PITX2 and *FOXC1* Gene Analysis in Axenfeld-Rieger Syndrome

Clinical Features:
Axenfeld-Rieger syndrome (ARS) represents a spectrum of diseases that involve congenital anomalies of the anterior segment of the eyes. In addition, about 50% of patients will develop glaucoma, leading to decline of vision and potential blindness. The most prominent eye defects in ARS include (1) Axenfeld anomaly, characterized by a prominent Schwalbe's line and adherence of the iris to the cornea and trabecular meshwork, (2) Rieger anomaly, consistent with Axenfeld anomaly plus iris hypoplasia, eccentric pupils (corectopia) and/or iris holes (polycoria) and (3) Rieger syndrome, which includes Rieger anomaly as well as the non-ocular symptoms. These non-occular findings include dental hypoplasia, mild craniofacial dysmorphism, and redundant umbilical skin. Cardiac defects, limb anomalies, pituitary abnormalities, sensory hearing loss and/or mental defects may also be present. Additional disorders such as iridogoniodysgenesis, iris hypoplasia and Peter's anomaly fall under the umbrella of ARS. ARS is fully penetrant but shows variable expression, even within a family.

Inheritance Pattern/Genetics:
ARS may be caused by variants in one of several different genes, the most common of which are in the PITX2 and FOXC1 genes, which encode different transcription factors. In general, variants in the PITX2 gene has been seen more frequently in patients with ocular and systemic anomalies, whereas variant in FOXC1 was found in patients with isolated ocular findings.

The inheritance pattern is autosomal dominant in the vast majority of cases and sporadic variants in Axenfeld anomaly and Rieger syndrome are not uncommon. Rarely, autosomal recessive inheritance has been reported in Rieger syndrome and Peter's anomaly.

Test Methods:
Sequencing of the FOXC1 and PITX2 genes is offered as separate tests. Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the coding region and splice junctions of the FOXC1 gene (one coding exon) and PITX2 gene (exons 2-5) is analyzed. 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.

Test Sensitivity:
Several studies of individuals diagnosed with various developmental eye defects of the Axenfeld-Rieger syndrome spectrum revealed a variant in the PITX2 gene in approximately 10% of patients. The sensitivity is higher among those patients who have both ocular and systemic manifestations (up to 40%). Overall, more then 30 distinct variants have been identified in this gene to date. In another study, 9 out of 70 patients (13%) with isolated ocular

anomalies who tested negative for a PITX2 variant were found to have a variant in the transcription factor gene, FOXC1. Variant in the PAX6 gene is very rare in ARS. Since approximately 40% of all ARS cases have no identifiable variant in these genes, additional genetic loci are presumed to exist, and genes on chromosome 16q and 13q14 have been implicated in some studies. Sequence analysis as performed by GeneDx is expected to identify most types of variants in PITX2 and FOXC1, if they exist, with the exception of gross rearrangements, which have occasionally been observed in ARS.

Most common in full-spectrum ARS are missense variants of PITX2 affecting the homeodomain of the transcription factor and resulting in haploinsufficiency, i.e., reduced DNA binding and transactivation of downstream target genes. Missense, nonsense, splicing and regulatory variants as well as small deletions and insertions have been reported. Gross chromosomal deletions involving PITX2 are not uncommon and account for about 5% of patients with ARS.[3] Variants in FOXC1 include missense, and nonsense variants, small deletions/insertions and gene duplications.

References:

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