AAAS Gene Analysis in Achalasia-Addisonianism-Alacrima Syndrome (Triple-A Syndrome)

Disorder also known as: Triple-A Syndrome; Allgrove Syndrome; Alacrima-Achalasia-Adrenal Insufficiency Neurologic Disorder; ACTH-Resistant Adrenal Insufficiency; Glucocorticoid Deficiency and Achalasia

Clinical Features:
The Triple-A (Allgrove) syndrome is characterized by the triad of familial adrenoinsufficiency due to corticotropin (ACTH) resistance, achalasia (swallowing difficulties), and alacrima (deficient secretion of tears). The disorder usually manifests within the first decade of life with alacrima and/or achalasia, followed by glucocorticoid deficiency. Life-threatening complications include hypoglycemic episodes and severe feeding difficulties. Affected individuals typically have several additional clinical concerns, such as progressive peripheral and/or autonomic neuropathy, punctate palmoplantar keratoderma (patches of callused skin on palms and soles), dry mouth, angular cheilitis and fissured tongue, mild mental retardation, osteoporosis and, rarely, short stature. The pattern and severity of neurologic and autonomic dysfunction in Triple-A syndrome is quite variable, including hyperreflexia, impaired visual evoked potentials, optic nerve atrophy, anisocoria (unequal pupil size), abnormal sweating, postural (orthostatic) hypotension with compensatory tachycardia, muscle weakness, ataxia, parkinsonism, and motor peripheral neuropathy. Hence the clinical diagnosis of Triple-A syndrome may be difficult. Because autonomic neuropathy and amyotrophy (muscle wasting) appear to be integral features of this disorder, the name “4A syndrome” has been considered.

Genetics:
Autosomal recessive

Test Sensitivity:
On average, ~50% of families with features consistent with Triple-A syndrome were found to have pathogenic variants in the AAAS gene. In one study, 6/20 families with Triple-A syndrome had AAAS pathogenic variants[1], while in another study 6/6 families with Triple-A syndrome but 0/4 families with isolated ACTH resistance had AAAS pathogenic variants.[2] A third research study reported AAAS pathogenic variants in 3/6 families with classical Triple-A syndrome.[3] The bi-directional sequence analysis and deletion/duplication testing as performed by GeneDx are expected to identify all types of previously identified variants in the AAAS gene, if they are present.

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.

References:

1. Houlden H et al. (2002) Brain 125: 2681-90.
2. Sandrini F et al., (2001) J Clin Endocrinol. 86: 5433-7.
3. Brooks BP et al., (2005) Clin Genet. 68: 215-21.
4. Milenkovic T et al., (2010)Eur J Pediatr. 169(11):1323-8.
5. Qin K et al., (2007) Mol Genet Metab 92(4):359-63.