SOX2, OTX2, VSX2, SIX6, RAX and STRA6 gene analysis in Developmental Eye Disorders, including Microphthalmia and Anophthalmia

Clinical Features:
Several developmental eye disorders have a known genetic basis, including microphthalmia and anophthalmia. Anophthalmia is the complete absence of the globe, or bulb, of the eye and, therefore, the most severe structural eye malformation. A milder form is microphthalmia, where the total axial length of the eye globe is at least two standard deviations below the mean for age. Simple microphthalmos refers to a structurally normal eye with short total axial length. In each of these conditions, the eyelids, conjunctiva and lacrimal apparatus are normal. In complex microphthalmia, additional abnormalities are present and may include anterior segment dysgenesis, cataract, persistent hyperplastic primary vitreous, chorioretinal coloboma and/or retinal dysplasia. Anophthalmia/microphthalmia has been observed in association with various genetic syndromes and approximately 25% of individuals with anophthalmia/microphthalmia have identifiable chromosomal abnormalities. Variants in the SOX2, OTX2, and VSX2 genes leading to haploinsufficiency may be associated with anophthalmia and microphthalmia. SOX2 variants are also known to be associated with hearing loss, developmental delay, esophageal atresia, genitourinary abnormalities, myopathy, and spastic diplegia. OTX2 variants have been reported in patients with anophthalmia/microphthalmia associated with brain malformations and pituitary insufficiency. VSX2 variants are usually associated with isolated ocular finding without other systemic malformations. Heterozygous deletions of the entire SIX6 gene have been seen in some cases of bilateral anophthalmia due to interstitial chromosomal deletions. Compound heterozygous variants in the RAX gene have been observed in individuals with anophthalmia with or without sclerocornea. Additionally, a single heterozygous RAX variant was identified in an individual with unilateral coloboma. The clinical presentation of individuals with homozygous or compound heterozygous variants in the STRA6 gene can vary greatly, with, in addition to anophthalmia/microphthalmia, most individuals presenting additional features such as: congenital heart defects, cognitive impairment, lung malformations, renal malformations and facial dysmorphism. PAX6 variants have also been associated with anophthalmia (analysis of PAX6 is available, for further information see [http://www.genedx.com](http://www.genedx.com)).

Genetics:
Isolated anophthalmia is genetically heterogeneous and may be inherited as autosomal dominant, recessive or X-linked trait.
Autosomal dominant: SOX2, OTX2, and SIX6.
Autosomal Recessive: VSX2, RAX and STRA6
Test Methods:
Using genomic DNA obtained from buccal (cheek) brushes or blood in EDTA, bi-directional DNA sequence of the coding region of the SOX2 (single large exon), VSX2 (exons 1-5), OTX2 (exons 3-5), RAX (exons 1-3) and/or STRA6 (exons 2-19) genes is obtained and analyzed. As STRA6-related anophthalmia is inherited in an autosomal recessive manner, if sequencing identifies a variant on only one allele, targeted 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. If indicated, for a charge, deletion/duplication analysis is available to evaluate for a deletion or duplication of one or more exons of the following genes (SOX2, OTX2, VSX2, SIX6 and RAX). Any variant found in the first person of a family to be tested is confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method. Whole-genome cytogenetic oligonucleotide array CGH testing (GenomeDx) is also available to evaluate for unbalanced chromosomal abnormalities. For further information, please see the GenomeDx information sheet found at http://www.genedx.com.

Test Sensitivity:
Heterozygous missense and protein-truncating variants in the SOX2 gene have been observed in 11-20% of individuals with anophthalmia/microphthalmia. SOX2 whole gene deletions have been observed in approximately 10% (5/52) of individuals with severe microphthalmia/anophthalmia. OTX2 variants and deletions account for 2-3% of anophthalmia/microphthalmia cases. VSX2 variants account for approximately 2% (2/117) of the patients with non-syndromic microphthalmia. In 173 patients with microphthalmia, anophthalmia, and coloboma, no sequence change causing the disease has been identified in the SIX6 gene. In a study of 75 individuals with anophthalmia/microphthalmia, one individual was observed to be compound heterozygote for two variants in the RAX gene. STRA6 variants have been observed in approximately 14-23% of individuals with syndromic anophthalmia/microphthalmia. Sequence analysis, as performed by GeneDx, is expected to identify most type of variants in SOX2, VSX2, OTX2, RAX and STRA6, if they exist, with the exception of gross deletions. Deletion/duplication testing by targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons involving the SOX2, OTX2, VSX2, SIX6 and RAX genes. In addition, GeneDx offers deletion/duplication testing analysis for several other genes implicated in anophthalmia/microphthalmia including: BMP4 and PAX6.

Variant Spectrum:
The majority of OTX2 variants are nonsense and frameshift variants leading to haploinsufficiency. Nonsense and frameshift variants, as well as whole gene deletions, have been observed in the SOX2 gene. VSX2 variants are mainly missense and a partial gene deletion including the entire exon 3 has been also reported. Only one missense variant (c.493A>G; T165A) has been reported in SIX6. Interstitial deletions involving both SOX2 and
SIX6 have been observed in patients with bilateral anophthalmia. Interstitial deletions at 14q22-q23 including the OTX2 gene have been reported in two cases with bilateral anophthalmia and pituitary abnormality. Five variants have been reported in the RAX gene: two missense, two nonsense and one frameshift. The majority of variants in the STRA6 gene are either missense or nonsense variants. Small deletions/insertions and splice variants have also been observed; however, to date, no gross deletions or duplications in the STRA6 gene have been reported.

References: