ELN Gene Analysis in Supravalvular Aortic Stenosis, Autosomal Dominant Cutis Laxa and Williams-Beuren syndrome

Disorder Also Known As: Supravalvular Aortic Stenosis, Eisenberg type; SVAS; Chromosome 7q11.23 Deletion Syndrome, WMS, WS, Infantile Hypercalcemia, Elfin Facies with Hypercalcemia

Clinical Features:
Three clinical disorders, Supravalvular Aortic Stenosis (SVAS), Autosomal Dominant Cutis Laxa and Williams-Beuren syndrome, have been associated with intragenic variants or deletion of the elastin gene (ELN). Supravalvular aortic stenosis is an obstructive vascular disorder that occurs in 1 in 20,000 live births and is characterized by narrowing of the aorta or diffuse aortic hypoplasia. Although the severity of supravalvular aortic stenosis is variable, it often requires surgical intervention. A lack of treatment may result in progressive heart failure and can be fatal. Supravalvular aortic stenosis is often associated with stenosis of other vessels, most commonly pulmonary arterial stenosis.[3]

Cutis laxa is a rare connective tissue disorder that is characterized by lax, inelastic and redundant skin that gives an appearance of premature aging. Although any part of the body may be affected, the loose skin appearance is most prominent around the eyes, face, neck, shoulders, and thighs. Skin fragility, easy bruising, and poor wound healing are not associated with cutis laxa. The autosomal dominant inherited form of cutis laxa due to pathogenic variants in the elastin gene (ELN) typically involves the skin but severe congenital pulmonary manifestations and thoracic aortic aneurysm have been observed in individuals with particular ELN deletions [2,4,5,6].

Williams-Beuren syndrome is a microdeletion syndrome associated with dysmorphic facial features, endocrine and cardiac abnormalities, and cognitive deficits. Severely affected individuals usually have short stature, mental disability, supravalvular aortic stenosis, hypercalcemia, elfin facies, and a distinctive personality often described as “cocktail party” personality. Williams-Beuren Syndrome occurs in 1 in 20,000 to 50,000 live births. The cardiovascular aspects of this disorder are attributed to haploinsufficiency for elastin but at least 15 neighboring genes have been implicated in the various other manifestations of this syndrome.[7]

Inheritance Pattern/Genetics:
The ELN gene is located in cytogenetic band 7q11.23 and has 33 exons. The encoded gene product, elastin, is a major component of elastic fibers. It consists predominantly of hydrophobic residues, such as glycine and proline. Lysine cross-links connect individual

polypeptide chains into a network of elastic fibers. Structural changes and disruption of elastin molecules result in reduced integrity of elastic fiber-containing tissues, such as skin, lungs, and large blood vessels, thus leading to a cardiovascular and connective tissue phenotype.

ELN-related disorders are autosomal dominant, but sporadic cases are common. Autosomal recessive and X-linked cases of Cutis Laxa have been reported, however are not associated with ELN variants. The spectrum of variants depends on the disorder.

Supravalvular Aortic Stenosis: Translocations, deletions, and point variants of the ELN gene on 7q11.23 have been found in SVAS, resulting in functional haploinsuffiency for the elastin gene. In one large family with SVAS, an amplification of 7q11.23, including the ELN gene, was identified[8]. The variant spectrum includes nonsense or frameshift (63%), splice site (17%), missense variants (11%), and changes affecting initiation of translation (9%).[3] Two hotspot variants were reported, Y150X and Q442X. No clear genotype-phenotype correlations have emerged. The phenotypic features of SVAS significantly vary between and even within affected families, and both missense and nonsense variants may result in significant SVAS.[3]

Autosomal Dominant Cutis Laxa (ADCL): Only a handful of ADCL families with variants in ELN have been described to date, including missense, splice, and frameshift variants.[4] The observed phenotype is thought to result from a dominant-negative effect on elastic fiber structure. Frameshift variants are suspected to cause the formation of abnormal tropoelastin protein molecules, which alter the architecture of elastic fibers once incorporated into the elastic matrix[5].

Williams-Beuren Syndrome: Over 99% of individuals with WS have a contiguous gene deletion of 1.5Mb involving the WBSCR at chromosomal band 7q11.23 that encompasses the elastin gene.[7] A cytogenically balanced translocation t(7:16)(q11.23;q13), which disrupts the ELN gene, has been reported in eight members of one family. The resulting phenotype in affected family members was variable, ranging from mild to severe WBS[1].

Test Sensitivity:

In one study of SVAS patients with a normal karyotype, ELN variants were identified in 35 of 100 (35%) participants. ELN is the only gene known to be associated with Autosomal Dominant Cutis Laxa. Although very few patients have been reported in the literature to date, almost all had variants in the ELN gene by sequencing.[4] The sequencing and deletion/duplication approach used by GeneDx Is expected to identify >99% of existing small intragenic variants in the ELN gene as well as large deletions and duplications of one or more exons. Over 99% of patients with the clinical diagnosis of WS are found to have the contiguous gene deletion of the Williams-Beuren syndrome critical region (WBSCR), which can be

detected by FISH analysis.[7] This contiguous gene deletion would appear as a whole deletion of the ELN gene if using the gene-specific assay described here.

Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Additionally, GeneDx offers FISH analysis using the ELN probe to detect microdeletions involving the ELN gene. FISH is a reliable and sensitive assay for detecting a genomic deletion of the Williams-Beuren syndrome critical region (WBSCR).

References:

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