

Alport Syndrome

Clinical Background

Alport syndrome is a progressive, hereditary renal disease characterized by abnormalities in the glomerular basement membrane and commonly associated with cochlear and/or ocular involvement.

Epidemiology

- Incidence – 1/50,000 live births
- Age – variable
 - Autosomal recessive – earliest onset
 - X-linked – next onset
 - Autosomal dominant – onset in middle age
- Sex
 - M>F for X-linked Alport syndrome (100% penetrance in males, variable in females)
 - M:F, equal for autosomal dominant and recessive forms of Alport syndrome

Inheritance

- 80% X-linked, 15% autosomal recessive and <5% autosomal dominant
- Autosomal recessive and dominant forms of Alport syndrome are due to gene mutations in *COL4A3* and *COL4A4*
- X-linked form is due to mutations in the *COL4A5* gene
 - Sequencing of *COL4A5* identifies 70% of mutations in affected females and 80% of mutations in affected males of all ages
 - Three common mutations, C1564S, L1649R, and R1677Q, are causative for 75% of adult (end stage renal disease after age 30) X-linked Alport syndrome
 - *de novo* mutations in 10-15% of affected males

Pathophysiology

- Caused by defects in type IV collagen alpha chain
- Leads to loss of type IV collagen in the basal lamina

Clinical Presentation

- Renal
 - Microscopic hematuria and proteinuria, progressive renal insufficiency, end-stage renal disease
 - 60% of males with X-linked Alport syndrome reach end-stage renal disease by age 30 and 90% by age 40
 - Most individuals with autosomal recessive Alport syndrome reach end-stage renal disease before age 30
 - End-stage renal disease is usually delayed until middle age in autosomal dominant Alport syndrome
- Cochlear
 - Sensorineural hearing loss
 - Usually presents in late childhood in X-linked Alport syndrome
 - 85% of males with X-linked Alport syndrome have sensorineural deafness by age 40
 - Individuals with autosomal recessive Alport syndrome have juvenile onset
 - Autosomal dominant Alport syndrome is associated with later adult onset
- Ocular – lenticonus, maculopathy, corneal endothelial vesicles and recurrent corneal abrasions
 - Ocular lesions are uncommon in adult-onset disease

Treatment

- Early disease
 - Antihypertensive drugs and angiotensin converting enzyme (ACE) inhibitors
- Renal transplantation for end-stage disease
 - Antibodies may redevelop, but repeat renal failure is uncommon
 - Genetic testing of family members for Alport syndrome is critical when selecting eligible donors

Diagnosis

- Indications for testing
 - Unexplained hematuria or chronic kidney disease in men
 - Unexplained hematuria in women with a family history of chronic kidney disease
- Detailed family and personal history to rule out other possible diseases
- Audiologic and ophthalmologic exams – may be abnormal
- Histology
 - Immunohistochemical analysis of basement membrane type IV collagen (α5) expression using renal or skin biopsies (skin biopsies have a higher incidence of false negatives than renal biopsies)
 - Electron microscopy of renal biopsy specimen
- Genetic testing
 - Diagnostic testing for symptomatic individuals
 - Exclude diagnosis of Alport syndrome in patients with thin basement membrane nephropathy

Differential Diagnosis

- Thin basement membrane nephropathy
- Other glomerular diseases
- Inherited hearing loss syndromes
- Fechtner/Epstein syndrome

Screening

- Presymptomatic and carrier testing for at-risk individuals who have previously diagnosed family members

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Alport Syndrome, X-linked (COL4A5) Sequencing 0051786 Method: Polymerase Chain Reaction/Sequencing	Determine the cause of X-linked Alport syndrome Clinical sensitivity is 80% in males and 70% in females Analytical sensitivity and specificity are 99%	Rare diagnostic errors can occur due to prime site mutations Regulatory and deep intronic mutations will not be detected Large deletions/duplications will not be detected in females	

<p>Alport Syndrome, X-linked (<i>COL4A5</i>) 3 Mutations 0051710</p> <p>Method: Polymerase Chain Reaction/Fluorescence Monitoring</p>	<p>Determine the cause of adult type X-linked Alport syndrome by examining three common <i>COL4A5</i> mutations: C1564S (c.4992G>A), L1649R (c.4946T>G), and R1677Q (c.5030G>A)</p> <p>Clinical sensitivity for adult type X-linked Alport syndrome is 75%</p> <p>Analytical sensitivity and specificity is 99%</p>	<p>Mutations other than those targeted will not be detected; analytical sensitivity may be compromised by rare primer or probe site mutations</p>	
<p>Alport Syndrome, X-linked (<i>COL4A5</i>) Deletion/Duplication 2002394</p> <p>Method: Polymerase Chain Reaction/Multiplex Ligation-dependent Probe Amplification</p>	<p>Detect large <i>COL4A5</i> coding region deletions and duplications</p> <p>Clinical sensitivity is 10% for X-linked Alport syndrome in males and females</p> <p>Analytical sensitivity and specificity: 99%</p>	<p>Rare diagnostic errors can occur due to primer or probe site mutations</p> <p>Breakpoints of deletions/duplications will not be determined</p> <p><i>COL4A5</i> base pair substitutions, small deletions/duplications, deep intronic, and regulatory region mutations will not be detected</p> <p>Mutations in genes other than <i>COL4A5</i> are not evaluated</p>	
<p>Alport Syndrome, X-linked (<i>COL4A5</i>) Sequencing and Deletion/Duplication 2002398</p> <p>Method: Polymerase Chain Reaction/ Sequencing/Multiplex Ligation-dependent Probe Amplification</p>	<p>Detect large <i>COL4A5</i> coding region deletions and duplications</p> <p>Clinical sensitivity greater than 80% for X-linked Alport syndrome in males and females</p> <p>Analytical sensitivity and specificity: 99%</p>	<p>Rare diagnostic errors can occur due to primer or probe site mutations</p> <p>Regulatory region and deep intronic mutations will not be detected</p> <p>Breakpoints of deletions/duplications will not be determined</p> <p>Mutations in genes other than <i>COL4A5</i> are not evaluated</p>	
<p>Familial Mutation, Targeted Sequencing 2001961</p> <p>Method: Polymerase Chain Reaction/Sequencing</p>	<p>Custom sequencing for a familial <i>COL4A5</i> mutation</p> <p>Must provide copy of laboratory report of affected family member detailing the specific mutation</p>	<p>Mutations other than the one targeted will not be identified</p>	

Immunohistochemistry Stain Offering arup005 Method: Immunohistochemistry	Identify collagen IV defects		
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General References

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