

PAX6 gene analysis in Aniridia & Other Developmental Eye Disorders

Clinical Features:

Aniridia is a developmental anomaly of the entire eye, characterized by varying degrees of iris hypoplasia. Ocular abnormalities associated with aniridia include persistent papillary membrane, congenital cataracts, ectopia lentis, developmental glaucoma, corneal pannus with progressive keratopathy and foveal hypoplasia. The most severe presentation of aniridia is complete absence of the iris. Milder disease may include enlargement and irregularity of the pupil and small, slit-like defects in the anterior layer. Vision is variably affected, and the severity of vision loss tends to correlate with the presence of other associated ocular defects. Approximately 70% of the cases with isolated aniridia (i.e. aniridia without associated anomalies) are familial while the remaining 30% of cases are sporadic. Aniridia may be caused by heterozygous variants in the PAX6 gene. PAX6 variants have also been described in a host of other ocular developmental abnormalities that appear clinically distinct from aniridia, including: microphthalmia with or without coloboma; optic nerve hypoplasia and other congenital optic nerve anomalies; and a specific form of corneal dystrophy. Aniridia may also be seen as part of the WAGR (Wilms tumor, aniridia, genital anomalies and mental retardation) syndrome, which is caused by a deletion of chromosome 11p13, the genomic region harboring both the PAX6 and WT1 genes. Some cases of sporadic aniridia involve de novo submicroscopic deletions in this chromosomal region and therefore could place the patient at risk for developing Wilms tumor. Large gross chromosomal deletion can be detected by cytogenetic analysis, fluorescent in situ hybridization (FISH) and oligo array Comparative Genomic Hybridization (oligo aCGH) analysis. However these methods will not detect partial PAX6 gene deletions involving only one or a few exons. 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. While heterozygous PAX6 variants typically cause aniridia, homozygous PAX6 variants were also found in a few patients with syndromic anophthalmia. For further genetic testing in anophthalmia or microphthalmia, GeneDx also offers variant analysis of the SOX2, OTX2, and VSX2 genes (sequence analysis and deletion/duplication testing) and deletion/duplication testing for the SIX6 gene.

Inheritance Pattern/Genetics:

Autosomal dominant inheritance with high penetrance and variable expressivity.

Test Methods:

Using genomic DNA obtained from a blood sample in EDTA, bi-directional sequence of the coding and noncoding exons of the PAX6 gene (exons 1-13), the alternatively spliced exon 5a

and splice junctions is obtained and analyzed. Deletion/duplication testing by targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of the PAX6, DCDC1, ELP4, and WT1 genes. Variants are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:

In cases of aniridia without a detectable PAX6 gene deletion, over 80% of individuals were found to have a small intragenic variant in the PAX6 gene, with a higher proportion in familial cases than in sporadic cases. One study also showed that 2 of 18 cases (11%) with other eye abnormalities (outside the aniridia spectrum) had a missense variant in the PAX6 gene. In a study of 70 unrelated probands affected with aniridia, deletions of one or more exons of the PAX6 gene were identified in 10% (7 out of 70 cases). In one of these cases, the deletion included two neighboring genes of PAX6 (DCDC1 and ELP4) while the PAX6 gene itself was intact.¹ The combination of sequencing and deletion testing has a sensitivity of approximately 90% for the identification of a variant in a patient diagnosed with aniridia.

Reference:

1. Redeker EJ et al, (2008); Mol Vis 7:836-40