

Treacher Collins Panel

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

Panel Gene List: DHODH, EFTUD2, POLR1C, POLR1D, SF3B4, TCOF1

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.¹ 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.^{2,3} Inter- and intra- familial variable expressivity has been observed. Approximately 54-60%% of autosomal dominant Treacher Collins cases (caused by the TCOF1 and POLR1D genes) are de novo.¹

Other syndromes share overlapping features with Treacher Collins syndrome:

Miller syndrome is caused by pathogenic variants in the DHODH gene, and presents with severe micrognathia, cleft lip/palate, hypoplasia/aplasia of postaxial elements of the limbs, coloboma of the eyelids, cup-shaped ears, and supernumerary nipples.^{4,5}

Mandibulofacial dysostosis with microcephaly, associated with the EFTUD2 gene, involves developmental delay, microcephaly, micrognathia, malar hypoplasia, abnormal pinnae and hearing loss; other prominent features may include cardiac defects, thumb abnormalities, esophageal atresia, and abnormal structures of the middle ear, among others. The majority of EFTUD2 pathogenic variants are de novo.^{6,7}

Nager and Rodriguez syndromes are both acrofacial dysostosis syndromes caused by pathogenic variants in the SF3B4 gene. Patients with both syndromes present with preaxial limb abnormalities, facial dysmorphism including micrognathia, cleft palate, conductive hearing loss, and external ear malformations.^{8,9} Rodriguez syndrome is an allelic disorder that involves more severe manifestations of mandibular underdevelopment and limb anomalies; pathogenic variants causing Rodriguez syndrome occur de novo.¹⁰

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Gene	Protein	Inheritance	Disease Associations	Sensitivity Per Disease
<i>DHODH</i>	Dihydroorotate dehydrogenase (quinone)	AR	Miller syndrome (aka postaxial acrofacial dysostosis)	Unknown ^{4,5}
<i>EFTUD2</i>	Elongation factor Tu GTP-binding domain-containing 2	AD	Mandibulofacial dysostosis with microcephaly	100% ^{6,7}
<i>POLR1C</i>	Polymerase (RNA) I polypeptide C	AR	Treacher Collins	1.2% ^{1,11}
<i>POLR1D</i>	Polymerase (RNA) I polypeptide D	AD; AR	Treacher Collins	6% ^{1,12}
<i>SF3B4</i>	Splicing factor 3b subunit 4	AD	Nager and Rodriguez syndromes	Nager - ~57% ^{8,9} Rodriguez – unknown ¹⁰
<i>TCOF1</i>	Treacle ribosome biogenesis factor 1	AD	Treacher Collins	63-93% (86% of those with typical features) ¹

AD – Autosomal dominant

AR – Autosomal recessive

References:

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