AIRE Gene Analysis in Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy

Disorder also known as:
APECED; Autoimmune Polyendocrinopathy Type 1 (APS1), Autoimmune Polyglandular Syndrome (PGA1), Polyglandular Autoimmune Syndrome Type 1

Clinical Features:
APECED is diagnosed in patients who have 2 of the triad of adrenal insufficiency (Addison disease), hypoparathyroidism, and chronic mucocutaneous candidiasis. Some allelic variants, in particular the Iranian-Jewish polyglandular syndrome, are recognized with only parathyroid involvement. Polyendocrinopathy can include IDDM, hypergonadotropic hypogonadism, and autoimmune thyroid disease. Other autoimmune manifestations can include hepatitis, malabsorption, alopecia, vitiligo, and pernicious anemia. Typically candidiasis appears in early childhood, followed by hypoparathyroidism and then Addison disease, but presentation and severity can vary.

Inheritance Pattern/Genetics:
Autosomal recessive in most cases, with one dominant variant described[1]

Test Methods:
Bi-directional sequencing of the coding regions and splice sites of exons 1-14 of the AIRE gene is offered in two tiers or all at once. If sequencing identifies a variant on only one allele, focused array CGH analysis with exon-level resolution (ExonArrayDx) will be performed to evaluate for a deletion or duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

Test Sensitivity:
Tier 1 of the test (sequencing of exons 2, 3, 6, 8, and 10) is expected to detect at least one variant in 90% of patients in most ethnic groups. Tier 2 testing (sequencing of the remainder of the gene plus exon-level array CGH if indicated) is available for patients who are negative or have only one variant with Tier 1. Altogether the methods use by GeneDx are expected to detect at least 98% of variants.

Most variants to date have been missense, nonsense, splice site, or small insertion/deletions variants.[2] There are known hotspots for two recurring variants in exons 6 and 8 accounting for at least one of the variants in the majority of patients.[2] In addition, gross deletions of several or all exons have been reported.[2,3]

References:

1. Cetani F et al, 2001, A novel mutation of the [AIRE] gene… acting in a dominant fashion and strongly cosegregating with hypothyroid autoimmune thyroiditis: Journal of Clin Endocr Metab 86:4747.
2. Heino M. et al., 2001, APECED Mutations in the Autoimmune Regulator (AIRE) Gene; Human Mutation 18:205-211.
3. Podkrajsek KT et al., 2008, Detection of complete autoimmune regulator gene deletion and two additional novel mutations [in atypical] autoimmune polyglandular syndrome type 1; Eur J Endocrinol 159: 633.