**TCOF1 Gene Analysis in Treacher Collins Syndrome (TCS)**

**Also known as:** Treacher Collins-Franceshetti Syndrome (TCOF); Mandibulofacial Dysostosis (MFD)

**Mendelian Inheritance in Man Number:** 154500 (Treacher Collins Syndrome, TCS); 606847 (TCOF1 gene)

**Clinical features:**
The classic clinical features of Treacher Collins Syndrome (TCS) are present at birth and can include down-slanted palpebral fissures, lower eyelid coloboma and lower eyelash anomalies, hypoplasia of the zygomatic bones and mandible, preauricular hair growth, and ear anomalies of the middle and external ear, which can lead to conductive hearing loss. Additional secondary medical concerns may include vision loss, dental abnormalities, and breathing difficulties. The presence of zygomatic arch and malar bone hypoplasia by imaging studies can aid in the diagnosis of TCS. Mandibular micrognathia has been observed on prenatal ultrasound (Edwards et al., 1996; Hsu et al., 2002; Tanaka et al., 2002; Rotten et al., 2002). Inter- and intra-familial variable expressivity has been observed.

**Inheritance pattern:** Autosomal dominant; 60% of cases are de novo mutations.

**Reasons for referral:**
1. Confirmation of a clinical diagnosis
2. Targeted testing for a known familial mutation
3. Prenatal diagnosis in families with a known mutation
4. Genetic counseling

**Genetics:** The TCOF1 gene, located on chromosome 5q32, codes for the nucleolar phosphoprotein treacle, which is believed to contribute to ribosome biogenesis and the regulation of the neuroepithelial and neural crest cell proliferation. Haploinsufficiency of treacle likely results in an increase in apoptotic events leading to improper tissue formation during embryonic development, ultimately causing the characteristic craniofacial abnormalities associated with TCS (Trainor et al., 2009). Mutations in the POLR1C and POLR1D genes have also been associated with a TCS phenotype, but more research is needed to support these findings (Dauwerse et al., 2011).

**Mutation spectrum:** The majority (~80%) of mutations identified in the TCOF1 gene causing TCS are frameshift mutations leading to protein truncation (Splendore et al., 2005). Nonsense, splice site, and missense mutations, have also been identified in the TCOF1 gene. There is a recurrent 5 bp deletion in exon 24, c.4369_4373delAAGAA (NM_001135243.1), that accounts for up to 20% of mutations identified in affected individuals (Edwards et al., 1997; Splendore et al., 2000; Splendore et al., 2005). Large, partial deletions of the TCOF1 gene have been reported in the literature as well (Bowman et al., 2012).

**Test method:**
Using genomic DNA from a submitted specimen, bi-directional sequence analysis of the complete coding region (exons 1-26) and splice sites of the TCOF1 gene is performed. If no mutation is found by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons in the TCOF1 gene. The presence of a mutation or deletion is confirmed by repeat analysis using sequencing, restriction fragment analysis, or other appropriate method.

**Test sensitivity:**
Mutations have been identified in the TCOF1 gene by SSCP and/or direct sequence analysis in approximately 40-90% of patients with a clinical diagnosis of TCS (Edwards et al., 1997; Splendore et al., 2000; Splendore et al., 2002; Ellis et al., 2002; Dixon et al., 2004; Conte et al., 2011). One study has shown that approximately 5% of patients with TCS without a mutation identified by sequence analysis harbor a large partial deletion of the TCOF1 gene (Bowman et al., 2012).
Specimen Requirements and Shipping/Handling:
- **Blood**: A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes**: **CANNOT be accepted for this test.**
- **Prenatal Diagnosis**: For prenatal testing for a known mutation in the TCOF1 gene, please refer to the specimen requirements table on our website at: [http://www.genedx.com/test-catalog/prenatal/](http://www.genedx.com/test-catalog/prenatal/). Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

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

For test codes, prices, CPT codes, and turn-around-times, please refer to the “Treacher Collins Syndrome” page on our website: [www.genedx.com](http://www.genedx.com)

References: