

TCOF1 Gene Analysis in Treacher Collins Syndrome (TCS)

Disorder also known as: Treacher Collins-Franceschetti Syndrome (TCOF); Mandibulofacial Dysostosis (MFD)

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.^{6,10,18,13} Inter- and intra- familial variable expressivity has been observed.

Inheritance Pattern/Genetics:

Autosomal dominant; 60% of cases are de novo variants.

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.¹⁹ Possible pathogenic variants in the POLR1C and POLR1D genes have also been associated with a TCS phenotype, but more research is needed to support these findings.³

Test Methods:

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 variant 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 variant or deletion is confirmed by repeat analysis using sequencing, restriction fragment analysis, or other appropriate method.

Test Sensitivity:

Pathogenic variants 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.^{7,15,16,8,5,2} One study has shown that approximately 5% of patients with TCS without a pathogenic variant identified by sequence analysis harbor a large partial deletion of the TCOF1 gene.¹

References:

1. Bowman et al., (2012) *Eur J Hum Genet* 20(7): 769-777.
2. Conte et al., (2011) *BMC Medical Genetics* 12: 125.
3. Dauwerse et al., (2011) *Nat Genet* 43(1): 20-22.
4. Dixon et al., (1997) *Genome Res* 7(3): 223-234.
5. Dixon et al., (2004) *Am J Med Genet A* 127A:244-248.
6. Edwards et al., (1996) *J Med Genet* 33:603-606.
7. Edwards et al., (1997) *Am J Hum Genet* 60:515-524.
8. Ellis et al., (2002) *J Orthod* 29(4):293-297.
9. Fisher E., (2011) *Clin Genet* 79(4): 330-332.
10. Hsu et al., (2002) *Ultrasound Obstet Gynecol* 19:413-422.
11. Marszalek et al., (2002) *J Appl Genet* 43(2): 223-233.
12. Massotti et al., (2009) *BMC Medical Genetics* 10:136.
13. Rotten et al., (2002) *Ultrasound Obstet Gynecol* 19:122-130.
14. So et al., (2004) *Gene* 328: 49-57.
15. Splendore et al., (2000) *Hum Mut* 16:315-322.
16. Splendore et al., (2002) *J Med Genet* 39:493-495.
17. Splendore et al., (2005) *Hum Mut* 25:429-434.
18. Tanaka et al., (2002) *Ultrasound Obstet Gynecol* 19:413-422.
19. Trainor et al., (2009) *Eur J Hum Genet* 17:275-283.