# Alport Syndrome Panel, Sequencing and Deletion/Duplication

Alport syndrome (AS) is a spectrum of disorders that may range from isolated nonprogressive microscopic hematuria and proteinuria to progressive renal insufficiency, end stage renal disease (ESRD), eye findings, and sensorineural hearing loss (SNHL). The three main genes causative for AS (*COL4A3*, *COL4A4*, and *COL4A5*) are critical to the collagen IV a345 network of basement membranes. Pathogenic variants in *COL4A5*, causative for approximately 80-85% of AS, are inherited in an X-linked recessive (XLR) manner. Approximately 15-20% of AS is autosomal dominant (AD) or autosomal recessive (AR) due to pathogenic variants in the *COL4A3* or *COL4A4* genes.

## Disease Overview

### Symptoms

**Symptoms of AS and Related Disorders**

| Symptom Categories | X-Linked and Autosomal Recessive AS | Autosomal Dominant AS | *MYH9*-Related Disease |
|---|---|---|---|
| Renal symptoms | Renal disease progressing from microhematuria and proteinuria to renal insufficiency and ESRD<br>• Males with X-linked AS: 60% have ESRD by age 30 and 90% by age 40<br>• Females with X-linked AS: 12% have ESRD by age 40, 30% by age 60, and 40% by age 80<br>• Individuals with autosomal recessive AS: most develop ESRD by age 30 | Slowly progressive renal insufficiency presenting later in life | Early adult onset of renal disease, initially presenting as glomerular nephropathy |
| Hearing loss | Progressive SNHL in late childhood | Slowly progressive SNHL later in life | SNHL |

## Tests to Consider

### Alport Syndrome Panel, Sequencing and Deletion/Duplication 3002685

**Method:** Massively Parallel Sequencing/ Multiplex Ligation-dependent Probe Amplification

- Recommended test to confirm carrier status or a diagnosis of AS or *MYH9*-related disease.
- Regions of low coverage and reported variants are confirmed by Sanger sequencing as necessary.

### Familial Mutation, Targeted Sequencing 2001961

**Method:** Polymerase Chain Reaction/Sequencing

- Recommended test for a sequence variant previously identified in a family member.
- A copy of the family member's test result is required.

### Deletion/Duplication Analysis by MLPA 3003144

**Method:** Multiplex Ligation-dependent Probe Amplification

- Recommended test for a large deletion/duplication previously identified in a family member.
- A copy of the family member's test result is recommended.

| Symptom Categories | X-Linked and Autosomal Recessive AS | Autosomal Dominant AS | *MYH9*-Related Disease |
|---|---|---|---|
| Ocular issues | Anterior lenticonus<br>• Presents in second or third decade of life<br>• Observed in ~13% of males with X-linked AS<br>• Associated with certain COL4A5 variants<br><br>Maculopathy<br>• Defined by whitish yellow flecks in the perimacular region<br>• Observed in 14% of males with X-linked AS<br><br>Corneal endothelial vesicles or corneal erosion in X-linked AS<br><br>Posterior subcapsular cataracts in X-linked AS | Ocular lesions are uncommon | Cataracts |
| Other | Diffuse leiomyomatosis (benign smooth muscle cell proliferation) of the esophagus and tracheobronchial tree may occur in X-linked AS<br><br>Thoracic and abdominal aortic aneurysms in a few males with X-linked AS at <40 years | – | Congenital presentation of large platelets and thrombocytopenia<br><br>Adult onset of elevated liver enzymes |

## Etiology of Alport Syndrome

AS is caused by pathogenic variants in collagen genes that contribute to the collagen IV network of basement membranes.

## Penetrance of Alport Syndrome and *MYH9*-Related Disease

- Complete for males with X-linked AS and both males and females with AR *COL4A3* and *COL4A4* variants and *MYH9*-related disease
- Possible incomplete penetrance for AD *COL4A3* and *COL4A4* variants

## Prevalence of Alport Syndrome

- 1/50,000 births[1]
- 0.2% of U.S. adults and 3% of children with ESRD have AS[2]

## Inheritance

- *COL4A5*: XLR
- *COL4A3* and *COL4A4*: AD and AR, depending on the variant
- *MYH9*: AD

## Genotype-Phenotype Correlation

- Large *COL4A5* rearrangements, nonsense, frameshift, and splice site variants are associated with a 50% risk for ESRD by age 20, 90% risk of ESRD by age 30, and a 50% risk for SNHL by age 10.
- Pathogenic missense *COL4A5* variants confer a 50% risk for ESRD by age 30 and 50% risk of SNHL by age 20.
- Leiomyomatosis only occurs in individuals with a deletion of both *COL4A5* and *COL4A6* when the *COL4A6* breakpoint is in the second intron of the gene.

# Test Interpretation

## Clinical Sensitivity

- ~97-100% for AS[3-11]
- 98% for *MYH9*-related disease[12]

## Analytical Sensitivity

For massively parallel sequencing:

| Variant Class | Analytical Sensitivity (PPA) Estimate[a] (%) | Analytical Sensitivity (PPA) 95% Credibility Region[a] (%) |
|---|---|---|
| SNVs | 99.2 | 96.9-99.4 |
| Deletions 1-10 bp | 93.8 | 84.3-98.2 |
| Deletions 11-44 bp | 99.9 | 87.8-100 |
| Insertions 1-10 bp | 94.8 | 86.8-98.5 |
| Insertions 11-23 bp | 99.9 | 62.1-100 |

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

## Limitations

- A negative result does not exclude a diagnosis of AS or *MYH9*-related disease.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted genes
  - Regulatory region and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in *COL4A3*, *COL4A4*, and *MYH9* genes
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:
    - *COL4A5* (NM_000495) 8, 25, 40, 42, 43

## Genes Tested

| Gene Symbol | MIM # | Disorders | Inheritance |
|---|---|---|---|
| *COL4A3* | 120070 | Alport syndrome 2<br>Alport syndrome 3<br>Hematuria, benign familial | AR/AD |
| *COL4A4* | 120131 | Alport syndrome 2<br>Hematuria, familial benign | AR/AD |

| Gene Symbol | MIM # | Disorders | Inheritance |
|---|---|---|---|
| *COL4A5* | 303630 | Alport syndrome 1, X-linked | XLR |
| *MYH9* | 160775 | Deafness 17<br>Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss | AD |

## References


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## Additional Resources


Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2019 Annual Data Report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2020;75(1 Suppl 1):A6-A7.

United States Renal Data System. USRDS home page. [Accessed: Jun 2020]


## Related Information

Alport Syndrome


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