

Alport Syndrome, X-Linked (COL4A5) Sequencing and Deletion/Duplication

TO DETERMINE CARRIER, PRESYMPTOMATIC, OR AFFECTED STATUS

Disease Overview

- Alport syndrome (AS) is a progressive renal disease with cochlear and ocular involvement.
- X-linked Alport syndrome (XLAS) occurs due to defects in type IV collagen alpha chain five, which results in loss of type IV collagen in the basal lamina.
- All males with XLAS have childhood microscopic hematuria progressing to proteinuria, hypertension, renal insufficiency, and end-stage renal disease (ESRD). 60 percent of affected males reach ESRD by age 30 and 90 percent by age 40.
- 90 percent of female carriers of XLAS have microscopic hematuria, with 10 percent progressing to ESRD by age 40, 30 percent by age 60, and 40 percent by age 80.
- Bilateral high-frequency hearing loss is usually detectable by early adolescence in males with XLAS; this progresses to sensorineural deafness by age 40 in about 85 percent of males with XLAS. Females are less frequently affected with hearing loss.
- Ocular lesions occur in 30–40 percent of affected individuals; anterior lenticonus is pathognomonic of AS. Maculopathy, corneal endothelial vesicles, and recurrent corneal erosion may also occur.
- Diagnosis requires a physical exam, audiologic and ophthalmic evaluations, detailed family history, including possible urinalysis on first- and second-degree relatives, immunohistochemical analysis of basement membrane type IV collagen expression using renal or skin biopsies, and electron microscopy of renal biopsy specimen.
- Disease management entails: use of angiotensin-converting enzyme inhibitors when proteinuria appears, renal transplantation for ESRD, hearing aids, and cataract removal as needed.

Prevalence

- Prevalence varies from one in 5,000 (OMIM) to one in 50,000 (<http://home.utah.edu/~cla6202/ASHP.htm#UAS>).
- In the United States, AS is responsible for 0.2 percent of adult and 3 percent of childhood ESRD (OMIM).

Genetics

- 80 percent of AS is X-linked recessive; 15 percent is autosomal recessive; and 5 percent is autosomal dominant.

- The X-linked form occurs due to mutations in the *COL4A5* gene, while the autosomal forms occur due to mutations in either the *COL4A3* or *COL4A4* genes.
- 10–15 percent of XLAS is caused by de novo mutations.
- Several hundred mutations have been described in *COL4A5*.
- Sequencing of *COL4A5* identifies >80 percent of the mutations in males and >70 percent of mutations in females with XLAS. Duplication/deletion analysis is necessary to detect an additional 10 percent of large exonic or full-gene deletions in females that cannot be identified by sequencing alone.

Indications for Ordering

- Males with unexplained, persistent hematuria or chronic kidney disease.
- Females with unexplained, persistent hematuria with a family history of adult chronic kidney disease.
- Diagnostic, presymptomatic, or carrier testing of individuals with a family history of XLAS when the specific familial mutation is unknown.

Contraindication

- When the specific *COL4A5* familial mutation has already been determined, testing can be performed on at-risk family members by ordering custom sequencing (ARUP test # 0050358) for the known *COL4A5* mutation only.

Interpretation

- A negative result does not rule out XLAS since deep intronic mutations and promoter mutations are not identified. Furthermore, mutations in genes associated with autosomal recessive and dominant AS will not be detected.
- Males with one deleterious *COL4A5* mutation are predicted to be affected with XLAS.
- Females with one deleterious *COL4A5* mutation are at least carriers of XLAS; 10 percent will progress to end-stage renal disease by age 40 and 30 percent by age 60.
- An uncertain result means that a gene mutation was detected, but it is not known whether this mutation is benign or deleterious.
- For individuals with unclear or negative results, medical management should rely on clinical findings and family history.

Limitations

- Mutations in the *COL4A3* and *COL4A4* genes causing autosomal recessive and dominant forms of AS will not be detected.
- Analytic sensitivity may be compromised by rare primer- or probe-site mutations.
- Deep intronic mutations or those within the promoter will not be detected.
- The breakpoints of large *COL4A5* gene duplications or deletions will not be determined.

Methodology

- Bi-directional sequencing of the entire *COL4A5* coding region and intron-exon borders.
- Multiplex ligation-dependent probe amplification (MLPA) is performed for large deletion/duplication analysis of the *COL4A5* gene.
- Analytic sensitivity and specificity are 99 percent.
- Clinical sensitivity is >80 percent in males and females. Clinical specificity may vary depending on the mutation identified.

Related Tests

- Alport syndrome, X-Linked (*COL4A5*) Sequencing (0051786): detects >80 percent of mutations in males and >70 percent of mutations in females with X-linked AS.
- Alport syndrome, X-Linked (*COL4A5*) Deletion/Duplication (2002394): detects 10 percent of mutations in males and females with X-linked AS.
- Alport Syndrome, X-linked (*COL4A5*) 3 Mutations (0051710): identifies three common mutations found only in adult-type, X-linked AS.
- Familial Mutation, Targeted Sequencing (2001961): order in individuals when the familial *COL4A5* mutation is known; a completed AS patient history form detailing the familial mutation must accompany the sample.

References

1. Barker DF, et al. Identification of mutations in the *COL4A5* collagen gene in Alport syndrome. *Science* 1990;248:1224–7.
2. Barker, et al. A mutation causing Alport syndrome with tardive hearing loss is common in the Western United States. *Am J Hum Gen* 1996;58(6):1157–65.
3. Barker, et al. Common ancestry of three Ashkenazi-American families with Alport syndrome and *COL4A5* R1677Q. *Hum Gen* 1997;99:681–4.

Test Information

2002398 Alport syndrome, X-Linked (*COL4A5*) Sequencing and Deletion/Duplication

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.