

Alport Syndrome, Adult Type (COL4A5) 3 Mutations

*TO IDENTIFY THREE COMMON COL4A5 GENE MUTATIONS
CAUSING ADULT-TYPE, X-LINKED ALPORT SYNDROME*

Disease Overview

- Alport syndrome (AS) is a progressive renal disease with cochlear and ocular involvement.
- AS occurs due to defects in one of the type IV collagen alpha chains that result in loss of type IV collagen in the basal lamina.
- In adult-type AS, end-stage renal disease occurs in males in their fourth decade of life or later. The mean age of end-stage renal disease in juvenile type AS is less than 30 years.
- All males with X-linked Alport syndrome (XLAS) experience childhood microscopic hematuria progressing to proteinuria, hypertension, renal insufficiency, and renal failure.
- 90 percent of females with XLAS experience microscopic hematuria.
- Bilateral high-frequency hearing loss is commonly diagnosed in males age 24–45 with adult-type XLAS but may not be obvious until after age 60 in men with the L1649R mutation. Females are less frequently affected with hearing loss.
- Ocular lesions are uncommon in adult-type AS.
- Diagnosis includes 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 prescribing angiotensin-converting enzyme inhibitors when proteinuria appears, renal transplantation, hearing aids, and cataract removal as needed.

Prevalence

In the United States, Alport syndrome accounts for 0.2 percent of adults and 3 percent of children with end-stage renal disease (OMIM).

Genetics

- 80 percent of AS is X-linked, 15 percent is autosomal recessive, and <5 percent is autosomal dominant.
- The X-linked form occurs due to pathogenic mutations in the *COL4A5* gene.
- 10–15 percent of XLAS cases are caused by de novo mutations in *COL4A5*.
- Although several hundred mutations have been described in *COL4A5*, 75 percent of adult-type XLAS is predicted to be caused by three common mutations.

Indications for Ordering

- Unexplained hematuria or chronic kidney disease in individuals with a family history of end stage renal disease in relatives over the age of 30.
- Diagnostic, presymptomatic, or carrier testing of individuals from families known to carry one of the common *COL4A5* mutations tested: C1564S, L1649R, or R1677Q.

Contraindications

Prenatal testing.

Interpretation

- Negative: Absence of the three *COL4A5* mutations tested does not exclude other mutations in the *COL4A5* gene implicated in XLAS or mutations in genes for autosomal recessive and dominant AS.
- Positive male: Males with one *COL4A5* mutation are predicted to be affected with AS.
- Positive female: Females with one *COL4A5* mutation are at least carriers of AS. They may or may not develop symptoms.

Limitations

- Juvenile onset AS will not be detected.
- 25 percent of adult-onset AS will not be detected.
- Only the C1564S, L1649R, and R1677Q mutations in the *COL4A5* gene will be identified.
- 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.

Methodology

- Polymerase chain reaction (PCR) followed by melting-curve analysis of three fluorescent probes. Each probe is specific for one of the following mutations: C1564S (c.4692G>A), L1649R (c.4946T>G), or R1677Q (c.5030 G>A).
- Analytic sensitivity and specificity are 99 percent.
- Clinical sensitivity for adult-type XLAS in United States Caucasians is estimated to be 75 percent. Clinical specificity is 100 percent.

Related Tests

- Alport Syndrome, X-Linked (*COL4A5*) Sequencing and Deletion/Duplication ([2002398](#))
- Alport Syndrome, X-Linked (*COL4A5*) Sequencing ([0051786](#))
- Alport Syndrome, X-linked (*COL4A5*) Deletion/Duplication ([2002394](#))

References

1. Barker DF, et al. Identification of mutations in the COL4A5 collagen gene in Alport syndrome. *Science* 1990;248:1224–27.
2. Barker DF, 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 DF, et al. Common ancestry of three Ashkenazi-American families with Alport syndrome and COL4A5 R1677Q. *Hum Gen* 1997;99:681–4.

Test Information

0051710 **Alport Syndrome, X-Linked (*COL4A5*) 3 Mutations**

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.