SALL4 Gene Analysis in
Duane-Radial Ray syndrome / Acro-Renal-Ocular syndrome

Disorder also known as: DRRS; AROS; Okihiro Syndrome

Clinical Features:
Duane-Radial Ray syndrome (DRRS): is characterized by the Duane eye anomaly and radial ray malformations of the limbs. The Duane anomaly is a congenital disorder of eye movement defined by the limited or absent ability to move the eye outward (abduction) and/or inward (adduction). Radial ray malformations observed in this syndrome can include triphalangeal thumbs, preaxial polydactyly, hypoplasia/aplasia of the thumbs, hypoplasia/aplasia of the radii, and shortening and radial deviation of the forearms.

Acro-Renal-Ocular syndrome (AROS): is allelic to DRRS, presents with radial ray malformations and Duane anomaly, along with other features such as ocular coloboma and renal abnormalities (renal hypoplasia, horseshoe kidney, vesico-utereral reflux, bladder diverticula, ectopia, and mild malrotation).

The overlap between DRRS and AROS is appreciable, and each syndrome has a highly variable intra- and interfamilial clinical phenotype. Other less common features belonging to both syndromes include hearing loss, ear malformations, epicanthal folds and very rarely, heart defects (atrial and ventricular septal defects). The limb anomalies characteristic of DRRS/AROS overlap with two other clinically defined genetic syndromes: Holt-Oram syndrome (HOS), which is due to pathogenic variants in the TBX5 gene, and Townes-Brocks syndrome (TBS), caused by pathogenic variants in the SALL1 gene. Both DRRS/AROS and HOS are associated with upper limb malformations, hypoplasia/aplasia of the thumbs, and triphalangeal thumbs. Shared limb abnormalities observed in DRRS/AROS and TBS include preaxial polydactyly and triphalangeal thumbs. Genetic testing for all three disorders is available at GeneDx.

Genetics:
Autosomal dominant; up to one-third of cases are sporadic.

Test Methods:
Analysis is performed by bi-directional sequencing of the coding regions (exons 1-4) and splice sites of the SALL4 gene. Concurrently, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed to evaluate for a deletion or duplication of one or more exons of this gene. Variants/deletions/duplications found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, qPCR or another appropriate method.
Test Sensitivity:
In one study, SALL4 variants were found in patients with DRRS/AROS in 5 out of 8 (62%) families\(^1\). The remaining 3 families were determined to have partial or whole SALL4 gene deletions. \(^2\) Further studies revealed SALL4 variants in 12/12 (100%) unrelated families with DRRS/AROS.\(^3,4,5\) The sequencing approach used by GeneDx will identify >99% of existing small, intragenic variants in the SALL4 gene but not partial or whole gene deletions, which can be detected by ExonArrayDx deletion/duplication testing.

References:
3. Al-Baradie R. et al., Duane Radial Ray Syndrome (Okihiro Syndrome) Maps to 20q13 and Results from Mutations in SALL4, a New Member of the SAL Family. Am J Hum Genet. 71:1195-1199, 2002.