

X-Linked Alport Syndrome

Indications for Ordering

- Males with unexplained, persistent hematuria or chronic kidney disease
- Females with unexplained, persistent hematuria or chronic kidney disease, and a family history of adult chronic kidney disease
- Diagnostic, presymptomatic, or carrier testing of individuals with a family history of X-linked Alport syndrome when the familial variant is unknown

Test Description

Polymerase chain reaction/sequencing/multiplex ligation-dependent probe amplification

Tests to Consider

Primary Test

[Alport Syndrome, X-linked \(COL4A5\) Sequencing and Deletion/Duplication 2002398](#)

- Genetic test for the detection of variants causing X-linked Alport syndrome

Related Tests

[Familial Mutation, Targeted Sequencing 2001961](#)

- Useful for confirming a diagnosis when a pathogenic sequence variant has been identified in a family member

[Deletion/Duplication Analysis by MLPA 3003144](#)

- Useful for confirming a diagnosis when a large deletion/duplication has been identified in family member

Disease Overview

Prevalence: varies from 1/5,000-50,000

Symptoms

- Males
 - Renal disease
 - Microscopic hematuria
 - Progressive proteinuria, hypertension
 - End stage renal disease (ESRD)
 - 100% develop proteinuria and 60% have ESRD by 30 years and 90% by 40 years
 - Cochlear disease
 - Bilateral, high-frequency hearing loss
 - 80-90% develop significant hearing loss by 40 years
 - Ocular disease
 - ~40% develop anterior lenticonus or other characteristic ocular lesions
- Female carriers
 - Renal disease
 - 90% have episodic hematuria
 - 12% develop ESRD before 40 years, 30% by 60 years, and 40% by 80 years
 - Cochlear disease
 - Hearing loss is infrequent and tends to occur later in life
 - Ocular disease
 - Anterior lenticonus is uncommon

Physiology

- Disorder of alpha 5 chain of type IV collagen
- Disorder results in loss of type IV collagen in basal lamina
 - Leads to disease where this collagen is found
 - Renal
 - Cochlear
 - Ocular

Diagnosis

- Combination of
 - Family history (possible urinalysis on first- and second-degree relatives)
 - Physical examination (including ophthalmologic exam)
 - Audiologic evaluation
 - Immunohistochemical analysis of basement membrane type IV collagen expression using renal or skin biopsies
 - Electron microscopy of renal biopsy

Genetics

Gene: *COL4A5*

Inheritance: X-linked

- 80-85% of Alport syndrome is X-linked (related to the *COL4A5* gene)
- 15-20% of Alport syndrome is autosomal recessive or autosomal dominant and is caused by variants in either the *COL4A3* or *COL4A4* genes

Penetrance: 100% males, variable in females (presentation is variant dependent)

De novo variants: 10-15%

Variants: >400 reported

- 20% deletions
- 35-40% missense variants
- 15% splice-site variants
- 25-30% nonsense variants or small frameshifting deletions/insertions

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity for sequencing: ~82% (Martin, 1998; Jais, 2003)
- Clinical sensitivity for MLPA: ~10% (Martin, 1998; Jais, 2003)
- Analytic sensitivity/specificity: 99%

Results

- Positive: diagnosis/carrier status confirmed
- Negative: X-linked Alport syndrome is less likely, but not excluded
- Inconclusive: variant detected, but it is unclear whether it is benign or pathogenic

Limitations

- Not detected:
 - Deletions/duplications of *COL4A5* exons 8, 25, 40, 42, and 43
 - Regulatory region or deep intronic variants
 - *COL4A3* and *COL4A4* gene variants associated with autosomal recessive or dominant disease
- Diagnostic errors can occur due to rare sequence variations.
- Large deletion/duplication breakpoints will not be determined.

References

- Martin P, Heiskari N, Zhou J, et al. [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(12):2291-2301. PubMed
- Jais JP, Knebelmann B, Giatras I, et al. [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(10):2603-2610. PubMed