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 genes causative for AS (COL4A3, COL4A4, and COL4A5) are critical to the collagen IV α345 network of basement membranes. Pathogenic variants in COL4A5, causative for approximately 80-85% of AS, are inherited in an X-linked (XL) 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

<table>
<thead>
<tr>
<th>Symptom Categories</th>
<th>X-Linked and Autosomal Recessive AS</th>
<th>Autosomal Dominant AS</th>
<th>MYH9-Related Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal symptoms</td>
<td>Renal disease progressing from microhematuria and proteinuria to renal insufficiency and ESRD</td>
<td>Slowly progressive renal insufficiency presenting later in life</td>
<td>Early adult onset of renal disease, initially presenting as glomerular nephropathy</td>
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<td></td>
<td>Males with X-linked AS: 60% have ESRD by age 30 and 90% by age 40</td>
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<td>Females with X-linked AS: 12% have ESRD by age 40, 30% by age 60, and 40% by age 80</td>
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<tr>
<td></td>
<td>Individuals with autosomal recessive AS: most develop ESRD by age 30</td>
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<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Progressive SNHL in late childhood</td>
<td>Slowly progressive SNHL later in life</td>
<td>SNHL</td>
</tr>
<tr>
<td>Ocular issues</td>
<td>Anterior lenticonus</td>
<td>Ocular lesions are uncommon</td>
<td>Cataracts</td>
</tr>
<tr>
<td></td>
<td>Presents in second or third decade of life</td>
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<tr>
<td></td>
<td>Observed in ~13% of males with X-linked AS</td>
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<tr>
<td></td>
<td>Associated with certain COL4A5 variants</td>
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<tr>
<td>Maculopathy</td>
<td>Defined by whitish yellow flecks in the perimacular region</td>
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<tr>
<td></td>
<td>Observed in 14% of males with X-linked AS</td>
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</tbody>
</table>

Featured ARUP Testing

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 Targeted Sequencing 3005867
Method: Massively Parallel Sequencing
- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member’s test result documenting the familial gene variant is REQUIRED.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.
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 individuals 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
- 0.2% of U.S. adults and 3% of children with ESRD have AS

Inheritance

- COL4A5: XL
- 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

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS, also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

- Approaching 100% for AS
- At least 98% for MYH9-related disease
Analytic Sensitivity

For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytic Sensitivity (PPA) Estimate (%) and 95% Credibility Region</th>
<th>Analytic Specificity (NPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>&gt;99 (96.9-99.4)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Deletions 1-10 bp</td>
<td>93.8 (84.3-98.2)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Insertions 1-10 bp</td>
<td>94.8 (86.8-98.5)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Exon-level deletions</td>
<td>97.8 (90.3-99.8) [2 exons or larger]</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td></td>
<td>62.5 (38.3-82.6) [single exon]</td>
<td></td>
</tr>
<tr>
<td>Exon-level duplications</td>
<td>83.3 (56.4-96.4) [3 exons or larger]</td>
<td>&gt;99.9</td>
</tr>
</tbody>
</table>

aGenes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

bVariants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

cIn most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; 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
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Noncoding transcripts
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

Genes Tested

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>MIM #</th>
<th>Disorders</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL4A3</td>
<td>120070</td>
<td>Alport syndrome 2</td>
<td>AR/AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alport syndrome 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematuria, benign familial</td>
<td></td>
</tr>
<tr>
<td>COL4A4</td>
<td>120131</td>
<td>Alport syndrome 2</td>
<td>AR/AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematuria, benign familial</td>
<td></td>
</tr>
<tr>
<td>COL4A5</td>
<td>303630</td>
<td>Alport syndrome 1, X-linked</td>
<td>XL</td>
</tr>
<tr>
<td>MYH9</td>
<td>160775</td>
<td>Deafness 17</td>
<td>AD</td>
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<td></td>
<td></td>
<td>Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss</td>
<td></td>
</tr>
</tbody>
</table>

References

2022


### Additional Resources


United States Renal Data System. [USRDS home page](#). [Accessed: May 2022]

### Related Information

**Alport Syndrome**

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108

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