Prenatal Testing for SALL4 Gene Variants: Duane-Radial Ray / 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), which 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 diverticular, ectopia, and mild malrotation).

Prenatal Ultrasound Findings: Ultrasound detection of fetal renal malformations accompanied by characteristic abnormalities of the limbs and extremities, most usually detected in the 2nd trimester of pregnancy, are indications that prenatal molecular analysis for SALL4 variants should be considered even in the absence of known family history. Ultrasound examination may be normal in affected fetuses; therefore, pregnancies at risk to inherit a specific known familial pathogenic variant can be offered targeted molecular testing regardless of ultrasound findings, if desired.

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

Test Methods:
Using genomic DNA, analysis is performed by bi-directional sequencing of the coding regions (exons 1-4) and flanking 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. For known familial variants, the relevant portion of the gene will be analyzed in duplicate.

Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contaminations will be performed. Therefore, in all prenatal cases a maternal sample should accompany the fetal sample.

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.[3-5] The sequence analysis 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. The sensitivity of SALL4 analysis in prenatal cases ascertained based on fetal ultrasound abnormalities is currently unknown.

References:

1. Kohlhase, J. et al., Hum Mol Genet. 11:2979-2987, 2002.
2. Borozdin, W. et al., J Med Genet. 41(9):e113, 2004.
3. Al-Baradie R. et al., Am J Hum Genet. 71:1195-1199, 2002.
4. Kohlhase J. et al., J Med Genet. 40:473-478, 2003.
5. Borozdin, W. et al., J Med Genet.41(8):e102, 2004.
6. Kohlhase, J. et al., Hum Mutat. 26:176-183, 2005.
7. Miertus, J. et al., Hum Genet. 119: 154-161, 2006.