

## 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<sup>1</sup>.

### 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. If present, apparently homozygous sequence variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. 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.

### TEST SENSITIVITY

The methods used by GeneDx are expected to detect at least 98% of variants in the AIRE gene.

Most variants to date have been missense, nonsense, splice site, or small insertion/deletions variants.<sup>2</sup> 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.<sup>2</sup> In addition, gross deletions of several or all exons have been reported.<sup>2,3</sup>

### 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.