THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Aniridia Testing: Mutation Analysis of *PAX6*

Clinical Features

Aniridia is characterized by complete or partial hypoplasia and can result in a range from readily visible, almost complete absence of the iris, through enlargement and irregularity of the pupil mimicking a coloboma, to small slit-like defects in the anterior layer seen only with a slit-lamp (1). Although the phenotype can be variable within a family, individuals usually show little difference between the two eyes.

Molecular Genetics

Aniridia may be caused by heterozygous mutations in *PAX6* [OMIM#607108]. *PAX6* encodes a transcription factor involved in islet cell differentiation and function and members of families carrying *PAX6* mutations also exhibit impaired glucose tolerance and diabetes later in life (2). *PAX6* haploinsufficiency through loss of function mutations result in classic aniridia, while *PAX6* missense mutations typically produce atypical or variable-phenotype aniridia. *PAX6* mutations have also been described in a number of other ocular developmental disorders including Aniridia, Cerebellar Ataxia and Mental retardation [OMIM#206700], Foveal Hypoplasia and Presenile Cataract syndrome [OMIM#136520] and Peters anomaly [OMIM#604229].

Inheritance

While the majority of *PAX6* mutations are inherited in a dominant fashion, two cases carrying biallelic mutations in *PAX6* have been reported: the first case died at 1 week of life and exhibited severe brain malformations, microcephaly, and anopthalmia, without mention of hyperglycemia. Another surviving case had brain malformations, microcephaly, microphthalmia, and panhypopituitarism, along with neonatal-onset diabetes (3).

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *PAX6* gene is performed. Targets of interests are captured and amplified using Agilent SureSelect System. The constructed genomic DNA library is sequenced using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic or likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

PAX6 mutation analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405 81406
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Hingorani M, Moore A. Aniridia. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washingon, 2003.
2. Yasuda T, Kajimoto Y, Fujitani Y et al. PAX6 mutation as a genetic factor common to aniridia and glucose intolerance. Diabetes 2002: 51: 224-230.
3. Solomon BD, Pineda-Alvarez DE, Balog JZ et al. Compound heterozygosity for mutations in PAX6 in a patient with complex brain anomaly, neonatal diabetes mellitus, and microophthalmia. Am J Med Genet A 2009: 149A: 2543-2546.

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