Prenatal Testing for SALL1 Gene Mutations: Townes-Brocks Syndrome

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

Mendelian Inheritance in Man Number: 107580 (Townes-Brocks syndrome); 602218 (SALL1 gene)

Clinical Features in 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, multicycstic 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. 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 mutations 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 mutation can be offered targeted molecular testing regardless of ultrasound findings, if desired.

Inheritance Pattern: Autosomal dominant; most cases are sporadic

Indications for Fetal Testing:
- Full sequencing testing for fetuses with prenatal ultrasound findings suggestive of Townes-Brocks Syndrome (TBS)
- Mutation-specific testing for fetuses with a family history of a known SALL1 mutation

Test Method:
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 mutations, 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 mutations were identified in 64% and 83% of affected individuals, respectively.2,3 SALL1 mutations 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). The sensitivity of SALL1 testing in pregnancies with ultrasound anomalies suggestive of Townes-Brocks syndrome is currently unknown.
Mutation Spectrum:
According to a recent review, approximately 35 distinct mutations have been reported in the SALL1 gene, all of which occur in exon 2/intron 2. About 77% (27/35) are frameshift mutations (small deletions, small insertions, and one large 1150bp deletion) and 20% (7/35) are nonsense mutations, while splice site mutations are rare. The majority of SALL1 mutations (86%) cluster upstream or within the first double zinc finger motif. The R276X nonsense mutation has been established as a mutational hotspot, having been found in 15 sporadic and one familial case. This mutation is associated with a classical TBS phenotype and possibly a higher rate of cardiac defects. Otherwise, no clear genotype-phenotype correlation has been established with respect to mutation type or location. In addition to small intragenic DNA mutations, a few gross gene deletions and complex rearrangements have been found in patients with TBS.

Specimen Requirements and Shipping/Handling:

- **Prenatal Specimen – Based on Abnormal Ultrasound/Other Findings (test #2523):** 20mg villi preferred (minimum 15mg) or 20 mL amniotic fluid or 2 T25 flasks of cultured CV or cultured amniocytes. Ship overnight at ambient temperature, using a cool pack in hot weather.
- **Prenatal Specimen- Based on Specific Known Mutation (test #902):** 20mg villi preferred (minimum 15mg) or 20 mL amniotic fluid or 2 T25 flasks of cultured CV or cultured amniocytes. Ship overnight at ambient temperature, using a cool pack in hot weather.
- **Maternal cell contamination studies (required for all prenatal testing):** 1-4 ml maternal blood in a lavender-top EDTA tube. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping. Alternatively, buccal brushes (GeneDx kit only) or DNA can be used. The maternal sample should accompany the prenatal specimen or be shipped to arrive prior to or concurrently with the prenatal sample.

*If more than one prenatal test is ordered, 30 mL amniotic fluid, 30mg villi or 3 T-25 flasks of cultured cells are requested*

Required Forms:
- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions (last page of submission form)

Prices and Turn-Around Time – Fees subject to change without notice:
- Test #2523: Prenatal diagnosis based on abnormal ultrasound findings: $2,100 approx. 2-3 weeks
- Test #902: Prenatal diagnosis for a specific known mutation: $2,000 approx. 2 weeks

**CPT codes for Test # 2523 Prenatal Testing for Townes-Brocks Syndrome – All codes and units apply:**
- 83891 x 13 units = $ 200
- 83898 x 13 units = $ 540
- 83894 x 13 units = $ 200
- 83904 x 26 units = $1000
- 83892 x 2 units = $ 40
- 83912 x 4 units = $ 120
TOTAL $2,100

**CPT codes for Test #902 Prenatal Testing for Specific Known mutation - All codes and units apply:**
- 83891 x 5 units = $160
- 83898 x 10 units = $710
- 83894 x 5 units = $160
- 83904 x 10units = $750
- 83892 x 2 units = $ 60
- 83912 x 5 units = $160
TOTAL $ 2000

Possible ICD9 Codes: 655.83 – abnormal ultrasound findings; 655.23 – family history possibly affecting fetus