Anterior Segment Dysgenesis (ASD) (FOXE3)

Clinical Features:
Anterior segment dysgenesis (ASD) disorders can involve multiple ocular tissues, such as the iris, cornea and lens. Depending on the clinical presentation, these disorders can often be classified into different subtypes. Several subtype examples include Peters’ anomaly, which is identified by central corneal opacity and defects of Descemet’s membrane and corneal endothelium; posterior embryotoxon, which involves a thickening and opacity at Schwalbe’s ring; and aphakia, which is defined by the absence of the ocular lens. Variants in the FOXE3 gene have been associated with a variety of anterior segment dysgenesis disorders including those previously mentioned and others such as congenital cataracts, sclerocornea and coloboma.\(^1,2,3,4\) In addition, FOXE3 variants have also been observed in non-syndromic microphthalmia.\(^5\) Although FOXE3 disorders can be inherited in either an autosomal dominant or recessive pattern, the disease presentation is typically more severe in individuals who are homozygous or compound heterozygotes for recessively-inherited variants.\(^1\)

Inheritance Pattern:
Anterior segment dysgenesis (ASD) disorders have an autosomal dominant and autosomal recessive inheritance pattern with variable expressivity.

Test Sensitivity:
As the majority of reports identifying FOXE3 variants are small case studies involving one or a few families, the precise clinical sensitivity of identifying FOXE3 variants in affected individuals is not clear. However, in a study involving 26 cases of bilateral microphthalmia, recessive variants in the FOXE3 gene accounted for \(\sim 15\%\) of cases (4/26).\(^5\) FOXE3 variants also comprised approximately 4\% (1/27) of cases involving congenital cataracts.\(^4\) This analysis is expected to detect all currently known variants identified in the FOXE3 gene. The majority of variants observed in the FOXE3 gene that are associated with an autosomal pattern of inheritance comprise single base pair changes resulting in either missense or nonsense variants or small deletions/duplications resulting in frameshifts.\(^1,3,5,6\) The majority of variants associated with a dominant pattern of inheritance involve the loss of the normal stop codon, resulting in abnormal protein products of extended length.\(^1,2,4\) To our knowledge, there have been no reported large deletions or duplications involving this gene.

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: