filtration rates and absence of overt proteinuria that are characteristic of early Alport syndrome in both humans and animals. Therefore, it appears that proteinuria and renal insufficiency, as well as sensorineural deafness, come about as the result of processes initiated by the absence of the collagenα3-α4-α5(IV) network, rather than arising directly from the absence of this network.

The most straightforward demonstration of the consequences arising directly from the absence of the collagen α3-α4-α5(IV) network from basement membranes may be anterior lenticonus, in which the anterior lens capsule lacks the strength to maintain the normal conformation of the lens. Microhematuria, the first and invariable renal manifestation of Alport syndrome, probably reflects GBM thinning and a tendency to develop focal ruptures caused by the absent or defective expression of the collagenα3-α4- α5(IV) network. Episodic gross hematuria precipitated by infections, which is not uncommon during the first two decades of life, may reflect increased susceptibility of the Alport GBM to proteolysis.

The processes that bring about GBM thickening, proteinuria, and renal insufficiency in males with XLAS and in both males and females with ARAS remain undefined, although there are

some clues to what may be occurring. Unlike other glomerulopathies, Alport syndrome is characterized by the accumulation of the collagenα1(IV) and α2(IV) chains, along with types V and VI collagen, in the GBM. These proteins appear to spread from their normal subendothelial location, occupying the full width of the GBM. As Alport glomeruli undergo sclerosis, the collagenα1(IV) and α2(IV) chains disappear from the GBM, but type V and type VI collagen persist and, in fact, continue to accumulate. It is possible that the altered expression of the collagenα1(IV) and α2(IV) chains, type V collagen and type VI collagen represents a compensatory response to the loss of the collagen α3(IV), α4(IV), and α5(IV) chains from GBM, or it may simply reflect altered gene expression resulting from changes in signaling from the extracellular matrix to the nucleus. In transgenic mice with ARAS caused by partial deletion of *COL4A3*, renal mRNA levels for the collagen α1(IV) and α2(IV) chains progressively increase, suggesting activation of these genes. Whatever the underlying mechanism, the unrestrained deposition of certain collagens in GBM may contribute to glomerulosclerosis in Alport syndrome.

COL4A3

Normal allelic variants: *COL4A3* contains 52 exons. Several non-pathogenic polymorphisms in *COL4A3* have been described.

Pathologic allelic variants: Relatively few *COL4A3* mutations have been reported. However, mutations in this gene appear to exhibit the same variety as seen in *COL4A5*, with a predilection for glycine substitutions in the collagenous domains of the collagen α3(IV) chain.

Normal gene product: The gene products of *COL4A3*, *COL4A4*, and *COL4A5* are, respectively, the α3, α4, and α5 chains of type IV collagen [α3(IV), α4(IV), and α5(IV)]. The six type IV collagen α chains share basic structural features and show extensive sequence homology. The major structural features of α(IV) chains are: a collagenous domain of approximately 1400 residues containing the repetitive triplet sequence glycine (Gly)-X-Y, in which X and Y represent a variety of other amino acids; a carboxy-terminal non-collagenous (NC1) domain of approximately 230 residues; and a non-collagenous aminoterminal sequence of 15-20 residues. Approximately 20 interruptions of the collagenous triplet sequence are present in the collagenous domain. The NC1 domains each contain 12 completely conserved cysteine residues, which participate in intrachain and interchain disulfide bonds.

Type IV collagen chains form heterotrimers through associations between their COO- NC1 domains, associated with folding of the collagenous domains into triple helices.

Type IV collagen heterotrimers form networks through several types of intermolecular interaction. These include end-to-end linkages between the COO- NC1 domains of two heterotrimers, covalent interactions between four heterotrimers at their NH- ends, and lateral associations between heterotrimers via binding of the COO- domains to sites along the collagenous region of another heterotrimer. Disulfide bonds involving conserved cysteine residues are critical to the interactions between NC1 domains. These various linkages between type IV collagen molecules produce a nonfibrillar polygonal assembly that serves as scaffolding for the deposition of other matrix glycoproteins and for cell attachment.

Abnormal gene product: The abnormalities of type IV collagen expression observed in individuals with XLAS and ARAS indicate that a mutation affecting one of the chains involved in the putative collagen 3- 4- 5(IV) network can prevent basement membrane expression not only of that chain but of the other two chains as well. Similarly, a mutation involving the collagen 5(IV) chain can interfere with basement membrane expression of collagen 6(IV). The mechanisms that produce these effects remain under investigation. It is likely that at least some mutations interfere in various ways with the formation of trimeric type IV collagen molecules,

leading to degradation of normal chains that have been prevented from forming trimers or that have formed abnormal trimers. This kind of process accounts for abnormal type I collagen deposition in bone in osteogenesis imperfecta. Most of the available data suggest that *COL4A5* mutations do not suppress transcription of the *COL4A3*, *COL4A4*, and *COL4A6* genes.

COL4A4

Normal allelic variants: The *COL4A4* gene includes 48 exons. Several non-pathogenic polymorphisms in *COL4A4* have been described.

Pathologic allelic variants: Relatively few *COL4A4* mutations have been reported. However, mutations in this gene appear to exhibit the same variety as *COL4A5*, with a predilection for glycine substitutions in the collagenous domains of the collagen α4(IV) chain.

Normal gene product: See *COL4A3*.

Abnormal gene product: See *COL4A3*.

COL4A5

Normal allelic variants: *COL4A5* consists of 51 exons. A variety of non-pathogenic polymorphisms in *COL4A5* have been described.

Pathologic allelic variants: Of the several hundred reported *COL4A5* mutations, an estimated 20% are large rearrangements, predominantly deletions [Jais et al 2000]. Missense mutations account for approximately 35%-40%, approximately 15% are splice-site mutations, and 25%-30% are nonsense mutations or small frameshifting deletions or insertions that result in premature stop codons.

The great majority of missense *COL4A5* mutations are guanine substitutions in the first or second position of glycine codons that result in the replacement of a glycine residue in the collagenous domain of the collagenα5(IV) chain by another amino acid. Such mutations are thought to interfere with the normal folding of the mutant collagen α5(IV) chain into triple helices with other type IV collagen α chains. Glycine lacks a side chain, making it the least bulky of amino acids and small enough to allow three glycine residues to fit into the interior of a tightly wound triple helix. The presence of a bulkier amino acid in a glycine position presumably creates a kink or an unfolding in the triple helix. Glycine substitutions in the collagen α1(I) chain account for the majority of mutations causing osteogenesis imperfecta and are common in other genetic disorders of collagen. Abnormally folded collagen triple helices exhibit increased susceptibility to proteolytic degradation. The position of the substituted glycine, or the substituting amino acid itself, may influence the effect of the mutation on triple helical folding and ultimately the impact of the mutation on the severity of the clinical phenotype.

Normal gene product: See *COL4A3*.

Abnormal gene product: Rare missense mutations in *COL4A5* involve critical residues in the carboxy-terminal NC1 domain of the collagen α5(IV) chain — for example, one of the twelve conserved cysteine moieties. The loss of one of these cysteines would eliminate a disulfide bond, which could interfere with the formation of triple helices, or with the construction of networks involving collagenα5(IV) chains.

Resources

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

Alport Syndrome Foundation
1608 E Briarwood Terrace
Phoenix AZ 85048-9414
Phone: 480-460-0621
Email: info@alportsyndrome.org
www.alportsyndrome.org

National Library of Medicine Genetics Home Reference
Alport syndrome

NCBI Genes and Disease
Alport syndrome

The Kidney Foundation of Canada
700-15 Gervais Drive
Toronto M3C 1Y8
Canada
Phone: 800-387-4474;416-445-0373
Fax: 416-445-7440
Email: centralontario@kidneycob.on.ca
www.kidney.on.ca

National Association of the Deaf
8630 Fenton Street Suite 820
Silver Spring MD 20910
Phone: 301-587-1788 (voice); 301-587-1789 (TTY)
Fax: 301-587-1791
Email: NADinfo@nad.org
www.nad.org

National Kidney Foundation
30 East 33rd Street Suite 1100
New York NY 10016
Phone: 800-622-9010; 212-889-2210
Fax: 212-689-9261
Email: info@kidney.org
www.kidney.org

Alport Syndrome Treatments and Outcomes Registry (Astor)
Pediatric Nephrology University of Minnesota
MMC 491
420 Delaware St S.E.
Minneapolis MN 55455-0374
Phone: 612-626-2922
Fax: 612-626-2791
ASTOR

References

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

Published Statements and Policies Regarding Genetic Testing

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

Literature Cited

Adler L, Mathew R, Futterweit S, Frank R, Gauthier BG, Kashtan CE, Trachtman H. Angiotensin converting enzyme inhibitor therapy in children with Alport syndrome: effect on urinary albumin, TGF-beta, and nitrite excretion. BMC Nephrol. 2002;3:2. [PubMed: 11869456]

Antignac C, Heidet L. Mutations in Alport syndrome associated with diffuse esophageal leiomyomatosis. Contrib Nephrol. 1996;117:172–82. [PubMed: 8801045]

Badenas C, Praga M, Tazon B, Heidet L, Arrondel C, Armengol A, Andres A, Morales E, Camacho JA, Lens X, Davila S, Mila M, Antignac C, Darnell A, Torra R. Mutations in theCOL4A4 and COL4A3 genes cause familial benign hematuria. J Am Soc Nephrol. 2002;13:1248–54. [PubMed: 11961012]

Boye E, Mollet G, Forestier L, Cohen-Solal L, Heidet L, Cochat P, Grunfeld JP, Palcoux JB, Gubler MC, Antignac C. Determination of the genomic structure of the COL4A4 gene and of novel mutations causing autosomal recessive Alport syndrome. Am J Hum Genet. 1998;63:1329–40. [PubMed: 9792860]

Buzza M, Dagher H, Wang YY, Wilson D, Babon JJ, Cotton RG, Savige J. Mutations in the COL4A4 gene in thin basement membrane disease. Kidney Int. 2003;63:447–53. [PubMed: 12631110]

Byrne MC, Budisavljevic MN, Fan Z, Self SE, Ploth DW. Renal transplant in patients with Alport's syndrome. Am J Kidney Dis. 2002;39:769–75. [PubMed: 11920343]

Callis L, Vila A, Carrera M, Nieto J. Long-term effects of cyclosporine A in Alport's syndrome. Kidney Int. 1999;55:1051–6. [PubMed: 10027943]

Charbit M, Gubler MC, Dechaux M, Gagnadoux MF, Grunfeld JP, Niaudet P. Cyclosporin therapy in patients with Alport syndrome. Pediatr Nephrol. 2007;22:57–63. [PubMed: 17024394]

Ghiggeri GM, Caridi G, Magrini U, Sessa A, Savoia A, Seri M, Pecci A, Romagnoli R, Gangarossa S, Noris P, Sartore S, Necchi V, Ravazzolo R, Balduini CL. Genetics, clinical and pathological features of glomerulonephritis associated with mutations of nonmuscle myosin IIA (Fechtner syndrome). Am J Kidney Dis. 2003;41:95–104. [PubMed: 12500226]

Grodecki KM, Gains MJ, Baumal R, Osmond DH, Cotter B, Valli VE, Jacobs RM. Treatment of X-linked hereditary nephritis in Samoyed dogs with angiotensin converting enzyme (ACE) inhibitor. J Comp Pathol. 1997;117:209–25. [PubMed: 9447482]

Gross O, Netzer KO, Lambrecht R, Seibold S, Weber M. Meta-analysis of genotype-phenotype correlation in X-linked Alport syndrome: impact on clinical counselling. Nephrol Dial Transplant. 2002;17:1218–27. [PubMed: 12105244]

Gross O, Netzer KO, Lambrecht R, Seibold S, Weber M. Novel COL4A4 splice defect and in-frame deletion in a large consanguine family as a genetic link between benign familial haematuria and autosomal Alport syndrome. Nephrol Dial Transplant. 2003;18:1122–7. [PubMed: 12748344]

Gross O, Schulze-Lohoff E, Koepke ML, Beirowski B, Addicks K, Bloch W, Smyth N, Weber M. Antifibrotic, nephroprotective potential of ACE inhibitor vs AT1 antagonist in a murine model of renal fibrosis. Nephrol Dial Transplant. 2004;19:1716–23. [PubMed: 15128880]

Gubler MC, Knebelmann B, Beziau A, Broyer M, Pirson Y, Haddoum F, Kleppel MM, Antignac C. Autosomal recessive Alport syndrome: immunohistochemical study of type IV collagen chain distribution. Kidney Int. 1995;47:1142–7. [PubMed: 7783412]

Heidet L, Arrondel C, Forestier L, Cohen-Solal L, Mollet G, Gutierrez B, Stavrou C, Gubler MC, Antignac C. Structure of the human type iv collagen gene col4a3 and mutations in autosomal alport syndrome. J Am Soc Nephrol. 2001;12:97–106. [PubMed: 11134255]

Jais JP, Knebelmann B, Giatras I, De Marchi M, Rizzoni G, Renieri A, Weber M, Gross O, Netzer KO, Flinter F, Pirson Y, Verellen C, Wieslander J, Persson U, Tryggvason K, Martin P, Hertz JM,

Schroder C, Sanak M, Krejcova S, Carvalho MF, Saus J, Antignac C, Smeets H, Gubler MC. X-linked Alport syndrome: natural history in 195 families and genotype- phenotype correlations in males. J Am Soc Nephrol. 2000;11:649–57. [PubMed: 10752524]

Jais JP, Knebelmann B, Giatras I, De Marchi M, Rizzoni G, Renieri A, Weber M, Gross O, Netzer KO, Flinter F, Pirson Y, Dahan K, Wieslander J, Persson U, Tryggvason K, Martin P, Hertz JM, Schroder C, Sanak M, Carvalho MF, Saus J, Antignac C, Smeets H, Gubler MC. X-linked Alport syndrome: natural history and genotype-phenotype correlations in girls and women belonging to 195 families: a "European Community Alport Syndrome Concerted Action" study. J Am Soc Nephrol. 2003;14:2603–10. [PubMed: 14514738]

Jonsson JJ, Renieri A, Gallagher PG, Kashtan CE, Cherniske EM, Bruttini M, Piccini M, Vitelli F, Ballabio A, Pober BR. Alport syndrome, mental retardation, midface hypoplasia, and elliptocytosis: a new X linked contiguous gene deletion syndrome? J Med Genet. 1998;35:273–8. [PubMed: 9598718]

Kaito H, Nozu K, Iijima K, Nakanishi K, Yoshiya K, Kanda K, Przybyslaw Krol R, Yoshikawa N, Matsuo M. The effect of aldosterone blockade in patients with Alport syndrome. Pediatr Nephrol. 2006;21:1824–9. [PubMed: 17039334]

Kashtan CE. Alport syndrome. An inherited disorder of renal, ocular, and cochlear basement membranes. Medicine (Baltimore). 1999;78:338–60. [PubMed: 10499074]

Kashtan CE. Diagnosis of Alport syndrome. Kidney Int. 2004;66:1290–1. [PubMed: 15327435]

Kashtan CE. Renal transplantation in patients with Alport syndrome. Pediatr Transplant. 2006;10:651–7. [PubMed: 16911486]

Kashtan CE, Kleppel MM, Gubler MC. Immunohistologic findings in Alport syndrome. Contrib Nephrol. 1996;117:142–53. [PubMed: 8801043]

Kashtan CE, McEnery PT, Tejani A, Stablein DM. Renal allograft survival according to primary diagnosis: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol. 1995;9:679–84. [PubMed: 8747103]

King K, Flinter FA, Green PM. A two-tier approach to mutation detection in the COL4A5 gene for Alport syndrome. Hum Mutat. 2006;27:1061. [PubMed: 16941480]

Kunishima S, Matsushita T, Kojima T, Sako M, Kimura F, Jo EK, Inoue C, Kamiya T, Saito H. Immunofluorescence analysis of neutrophil nonmuscle myosin heavy chain-A in MYH9 disorders: association of subcellular localization with MYH9 mutations. Lab Invest. 2003;83:115–22. [PubMed: 12533692]

Lemmink HH, Nillesen WN, Mochizuki T, Schroder CH, Brunner HG, van Oost BA, Monnens LA, Smeets HJ. Benign familial hematuria due to mutation of the type IV collagen alpha4 gene. J Clin Invest. 1996;98:1114–8. [PubMed: 8787673]

Levy M, Feingold J. Estimating prevalence in single-gene kidney diseases progressing to renal failure. Kidney Int. 2000;58:925–43. [PubMed: 10972657]

Longo I, Porcedda P, Mari F, Giachino D, Meloni I, Deplano C, Brusco A, Bosio M, Massella L, Lavoratti G, Roccatello D, Frasca G, Mazzucco G, Muda AO, Conti M, Fasciolo F, Arrondel C, Heidet L, Renieri A, De Marchi M. COL4A3/COL4A4 mutations: from familial hematuria to autosomal-dominant or recessive Alport syndrome. Kidney Int. 2002;61:1947–56. [PubMed: 12028435]

Martin P, Heiskari N, Zhou J, Leinonen A, Tumelius T, Hertz JM, Barker D, Gregory M, Atkin C, Styrkarsdottir U, Neumann H, Springate J, Shows T, Pettersson E, Tryggvason K. High mutation detection rate in the COL4A5 collagen gene in suspected Alport syndrome using PCR and direct DNA sequencing. J Am Soc Nephrol. 1998;9:2291–301. [PubMed: 9848783]

Meloni I, Vitelli F, Pucci L, Lowry RB, Tonlorenzi R, Rossi E, Ventura M, Rizzoni G, Kashtan CE, Pober B, Renieri A. Alport syndrome and mental retardation: clinical and genetic dissection of the contiguous gene deletion syndrome in Xq22.3 (ATS-MR). J Med Genet. 2002;39:359–65. [PubMed: 12011158]

Merchant SN, Burgess BJ, Adams JC, Kashtan CE, Gregory MC, Santi PA, Colvin R, Collins B, Nadol JB Jr. Temporal bone histopathology in alport syndrome. Laryngoscope. 2004;114:1609–18. [PubMed: 15475791]

Mothes H, Heidet L, Arrondel C, Richter KK, Thiele M, Patzer L, Sado Y, Gubler MC, Antignac C, Scheele J. Alport syndrome associated with diffuse leiomyomatosis: COL4A5-COL4A6 deletion

associated with a mild form of Alport nephropathy. Nephrol Dial Transplant. 2002;17:70–4. [PubMed: 11773466]

Nagel M, Nagorka S, Gross O. Novel COL4A5, COL4A4, and COL4A3 mutations in Alport syndrome. Hum Mutat. 2005;26:60. [PubMed: 15954103]

Norby SM, Cosio FG. Thin basement membrane nephropathy associated with other glomerular diseases. Semin Nephrol. 2005;25:176–9. [PubMed: 15880329]

Piccini M, Casari G, Zhou J, Bruttini M, Volti SL, Ballabio A, Renieri A. Evidence for genetic heterogeneity in benign familial hematuria. Am J Nephrol. 1999;19:464–7. [PubMed: 10460935]

Plant KE, Green PM, Vetrie D, Flinter FA. Detection of mutations in COL4A5 in patients with Alport syndrome. Hum Mutat. 1999;13:124–32. [PubMed: 10094548]

Proesmans W, Knockaert H, Trouet D. Enalapril in paediatric patients with Alport syndrome: 2 years' experience. Eur J Pediatr. 2000;159:430–3. [PubMed: 10867848]

Proesmans W, Van Dyck M. Enalapril in children with Alport syndrome. Pediatr Nephrol. 2004;19:271–5. [PubMed: 14745635]

Seri M, Cusano R, Gangarossa S, Caridi G, Bordo D, Lo Nigro C, Ghiggeri GM, Ravazzolo R, Savino M, Del Vecchio M, d'Apolito M, Iolascon A, Zelante LL, Savoia A, Balduini CL, Noris P, Magrini U, Belletti S, Heath KE, Babcock M, Glucksman MJ, Aliprandis E, Bizzaro N, Desnick RJ, Martignetti JA. Mutations in MYH9 result in the May-Hegglin anomaly, and Fechtner and Sebastian syndromes. The May-Heggllin/Fechtner Syndrome Consortium. Nat Genet. 2000;26:103–5. [PubMed: 10973259]

Tiebosch AT, Frederik PM, van Breda Vriesman PJ, Mooy JM, van Rie H, van de Wiel TW, Wolters J, Zeppenfeldt E. Thin-basement-membrane nephropathy in adults with persistent hematuria. N Engl J Med. 1989;320:14–18. [PubMed: 2909874]

van der Loop FT, Monnens LA, Schroder CH, Lemmink HH, Breuning MH, Timmer ED, Smeets HJ. Identification of COL4A5 defects in Alport's syndrome by immunohistochemistry of skin. Kidney Int. 1999;55:1217–24. [PubMed: 10200983]

van Paassen P, van Breda Vriesman PJ, van Rie H, Tervaert JW. Signs and symptoms of thin basement membrane nephropathy: a prospective regional study on primary glomerular disease-The Limburg Renal Registry. Kidney Int. 2004;66:909–13. [PubMed: 15327380]

Zhou J, Mochizuki T, Smeets H, Antignac C, Laurila P, de Paepe A, Tryggvason K, Reeders ST. Deletion of the paired alpha 5(IV) and alpha 6(IV) collagen genes in inherited smooth muscle tumors. Science. 1993;261:1167–9. [PubMed: 8356449]

Suggested Readings

Byers PH. Disorders of collagen, biosynthesis; structure. In: Scriver, CR.; Beaudet, AL.; Sly, WS.; Valle, D.; Vogelstein, B. The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 205. Available at www.ommbid.com. Accessed 1-22-08. eds

Pirson Y. Making the diagnosis of Alport's syndrome. Kidney Int. 1999;56:760–75. [PubMed: 10432421]

Chapter Notes

Author Notes

Web: experts.umn.edu

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Revision History

- 23 January 2008 (me) Comprehensive update posted to live Web site
- 8 January 2007 (cd) Revision: deletion/duplication analysis for *COL4A5* clinically available

- 26 September 2005 (me) Comprehensive update posted to live Web site
- 29 December 2003 (ck) Revision: sequence analysis for *COL4A5*, *COL4A3*, *COL4A4* clinically available; prenatal diagnosis available
- 28 August 2003 (me) Comprehensive update posted to live Web site
- 28 August 2001 (me) Review posted to live Web site
- March 2001 (ck) Original submission