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 tests

Alport Syndrome, X-linked (*COL4A5*) Sequencing and Deletion/Duplication 2002398

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

Alport Syndrome, X-linked (*COL4A5*) Sequencing 0051786

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

Related test

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

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

Limitations
- Not detected
  - Deep intronic variants
  - Promotor variants
  - *COL4A3* and *COL4A4* gene variants associated with autosomal recessive or dominant disease
  - Deletions/duplications of exons 8, 25, 40, 42, and 43 in the *COL4A5* gene

References

- Martin P, Heiskari N, 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):2291-301
- Jais JP, Knebelmann B, 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):2603-10