

COL4A5 Gene Analysis in Alport Syndrome

Disorder also known as:

Thin Basement Membrane Nephropathy

Clinical Features:

Alport syndrome (AS) is a progressive glomerulonephritis associated with sensorineural hearing loss with a prevalence of about 1 in 50,000 live births. X-linked Alport syndrome usually manifests in affected males with microscopic hematuria and progressive sensorineural hearing loss during childhood or adolescence. Later, patients develop proteinuria and progressive renal failure, which eventually leads to end-stage renal disease in their 30s and 40s. Ocular symptoms are also common and may include maculopathy, posterior polymorphous dystrophy, and recurrent corneal erosion. Anterior lenticonus is considered to be virtually pathognomonic for Alport syndrome. X-linked Alport syndrome is semi-dominant and often manifests in female carriers. Approximately 90% of female carriers have microscopic hematuria, which can lead to renal failure later in life. Hearing loss is less frequent in female carriers, with a later age of onset.

Alport syndrome with diffuse leiomyomatosis is a contiguous gene deletion syndrome. The submicroscopic genomic deletions involve the COL4A5 gene and parts of the adjacent COL4A6 gene. This disorder is characterized by features of Alport syndrome and by leiomyomatosis of the esophagus and tracheobronchial tree. It manifests in late childhood and can include dysphagia, postprandial vomiting, epigastric pain, recurrent bronchitis, dyspnea, cough, and stridor. Affected females may also have genital leiomyomas.

Alport syndrome associated with mental retardation, midface hypoplasia and elliptocytosis is another contiguous gene deletion syndrome involving COL4A5 and FACL4, which encodes a long-chain acyl-CoA synthetase.

Inheritance Pattern/Genetics:

Alport syndrome is a genetically heterogeneous disorder. Approximately 80% of Alport syndrome is inherited as X-linked trait; 15% as autosomal recessive, and 5% as autosomal dominant trait.

Test Methods:

Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the entire coding region and splice junctions of the COL4A5 gene (exons 1-51, as well as an additional 2 exons found in alternate isoforms) is obtained and analyzed. In females without an

identifiable variant by sequencing, focused array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of this gene. In males, deletions of one or more exons would be detectable by sequencing, however, ExonArrayDx is available to evaluate for duplications. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or other appropriate method.

Test Sensitivity:

In one study of 50 unrelated patients with suspected X-linked Alport syndrome, DNA sequencing analysis identified COL4A5 gene variants in 82% of these individuals.³ At least another 10% of patients will have a genomic deletion or chromosomal rearrangement that is not detectable by sequencing in a female carrier. Therefore, if a COL4A5 gene variant exists, sequencing analysis as performed at GeneDx is expected to identify >92% of variants in affected males. For females, it is expected that the combination of full gene sequence analysis and ExonArrayDx analysis for deletion/duplication identification will yield similar sensitivity results. If the inheritance of Alport syndrome in a family is unknown, an overall test sensitivity of approximately 75% is expected.

More than 300 distinct variants of all types have been reported in the COL4A5 gene. They are scattered across the gene without evidence for variant hot spots. A compilation of 267 previously published variants revealed that missense variants comprised the largest fraction (37%), followed by frameshift variants (21%), splice site (15%) variants, and a small fraction of nonsense variants. Large gene deletions or chromosomal rearrangements involving COL4A5 and possibly neighboring genes were found in 9-10%.² Duplications within the COL4A5 gene have been reported in rare cases and as a founder variant within the French Polynesian population.^{1,5} About two-third of missense variants affect the collagenous domain of the alpha 5 chain of type IV collagen encoded by exons 20-44, and result in glycine substitutions within the conserved Gly-X-Y repeats of this domain.^{3,4}

References:

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2. Gross O et al (2002). *Nephrol Dial Transplant* 17:1218-1227
3. Martin, P et al (1998). *J Am Soc Nephrol* 9:2291-2301.
4. Plant K et al (1999) *Human Mutation* 13:124-132.
5. Vetrie et al (1992) *Genomics* 14(3):624-633