Prenatal Testing for SALL1 Gene Variants: Townes-Brocks Syndrome

Disorder also known as: TBS; Renal-Ear-Anal-Radial (REAR) syndrome; Imperforate anus with hand, foot, and ear anomalies; Sensorineural deafness with imperforate anus and thumb anomalies; Townes-Brocks-branchiooto-renal-like syndrome

Clinical Features:
Newborns and Children: Townes-Brocks syndrome is a rare multiple malformation syndrome characterized by anal, limb, ear, and renal anomalies. Intelligence is normal in most affected individuals. Diagnostic features include ano-rectal abnormalities (imperforate or anteriorly placed anus, anal stenosis, prominent midline perineal raphe); abnormalities of the hands and feet (preaxial polydactyly, triphalangeal thumbs, bifid thumbs and toes, finger and toe syndactyly); external ear malformations (preauricular tags or pits, “lop” or “satyr” ear, microtia, abnormal helix) with hearing loss (sensorineural, conductive or mixed); and renal anomalies leading to impaired renal function or renal failure (unilateral or bilateral hypoplastic or dysplastic kidneys, multicystic kidneys, renal agenesis, posterior urethral valves, vesico-uretal reflex). Other, less common features are cardiac defects, mental retardation, eye, genitourinary and vertebral abnormalities, hypothyroidism, umbilical hernia, and gastroesophageal reflux.[1] The intra- and interfamilial clinical presentation of TBS varies widely and overlaps with several other disorders including VATER and VACTERL associations, Okihiro syndrome, Fanconi anemia, Baller-Gerold syndrome, branchio-oto-renal (BOR) syndrome and oculo-auriculo-vertebral (OAV) spectrum. Important differentiating characteristics of TBS are the absence of radial hypoplasia, craniosynostosis, and tracheo-esophageal fistula.

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 SALL1 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.

Genetics:
Autosomal dominant; most cases are sporadic.

Test Methods:
Using genomic DNA, analysis is performed by bi-directional sequencing of the coding regions (exons 1-3) and flanking splice sites of the SALL1 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 contamination will be performed. ***Therefore, in all prenatal cases a maternal sample should accompany the fetal sample.***

Test Sensitivity:

In two studies of 14 and 12 TBS patients with 'classical' presentation, SALL1 variants were identified in 64% and 83% of affected individuals, respectively.2,3 SALL1 variants have also been found in two families with features resembling branchio-oto-renal (BOR) syndrome and in one person with overlapping features of TBS and OAV spectrum (Goldenhar syndrome).[1] The sensitivity of SALL1 testing in pregnancies with ultrasound anomalies suggestive of Townes-Brocks syndrome is currently unknown.

References:

1. Botzenhart, E. et al., Human Mutation 26:282, 2005; (2) Kohlhase, J. et al., Am J Hum Genet. 64: 435-445, 1999. (3) Marlin, S. et al., Human Mutation 14: 377-386, 1999. (4) Borozdin, W. et al., Human Mutation 867(Online) 2006.