

NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.

Treacher Collins Syndrome

Synonyms: Mandibulofacial Dysostosis, Treacher Collins-Franceschetti Syndrome

Sara Huston Katsanis, MS and Ethylin Wang Jabs, MD.

Author Information

Initial Posting: July 20, 2004; Last Update: September 27, 2018.

Estimated reading time: 26 minutes

Summary

Clinical characteristics. Treacher Collins syndrome (TCS) is characterized by bilateral and symmetric downslanting palpebral fissures, malar hypoplasia, micrognathia, and external ear abnormalities. Hypoplasia of the zygomatic bones and mandible can cause significant feeding and respiratory difficulties. About 40%-50% of individuals have conductive hearing loss attributed most commonly to malformation of the ossicles and hypoplasia of the middle ear cavities. Inner ear structures tend to be normal. Other, less common abnormalities include cleft palate and unilateral or bilateral choanal stenosis or atresia. Typically intellect is normal.

Diagnosis/testing. The diagnosis of TCS is established in about 96% of probands by detection of a heterozygous (autosomal dominant) pathogenic variant in *TCOF1* or *POLRID* or biallelic (autosomal recessive) pathogenic variants in *POLRIC* or *POLRID* using molecular genetic testing and in about 4% of probands by clinical findings when molecular genetic testing has not been performed or does not identify pathogenic variants in one of the known genes.

Management. *Treatment of manifestations:* Treatment should be tailored to the specific needs of each individual, preferably by a multidisciplinary craniofacial management team. Neonates with airway issues may require special positioning or tracheostomy to facilitate ventilation. Hearing loss is treated with bone conduction amplification, speech therapy, and educational intervention. Craniofacial reconstruction is often necessary. Cleft palate repair (if needed) occurs at about age one year; zygomatic and orbital reconstruction at about age five to seven years; and bilateral microtia and/or narrow ear canal reconstruction after age six years. The age of maxillomandibular reconstruction varies by severity; orthognathic therapies are typically before age 16 years.

Genetic counseling. Treacher Collins syndrome (TCS) can be inherited in an autosomal dominant or autosomal recessive manner.

- *Autosomal dominant TCS.* About 54%-60% of probands have the disorder as the result of a de novo TCOF1 or POLRID pathogenic variant. Each child of an individual with TCS has a 50% chance of inheriting the pathogenic variant.
- *Autosomal recessive TCS.* The parents of a child with autosomal recessive TCS are obligate heterozygotes (i.e., carriers of one *POLRIC* or *POLRID* pathogenic variant). At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

Once the TCS-related pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Treacher Collins syndrome (TCS) **should be suspected** in individuals with the following craniofacial features (see Teber et al [2004], Figure 2; Trainor et al [2009], Figure 2; Dauwerse et al [2011], Figure 1; and Vincent et al [2016], Figure 1), hearing loss, and radiographic findings.

Craniofacial features

- **Midface hypoplasia** with a bilaterally symmetric convex facial profile, prominent nose, and characteristic downward slant of the eyes secondary to hypoplasia of the zygomatic arch and lateral aspects of the orbits
- **Micrognathia and retrognathia** with variable effects on the temporomandibular joints and jaw muscles
- **External ear abnormalities** including absent, small, malformed, and/or rotated ears, and atresia or stenosis of the external auditory canals
- **Lower eyelid abnormalities** including the following:
 - Coloboma (notching)
 - Sparse, partially absent, or totally absent lashes and tear ducts

Preauricular hair displacement, in which hair growth extends in front of the ear to the lateral cheekbones

Conductive hearing loss is attributed most commonly to ankylosis, hypoplasia, or absence of the ossicles and hypoplasia of the middle ear cavities. Inner ear structures are typically normal.

Radiographic features

- **Hypoplasia or aplasia (discontinuity) of the zygomatic arch**, detected by occipitomeatal radiographs (Waters' view) [Posnick & Ruiz 2000]
- **Mandibular retrognathia**, detected by orthopantomogram [Posnick & Ruiz 2000]

Establishing the Diagnosis

The diagnosis of TCS **is established** in about 96% of probands by detection of a heterozygous (autosomal dominant) pathogenic variant in *TCOF1* or *POLR1D* or biallelic (autosomal recessive) pathogenic variants in *POLR1C* or *POLR1D* using molecular genetic testing (Table 1) and in about 4% of probands by clinical findings when molecular genetic testing has not been performed or does not identify pathogenic variants in one of the known genes.

Molecular Diagnosis of TCS

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (concurrent or serial single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing):

- **Serial single-gene testing.** Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, whole-exon or whole-gene deletions/duplications are not detected. Perform sequence analysis of *TCOF1* first, since the majority of individuals with TCS will have a pathogenic variant in this gene (Table 1). If no pathogenic variant is found in *TCOF1*, perform sequence analysis of *POLRIC* and *POLRID*, and gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications for *TCOF1* and *POLRID*.
- **Chromosomal microarray analysis (CMA)**, which uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TCOF1* as well as surrounding genes) that cannot be detected by sequence analysis, could be considered when an individual with clinical features of TCS also has intellectual disability.
- **A multigene panel** that includes *TCOF1*, *POLRIC*, and *POLRID*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this GeneReview. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis or deletion/duplication analysis. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is an option when *TCOF1* sequence analysis does not reveal a pathogenic variant. **Exome sequencing** could be considered to assess variants in *POLRIC*, *POLRID*, and the rest of the genome. If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. **Genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Table 1.

Molecular Genetic Testing Used in Treacher Collins Syndrome

Gene ^{1,2}	Proportion of TCS Attributed to Pathogenic Variants in Gene	MOI	Proportion of Pathogenic Variants ³ Detectable by Method		
			Sequence analysis ⁴	Gene-targeted deletion/duplication analysis ⁵	CMA ⁶

Gene ^{1, 2}	Proportion of TCS Attributed to Pathogenic Variants in Gene	MOI	Proportion of Pathogenic Variants ³ Detectable by Method		
			Sequence analysis ⁴	Gene-targeted deletion/duplication analysis ⁵	CMA ⁶
<i>POLRIC</i>	1.2% ⁷	AR (3/3) ⁷	3/3 ⁷	No multiexon or whole-gene deletions / duplications reported	No whole-gene deletions / duplications reported
<i>POLRID</i>	6% ⁸	AD (28/31) ⁹ AR (3/31) ¹⁰	28/31 ^{9, 10}	3/31 ⁹	
<i>TCOF1</i>	63%-93% ¹¹ 86% w/typical features ¹²	AD	>97% ¹¹	14 deletions reported ¹³	2 large deletions ¹³
Unknown	4% ⁸	NA			

- Genes are listed in alphabetic order.
- See Table A. Genes and Databases for chromosome locus and protein.
- See [Molecular Genetics](#) for information on allelic variants detected in this gene.
- Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).
- Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by [Vincent et al \[2014\]](#)) may not be detected by these methods.
- Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TCOF1* or *POLRID*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 5q32-q33.1 or 13q12.2 regions.
- Three homozygous probands [[Dauwse et al 2011](#)]
- Individuals with typical clinical signs of TCS who do not have pathogenic variants in *TCOF1*, *POLRIC*, or *POLRID* [[Vincent et al 2016](#)]
- [Dauwse et al \[2011\]](#), [Vincent et al \[2016\]](#)
- The same homozygous variant, c.163C>G (p.Leu55Val), was reported in three families [[Schaefer et al 2014](#), [Vincent et al 2016](#)].
- The majority of individuals with TCS are heterozygous for a pathogenic variant in *TCOF1*. Differences in reported percentages could reflect variations in populations or clinical criteria for typical TCS. [Splendore et al \[2000\]](#) reported 93% sensitivity (26/28 individuals with clinical diagnosis of TCS); [Teber et al \[2004\]](#) reported 78% sensitivity (8/36 individuals who had unequivocal features of TCS had no pathogenic variant in

TCOF1); Bowman et al [2012] identified a *TCOF1* pathogenic variant in 70.6% (84/119) of unrelated individuals with a strong suspicion of TCS; Vincent et al [2016] reported 63% sensitivity among individuals (92/146) with typical and atypical clinical features of TCS.

12. Vincent et al [2016] reported 86% (72/84) of those with typical TCS features had a *TCOF1* variant.
13. Reported deletions range from single exon to whole gene [Beygo et al 2012, Bowman et al 2012, Vincent et al 2014, Vincent et al 2016]. Although >97% of reported cases had a pathogenic variant detectable by sequencing, Bowman et al [2012] reported 5% of cases (5/92) with a large deletion; therefore, the rate of large deletions may be higher than current data suggest.

Clinical Diagnosis of TCS

TCS is generally characterized by bilaterally symmetric abnormalities of the facial and mandibular structures; downward-slanting palpebral fissures, and hypoplasia of the zygomatic complex and mandible are almost always evident (see [Suggestive Findings](#) and [Clinical Description](#)).

Clinical Characteristics

Clinical Description

Treacher Collins syndrome (TCS) is characterized by facial features of bilateral and symmetric downslanting palpebral fissures, malar hypoplasia, and micrognathia. The hypoplasia of the zygomatic bones and mandible can cause significant feeding and respiratory difficulties. Ear abnormalities are associated with conductive hearing loss. Other, less common abnormalities include cleft palate and unilateral or bilateral choanal stenosis or atresia.

Significant inter- and intrafamilial clinical variability is common in TCS [Posnick & Ruiz 2000, Teber et al 2004]. While some individuals may be so mildly affected as to go undiagnosed (Figure 1), others can have severe facial involvement and life-threatening airway compromise [Trainor & Andrews 2013].

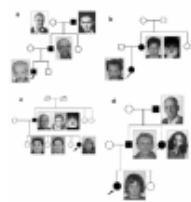


Figure 1.

Intrafamilial variation in families with a confirmed *TCOF1* pathogenic variant a. The proband (arrow) has the characteristic facial phenotype with downward-slanting palpebral fissures, hypoplastic zygomatic complex, hypoplasia of mandible, slightly dysplastic ([more...](#))

Classic features of TCS are bilaterally symmetric and evident at birth (Table 2). Table 3 presents a scoring system to rate the severity of clinical findings.

Table 2.

Classic Features of Treacher Collins Syndrome

Classic Feature	% (n) of Affected Individuals with the Feature		
	Vincent et al [2016]	Teber et al [2004]	Splendore et al [2000]

Classic Feature		% (n) of Affected Individuals with the Feature		
		Vincent et al [2016]	Teber et al [2004]	Splendore et al [2000]
Very frequent	Downward-slanting palpebral fissures	99% (76/77)	100% (35/35)	89%
	Malar hypoplasia / hypoplasia of zygomatic complex	97% (76/78)	97% (34/35)	81%
	Conductive hearing loss	92% (69/75)	83% (25/30)	
	Mandibular hypoplasia / micrognathia	88% (69/78)	91% (32/35)	78%
Frequent	Atresia of external ear canal	70% (46/65)	68% (23/34)	
	Microtia	70% (55/79)	71% (25/35)	77%
	Coloboma (notching) of the lower lid	63% (46/73)	54% (19/35)	69%
	Delayed speech development		57% (16/28)	
	Asymmetry	52% (34/65)		
	Preauricular hair displacement	49% (25/51)	24% (8/33)	
Rare	Nasogastric tube or gastrostomy in neonates	28% (17/60)		
	Cleft palate	21% (15/70)	33% (11/33)	28%
	Intubation or tracheostomy in neonates	18% (12/65)	12% (4/34)	
	Choanal stenosis/atresia	13% (8/64)	25% (8/32)	
	Cardiac malformation	11% (7/65)		
Very rare	Rachis malformation	7% (3/42)		
	Renal malformation	4% (2/50)		
	Microcephaly	3% (2/66)		
	Intellectual disability / delayed motor development	1.7% (1/58)	10% (3/30)	
	Limb anomaly	1.5% (1/67)		

Table 3.

Scoring Systems to Rate Severity of Clinical Findings

Feature	Points Assigned ¹	
	Teber et al [2004]	Vincent et al [2016]
Downward-slanting palpebral fissures	2	1
Malar hypoplasia / hypoplasia of zygomatic complex	2	1
Conductive hearing loss	1	2
Mandibular hypoplasia / micrognathia	2	1

Feature	Points Assigned ¹	
	Teber et al [2004]	Vincent et al [2016]
Atresia of external ear canal	1	1
Microtia	2	1
Coloboma (notching) of the lower lid	2	1
Delayed speech development	Not assigned	Not assigned
Asymmetry	Not assigned	1
Preauricular hair displacement	1	1
Nasogastric tube or gastrostomy in neonates	Not assigned	2
Cleft palate	1	1
Intubation or tracheostomy in neonates	1	2
Choanal stenosis/atresia	1	2
Cardiac malformation	Not assigned	Not assigned
Rachis malformation	Not assigned	Not assigned
Renal malformation	Not assigned	Atypical
Microcephaly	Not assigned	Atypical
Intellectual disability / delayed motor development	1	Atypical
Limb anomaly	Not assigned	Atypical
Total Points		

Adapted from Vincent et al [2016]

1. Maximum score is 17 for both systems. Scores ≤ 8 = mildly affected; scores ≥ 9 = severely affected.

In newborns with TCS, airway management may be required to address narrowing of the airway or extreme shortening of the mandible with severe micrognathia. Choanal atresia or stenosis, or severe micrognathia with glossoptosis can also obstruct the airway in an infant. Neonatal death is usually associated with obstructive sleep apnea as a result of these malformations.

External ear anomalies including absent, small, or rotated ears are typical. Conductive hearing loss is usually attributed to middle ear anomalies including hypoplasia or absence of the ossicles or middle ear cavities.

In those with atresia or stenosis of the external auditory canals, the presence and severity of external auditory canal defects correlate highly with the presence and severity of middle ear defects [Posnick 1997]. The inner ear structures are typically normal.

Ophthalmologic defects, including coloboma of the lower eyelid, can result in corneal exposure. Other possible causes of vision impairment include refractive errors, anisometropia, and strabismus [Hertle et al 1993].

Dental anomalies, found in 60% of individuals with TCS reported, include tooth agenesis (33.3%), enamel opacities (20%), and ectopic eruption of the maxillary first molars (13.3%) [da Silva Dalben et al 2006]. One to eight anomalies per individual have been identified.

Although craniosynostosis is not a feature of TCS, the cranium may have an abnormal shape (brachycephaly with bitemporal narrowing) [Posnick 1997].

Cardiac malformations are reported in some individuals with typical TCS caused by pathogenic variants in either *TCOF1* or *POLRID*.

Altered function of the upper digestive tract has been reported [Giabicani et al 2017].

Although mild developmental delay has been reported [Teber et al 2004, Vincent et al 2014], intelligence is usually normal.

Fertility is normal.

Less frequently observed features in individuals with TCS:

- Nasal deformity
- High-arched palate
- Angle class II anterior open-bite malocclusion
- Macrostomia

Abnormalities occasionally observed in individuals with TCS:

- Coloboma of the upper lid [Marszałek et al 2002]
- Ocular hypertelorism [Marszałek et al 2002]

Genotype-Phenotype Correlations

In most cases, the phenotype cannot be predicted by the genotype [Splendore et al 2000, Teber et al 2004, Vincent et al 2016].

Penetrance

While the penetrance of pathogenic variants associated with TCS is high, reduced penetrance in *TCOF1* has also been reported [Dixon et al 2004, Vincent et al 2016] and *POLRID* [Dauwerse et al 2011, Vincent et al 2016].

Nomenclature

Autosomal dominant TCS has variably been termed Fransceschetti-Zwahlen-Klein syndrome and zygoauromandibular dysplasia.

Prevalence

The prevalence of TCS is estimated at 1:50,000 [Fazen et al 1967, Trainor et al 2009].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *TCOF1*, *POLRIC*, or *POLRID*.

Differential Diagnosis

Table 4.

Disorders with Mandibulofacial Dysostosis to Consider in the Differential Diagnosis of Treacher Collins Syndrome

Disorder	Gene	MOI	Distinguishing Clinical Features
Mandibulofacial dysostosis with microcephaly	<i>EFTUD2</i>	AD	<ul style="list-style-type: none"> • Microcephaly • ID • Asymmetry of facial features • Esophageal atresia • Thumb abnormalities
Nager syndrome (OMIM 154400)	<i>SF3B4</i>	AD	Limb deformities, preaxial abnormalities (e.g., small or absent thumbs, triphalangeal thumbs, radial hypoplasia or aplasia, radioulnar synostosis)
Miller syndrome (OMIM 263750)	<i>DHODH</i>	AR	Limb deformities, postaxial abnormalities (e.g., small or absent 5th digit incl 5th metacarpal, ulnar hypoplasia, absent 5th toe)
Toriello-Carey syndrome (OMIM 217980)		AR	<ul style="list-style-type: none"> • Failure to grow • Microcephaly • Agenesis of the corpus callosum • ID • Urogenital anomalies in affected males • Facial dysmorphisms (hypertelorism, flattened nasal bridge, anteverted nares) • Short neck
Branchial arch syndrome (OMIM 301950)		XL	<ul style="list-style-type: none"> • Microcephaly • ID • High-arched palate • Webbed neck
Bauru syndrome (OMIM 604830)		AD	<ul style="list-style-type: none"> • Upslanting palpebral fissures • Hypoplastic tragus & ear lobes

Disorder	Gene	MOI	Distinguishing Clinical Features
Hedera-Toriello-Petty syndrome (OMIM 608257)		AD	Ptosis
Hemifacial macrosomia, Goldenhar syndrome, oculoauriculovertebral spectrum (OMIM 164210)	Unknown	AD	<ul style="list-style-type: none"> • Asymmetric • Preauricular tags & pits • Ocular epibulbar dermoid cyst • Cleft lip & palate • Vertebral anomalies, Kippel-Feil syndrome
Pierre Robin sequence (OMIM 261800)	Cases of disruption of long-range <i>cis</i> -regulatory element → misregulation of <i>SOX9</i>	AR	Micrognathia, glossoptosis, & airway obstruction w/cleft palate deformity may self-correct w/growth & w/out intervention. ¹
Nonsyndromic mandibular hypoplasia			<ul style="list-style-type: none"> • Severe mandibular deficiencies (e.g., temporomandibular joint, ankylosis, aglossia/microglossia, rare craniofacial cleft) • Progressive micrognathia or retrognathia ^{1, 2}

AD = autosomal dominant; AR = autosomal recessive; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Singh & Bartlett [2005]

2. In one study, 52 of 266 individuals with congenital mandibular hypoplasia had TCS [Singh & Bartlett 2005]. Molecular diagnosis was not confirmed on these individuals.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an infant diagnosed with Treacher Collins syndrome, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- The airway for evidence of choanal atresia/stenosis and/or micrognathia and glossoptosis predisposing to obstruction of the oropharynx
- The palate for clefts
- Swallowing function

- Hearing through formal audiologic examination (see [Hereditary Hearing Loss and Deafness Overview](#)). If conductive hearing loss is documented during the first six months of life, a craniofacial CT scan (axial and coronal slices) can be performed to document the anatomy of the head and neck and the external auditory canal, middle ear, and inner ear.
- Ophthalmologic evaluation with attention to extraocular movement, corneal exposure, and visual acuity
- Assessment for dental anomalies when teeth have erupted
- Cardiology and echocardiogram evaluation for structural heart defects
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Treatment should be tailored to the specific needs of each individual, preferably by a multidisciplinary craniofacial management team that typically comprises a clinical geneticist, plastic surgeon, head and neck surgeon, otolaryngologist, oral surgeon, orthodontist, audiologist, speech pathologist, and psychologist.

Major management issues can be stratified by three age groups and graded for severity [Thompson et al 2009, Trainor & Andrews 2013]:

Birth to age two years. Major management issues are airway and feeding difficulties.

- If a diagnosis of TCS is suspected prenatally, a detailed ("level II") fetal ultrasound examination and consultation(s) with a high-risk obstetrician and/or neonatologist should be considered. The delivering team should be aware of the potential for life-threatening neonatal airway compromise [Trainor & Andrews 2013]. Management of the airway in neonates typically includes special positioning of the infant called an EXIT (ex-utero intrapartum treatment), in which the neonate's head and neck are partially delivered by cesarean section in order to perform an oral intubation or tracheostomy during birth. With proper management, life expectancy approximates that of the general population.
- Procedures for surgical intervention for the airway, if needed, are standard, primarily for improving respiratory function or restoring patency of the nostrils and distraction of the mandible. Intubation techniques other than direct laryngoscopy may be required during surgeries [Hosking et al 2012].
- Repair of cleft palate (if present) at age one to two years is recommended [Kobus & Wojcicki 2006].
- Assess nutrition and feeding to determine if gastrostomy or tracheostomy is needed to assure adequate caloric intake while protecting the airway [Trainor & Andrews 2013].
- Bone conduction amplification, speech therapy, and educational intervention are indicated for treatment of hearing loss. The bone-anchored hearing aid (BAHA) is an alternative for individuals with ear anomalies [Trainor & Andrews 2013].
- Ophthalmologic evaluation is indicated to assess eye movement, vision, lower eyelid coloboma, and diminished tearing. When present, corneal exposure keratitis should be medically treated [Hertle et al 1993].
- Structural heart defects (e.g., patent ductus arteriosus, atrial septal defects, hypertrophic myopathy) are managed as per standard practice.

Age three to 12 years. Major management issues are speech therapy and integration into education system.

Craniofacial reconstruction is often necessary [Posnick 1997, Trainor & Andrews 2013]. Generally, bone reconstruction precedes soft tissue corrections. Reconstruction can prevent the progression of facial asymmetry:

- Zygomatic and orbital reconstruction can be undertaken once cranio-orbitozygomatic bony development is complete (age ~5-7 years).
- External ear reconstruction should be performed after age six years and should precede reconstruction of the external auditory canal or middle ear.
- External auditory canal and middle ear reconstruction should be performed for individuals with bilateral microtia and/or narrow ear canals.
- Coloboma of the lower eyelid can be treated with botulinum toxin and subsequent surgery [Warner et al 2008].
- Eyelid reconstruction to correct downward-slanting fissure can use redundant upper eyelid skin [Trainor & Andrews 2013].
- Misaligned teeth often require orthodonture.

Age 13 to 18 years. Major management issues:

- Orthognathic therapies are typically indicated before age 16 years.
- Nasal reconstruction, if needed, should follow orthognathic surgeries.
- Maxillomandibular reconstruction is recommended as follows:
 - Type I (mild) and type IIA (moderate) malformation at age 13 to 16 years
 - Type IIB (moderate to severe) malformation at skeletal maturity (~16 years)
 - Type III (severe) malformation at age six to ten years

Surveillance

The following are appropriate:

- Periodic assessment of growth and development (preferably by a pediatrician) with inquiry into symptoms of obstructive sleep apnea.
- Routine follow up by an audiologist, ophthalmologist, and dentist

Evaluation of Relatives at Risk

See [Genetic Counseling](#) for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Mode of inheritance of Treacher Collins syndrome (TCS) can be autosomal dominant or autosomal recessive (Table 1).

- Autosomal dominant inheritance accounts for most of TCS – most commonly heterozygous pathogenic variants in *TCOF1* and less commonly heterozygous pathogenic variants in *POLR1D* [Dauwerse et al 2011].
- Autosomal recessive inheritance accounts for a minority of TCS – biallelic pathogenic variants in *POLR1C* [Dauwerse et al 2011] and biallelic pathogenic variants in *POLR1D* [Schaefer et al 2014].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- About 54%-60% of probands with autosomal dominant TCS have the disorder as the result of a *de novo* *TCOF1* or *POLR1D* pathogenic variant [Trainor et al 2009, Vincent et al 2016]. About 40% of individuals diagnosed with autosomal dominant TCS have an affected parent.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant, or, if a pathogenic variant has not been identified in the proband, audiologic evaluation and radiographic examination by Waters' view of both parents may reveal mild zygomatic arch hypoplasia or even aplasia [Marres 2002].
- If the proband has a known pathogenic variant that cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Maternal and paternal somatic and germline mosaicism have been reported [Shoo et al 2004, Vincent et al 2016].
- The family history of some individuals diagnosed with TCS may appear to be negative because of failure to recognize the mild expression of the disorder in family members or the rare occurrence of reduced penetrance in a heterozygous parent.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the variant and may be unaffected or mildly/minimally affected [Shoo et al 2004].

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%. The specific malformations or their severity cannot be predicted in sibs who inherit a pathogenic variant because significant intrafamilial clinical variability and reduced penetrance have been reported.

- If the proband has a known *TCOF1* or *POLR1D* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Shoo et al 2004, Vincent et al 2016].
- If the parents have not been tested for the pathogenic variant identified in the proband but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for TSC because of the possibility of reduced penetrance in a parent or parental germline mosaicism.

Offspring of a proband

- Each child of an individual with autosomal dominant TCS has a 50% chance of inheriting the pathogenic variant.
- The specific malformations or their severity cannot be predicted.

Other family members. The risk to other family members depends on the clinical/genetic status of the proband's parents: if a parent is affected or has a TCS-related pathogenic variant, his or her family members may be at risk.

Autosomal Recessive Inheritance

Risk to Family Members

Parents of a proband

- The parents of a child with autosomal recessive TCS are obligate heterozygotes (i.e., carriers of one *POLR1C* or *POLR1D* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with autosomal recessive TCS are obligate heterozygotes (carriers) for a *POLR1C* or *POLR1D* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *POLR1C* or *POLR1D* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *POLR1C* or *POLR1D* pathogenic variants in the family.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified

in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the TCS-related pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Note: (1) The presence of a TCS-causing pathogenic variant detected by prenatal testing does not predict the specific malformation(s) or their severity. (2) The possibility of reduced penetrance (particularly of the common *TCOF1* c.4369_4373delAAGAA pathogenic variant) in the fetus needs to be considered (see Penetrance).

Ultrasound examination. In pregnancies known to be at risk for TCS, prenatal diagnosis using ultrasound examination to detect anomalies such as polyhydramnios, microcephaly, abnormal fetal facial features (micrognathia), and abnormal fetal swallowing is possible [Rotten et al 2002, Konstantinidou et al 2013]. Diagnostic features in a mildly affected fetus are likely to be missed. Three-dimensional imaging can assist with differential diagnosis prior to birth [Pereira et al 2013].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **Children's Craniofacial Association**
13140 Coit Road, Suite 517
Dallas TX 75240
Phone: 800-535-3643; 214-570-9099
Fax: 214-570-8811
Email: contactCCA@ccakids.com

www.ccakids.org

- **FACES: The National Craniofacial Association**

P.O. Box 11082

Chattanooga TN 37401

Phone: 800-332-2373 ; 423-266-1632

Fax: 800-332-2373

Email: faces@faces-cranio.org

[Treacher Collins syndrome](#)

- **Foundation for Faces of Children**

258 Harvard Street, #367

Brookline MA 02446-2904

Phone: 617-355-8299

Email: info@facesofchildren.org

[Treacher Collins syndrome](#)

- **My46 Trait Profile**

[Treacher Collins Syndrome](#)

- **National Library of Medicine Genetics Home Reference**

[Treacher Collins syndrome](#)

- **BabyHearing.org**

This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.

www.babyhearing.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

Treacher Collins Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
POLR1C	6p21.1	DNA-directed RNA polymerases I and III subunit RPAC1	POLR1C @ LOVD	POLR1C	POLR1C
POLR1D	13q12.2	DNA-directed RNA polymerases I and III subunit RPAC2	POLR1D @ LOVD	POLR1D	POLR1D
TCOF1	5q32-q33	Treacle protein	TCOF1 database	TCOF1	TCOF1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B.OMIM Entries for Treacher Collins Syndrome ([View All in OMIM](#))

154500	TREACHER COLLINS SYNDROME 1; TCS1
248390	TREACHER COLLINS SYNDROME 3; TCS3
606847	TCOF1 GENE; TCOF1
610060	POLYMERASE I, RNA, SUBUNIT C; POLR1C
613715	POLYMERASE I, RNA, SUBUNIT D; POLR1D
613717	TREACHER COLLINS SYNDROME 2; TCS2

Molecular Pathogenesis

Cartilage and bone making up the craniofacial complex is primarily derived from neural crest cells [Trainor & Andrews 2013]. Thus, TCS features can be explained by disturbances in neural crest cell development during embryogenesis. These disturbances can be attributed to pathogenic variants in the genetic pathway activating cell development.

TCOF1, *POLR1C*, and *POLR1D* are all expressed in neural crest cells, and their gene products (treacle; subunits C and D for RNA polymerase I and RNA polymerase III) colocalize to the nucleolus and are involved in ribogenesis. It is hypothesized that the variants in the three key proteins are disrupting cell division by triggering p53-directed apoptosis of neuroepithelial cells [Gonzales et al 2005]. Variants affecting RNA polymerase I and/or III result in a deficiency of ribosomal RNA and/or transfer RNA [Dauwerse et al 2011], potentially leading to an insufficient number of mature ribosomes in the neuroepithelium and neural crest cells during embryogenesis [Dixon et al 2000, Dauwerse et al 2011].

POLR1C

Gene structure. *POLR1C* comprises nine coding exons, with two isoforms. The longest transcript contains an open reading frame of 1,355 nucleotides with an 88-bp 5' UTR and a 226-bp 3' UTR. For a detailed summary of gene and protein information, see [Table A, Gene](#).

Pathogenic variants. To date, six compound heterozygous *POLR1C* pathogenic variants have been identified in three affected individuals without a *TCOF1* pathogenic variant [Dauwerse et al 2011]. These variants included three missense, one splice site, one nonsense, and one frameshift.

Normal gene product. *POLR1C* encodes the 16-kd (133-amino-acid) subunit that comprises both RNA polymerase I and RNA polymerase III complexes. RNA polymerase I and RNA polymerase III are involved in ribosomal RNA transcription [Dauwerse et al 2011].

Abnormal gene product. Compound heterozygous pathogenic variants in *POLR1C* lead to functional depletion of POLR1C at a critical time during embryogenesis [Dauwerse et al 2011, Noack Watt et al 2016].

POLR1D

Gene structure. *POLR1D* comprises three exons, with two isoforms. The longest transcript contains an open reading frame of 1,945 nucleotides with a 118-bp 5' UTR and a 1,458-bp 3' UTR. For a detailed summary of gene and protein information, see [Table A, Gene](#).

Pathogenic variants. More than 30 heterozygous *POLR1D* pathogenic variants have been identified in individuals with TCS without a *TCOF1* pathogenic variant [Dauwerse et al 2011,

Vincent et al 2016]. These include loss-of-function (e.g., nonsense) variants, splice site and missense variants, and small deletions and duplications. Whole-gene deletions have also been described [Dauwerse et al 2011, Vincent et al 2016].

Table 5.

POLR1D Pathogenic Variants Discussed in This GeneReview

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.163C>G	p.Leu55Val	NM_015972.3 NP_057056.1

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

Normal gene product. *POLR1D* encodes the 39 kd (346 amino acids) subunit that comprises both RNA polymerase I and RNA polymerase III complexes. RNA polymerase I and RNA polymerase III are involved in ribosomal RNA transcription [Dauwerse et al 2011].

Abnormal gene product. Pathogenic variants in *POLR1D* lead to haploinsufficiency of *POLR1D* [Dauwerse et al 2011, Noack Watt et al 2016].

TCOF1

Gene structure. *TCOF1* comprises 27 coding exons, three of which are alternatively spliced in-frame (6A, 16A, and 19) [Splendore et al 2005], and an additional exon containing the 3' UTR [So et al 2004]. The longest transcript (NM_001135243.1) contains an open reading frame of 4,467 nucleotides starting in the first exon. The open reading frame is preceded by a 93-bp 5' untranslated region (UTR) and followed by a 507-bp 3' UTR [Dixon et al 1997a]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Hundreds of pathogenic variants in *TCOF1* have been reported in individuals with TCS, with novel variants being identified in a significant proportion of families [Gladwin et al 1996, Treacher Collins Syndrome Collaborative Group 1996, Edwards et al 1997, Wise et al 1997, Splendore et al 2000, Ellis et al 2002, Splendore et al 2002, Dixon et al 2004, Horiuchi et al 2005, Trainor et al 2009, Bowman et al 2012, Vincent et al 2016]. The majority of pathogenic variants found to date are frameshift variants leading to a premature termination of the transcript. Pathogenic variants have been found throughout the gene.

Of *TCOF1* sequencing variants, 57%-60% are small deletions or insertions, 9%-16% are splice site variants, 19%-23% nonsense variants, and 3%-4% missense variants [Bowman et al 2012, Vincent et al 2016]. Large deletions of one or more exons have also been identified in up to 5% of individuals with TCS [Beygo et al 2012, Bowman et al 2012, Vincent et al 2016]. In one case, a synonymous pathogenic *TCOF1* variant led to missplicing of a constitutive exon [Macaya et al 2009].

While several pathogenic variants have occurred more than once, only one variant in *TCOF1*, c.4369_4373delAAGAA, has been identified as commonly recurrent. This variant is present in 16% of individuals with an identifiable pathogenic variant.

Table 6.*TCOF1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias ¹)	Predicted Protein Change (Alias ¹)	Reference Sequences
c.1021_1022delAG (790_791delAG)	p.Ser341GlnfsTer7 (Ser264GlnfsTer7)	
c.2490delA	p.Val831Ter	NM_001135243.1
c.2853dupT (2853_2854insT)	p.Ala952CysfsTer5	NP_001128715.1
c.4369_4373delAAGAA	p.Lys1457GlnfsTer12	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

Normal gene product. The 144-kd treacle protein comprises 1,488 amino acids. Treacle is a low-complexity, three-domain nucleolar protein having unique N and C termini that is structurally related to the nucleolar phosphoprotein Nopp140 [Isaac et al 2000]. A central ten-repeat motif contains protein kinase C and casein kinase 2 phosphorylation sites [Dixon et al 1997b, Winokur & Shiang 1998]. The protein has at least two functional nuclear localization signals and a nucleolar localization signal in the C terminus. Both Nopp140 and treacle contain LIS1 motifs, leading to speculation of involvement in microtubule dynamics [Emes & Ponting 2001].

Treacle interacts with the small nucleolar ribonucleoprotein hNop56p, suggesting that it is involved in ribosomal biogenesis [Hayano et al 2003]. Treacle is involved in rDNA transcription, nucleologenesis, or trafficking of proteins or ribosomal subunits between the nucleolus and cytoplasm [Winokur & Shiang 1998, Dauwerse et al 2011]; and perhaps neural crest cell migration [Sakai & Trainor 2009, Trainor & Andrews 2013, Calo et al 2018].

Abnormal gene product. Pathogenic variants in *TCOF1* lead to haploinsufficiency of the treacle protein [Isaac et al 2000]. Missense variants that allow production of an abnormal protein can disrupt either the N- or C-terminus nuclear localization signals and affect the protein's ability to transport into the nucleus during first and second branchial arch development, causing cephalic neural crest cells to undergo apoptosis during embryogenesis [Dixon et al 2000, Isaac et al 2000, Trainor & Andrews 2013]. Downregulation of *TCOF1* and *POLR1D* leads to relocalization of DDX21, a nucleolar protein involved in ribosome biogenesis [Calo et al 2018].

References

Literature Cited

Beygo J, Buiting K, Seland S, Lüdecke HJ, Hehr U, Lich C, Prager B, Lohmann DR, Wieczorek D. First report of a single exon deletion in TCOF1 causing Treacher Collins syndrome. *Mol Syndromol*. 2012;2:53–9. [PMC free article: PMC3326662] [PubMed: 22712005]

- Bowman M, Oldridge M, Archer C, O'Rourke A, McParland J, Brekelmans R, Seller A, Lester T. Gross deletions in TCOF1 are a cause of Treacher-Collins-Franceschetti syndrome. *Eur J Hum Genet.* 2012;20:769–77. [PMC free article: [PMC3376267](#)] [PubMed: [22317976](#)]
- Calo E, Gu B, Bowen ME, Aryan F, Zalc A, Liang J, Flynn RA, Swigut T, Chang HY, Attardi LD, Wysocka J. Tissue-selective effects of nucleolar stress and rDNA damage in developmental disorders. *Nature.* 2018;554:112–7. [PMC free article: [PMC5927778](#)] [PubMed: [29364875](#)]
- da Silva Dalben G, Costa B, Gomide MR. Prevalence of dental anomalies, ectopic eruption and associated oral malformations in subjects with Treacher Collins syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2006;101:588–92. [PubMed: [16632269](#)]
- Dauwerse JG, Dixon J, Seland S, Ruivenkamp CA, van Haeringen A, Hoefsloot LH, Peters DJ, Boers AC, Daumer-Haas C, Maiwald R, Zweier C, Kerr B, Cobo AM, Toral JF, Hoozeboom AJ, Lohmann DR, Hehr U, Dixon MJ, Breuning MH, Wiczorek D. Mutations in genes encoding subunits of RNA polymerases I and III cause Treacher Collins syndrome. *Nat Genet.* 2011;43:20–2. [PubMed: [21131976](#)]
- Dixon J, Brakebusch C, Fassler R, Dixon MJ. Increased levels of apoptosis in the pre-fusion neural folds underlie the craniofacial disorder, Treacher Collins syndrome. *Hum Mol Genet.* 2000;9:1473–80. [PubMed: [10888597](#)]
- Dixon J, Edwards SJ, Anderson I, Brass A, Scambler PJ, Dixon MJ. Identification of the complete coding sequence and genomic organization of the Treacher Collins syndrome gene. *Genome Res.* 1997a;7:223–34. [PubMed: [9074926](#)]
- Dixon J, Ellis I, Bottani A, Temple K, Dixon MJ. Identification of mutations in TCOF1: use of molecular analysis in the pre- and postnatal diagnosis of Treacher Collins syndrome. *Am J Med Genet A.* 2004;127A:244–8. [PubMed: [15150774](#)]
- Dixon J, Hovanes K, Shiang R, Dixon MJ. Sequence analysis, identification of evolutionary conserved motifs and expression analysis of murine *tcof1* provide further evidence for a potential function for the gene and its human homologue, TCOF1. *Hum Mol Genet.* 1997b;6:727–37. [PubMed: [9158147](#)]
- Edwards SJ, Gladwin AJ, Dixon MJ. The mutational spectrum in Treacher Collins syndrome reveals a predominance of mutations that create a premature-termination codon. *Am J Hum Genet.* 1997;60:515–24. [PMC free article: [PMC1712503](#)] [PubMed: [9042910](#)]
- Ellis PE, Dawson M, Dixon MJ. Mutation testing in Treacher Collins Syndrome. *J Orthod.* 2002;29:293–7. [PubMed: [12444270](#)]
- Emes RD, Ponting CP. A new sequence motif linking lissencephaly, Treacher Collins and oral-facial-digital type 1 syndromes, microtubule dynamics and cell migration. *Hum Mol Genet.* 2001;10:2813–20. [PubMed: [11734546](#)]
- Fazen LE, Elmore J, Nadler HL. Mandibulo-facial dysostosis. (Treacher-Collins syndrome). *Am J Dis Child.* 1967;113:405–10. [PubMed: [6024864](#)]
- Giabicani E, Lemale J, Dainese L, Boudjemaa S, Coulomb A, Tounian P, Dubern B. Chronic intestinal pseudo-obstruction in a child with Treacher Collins syndrome. *Archives de Pédiatrie.* 2017;24:1000–4. [PubMed: [28927774](#)]

Gladwin AJ, Dixon J, Loftus SK, Edwards S, Wasmuth JJ, Hennekam RC, Dixon MJ. Treacher Collins syndrome may result from insertions, deletions or splicing mutations, which introduce a termination codon into the gene. *Hum Mol Genet.* 1996;5:1533–8. [PubMed: 8894686]

Gonzales B, Henning D, So RB, Dixon J, Dixon MJ, Valdez BC. The Treacher Collins syndrome (TCOF1) gene product is involved in pre-rRNA methylation. *Hum Mol Genet.* 2005;14:2035–43. [PubMed: 15930015]

Hayano T, Yanagida M, Yamauchi Y, Shinkawa T, Isobe T, Takahashi N. Proteomic analysis of human Nop56p-associated pre-ribosomal ribonucleoprotein complexes. Possible link between Nop56p and the nucleolar protein treacle responsible for Treacher Collins syndrome. *J Biol Chem.* 2003;278:34309–19. [PubMed: 12777385]

Hertle RW, Ziylan S, Katowitz JA. Ophthalmic features and visual prognosis in the Treacher-Collins syndrome. *Br J Ophthalmol.* 1993;77:642–5. [PMC free article: PMC504607] [PubMed: 8218033]

Horiuchi K, Ariga T, Fujioka H, Kawashima K, Yamamoto Y, Igawa H, Sugihara T, Sakiyama Y. Mutational analysis of the TCOF1 gene in 11 Japanese patients with Treacher Collins Syndrome and mechanism of mutagenesis. *Am J Med Genet A.* 2005;134:363–7. [PubMed: 15759264]

Hosking J, Zoanetti D, Carlyle A, Anderson P, Costi D (2012) Anesthesia for Treacher Collins syndrome: a review of airway management in 240 pediatric cases. [PubMed: 22394325]

Isaac C, Marsh KL, Paznekas WA, Dixon J, Dixon MJ, Jabs EW, Meier UT. Characterization of the nucleolar gene product, treacle, in Treacher Collins syndrome. *Mol Biol Cell.* 2000;11:3061–71. [PMC free article: PMC14975] [PubMed: 10982400]

Kobus K, Wojcicki P. Surgical treatment of Treacher Collins syndrome. *Ann Plast Surg.* 2006;56:549–54. [PubMed: 16641634]

Konstantinidou AE, Tasoulas J, Kallipolitis G, Gasparatos S, Velissariou V, Paraskevakou H. Mandibulofacial dysostosis (Treacher-Collins syndrome) in the fetus: novel association with Pectus carinatum in a molecularly confirmed case and review of the fetal phenotype. *Birth Defects Res A Clin Mol Teratol.* 2013;97:774–80. [PubMed: 24288143]

Macaya D, Katsanis SH, Hefferon TW, Audlin S, Mendelsohn NJ, Roggenbuck J, Cutting GR. A synonymous mutation in TCOF1 causes Treacher Collins syndrome due to missplicing of a constitutive exon. *Am J Med Genet.* 2009;149A:1624–7. [PubMed: 19572402]

Marres HA. Hearing loss in the Treacher-Collins syndrome. *Adv Otorhinolaryngol.* 2002;61:209–15. [PubMed: 12408086]

Marszałek B, Wojcicki P, Kobus K, Trzeciak WH. Clinical features, treatment and genetic background of Treacher Collins syndrome. *J Appl Genet.* 2002;43:223–33. [PubMed: 12080178]

Noack Watt KE, Achilleos A, Neben CL, Merrill AE, Trainor PA. The roles of RNA polymerase I and III subunits Polr1c and Polr1d in craniofacial development and in zebrafish models of Treacher Collins syndrome. *PLoS Genet.* 2016;12:e1006187 [PMC free article: PMC4957770] [PubMed: 27448281]

Pereira DC, Bussamra LC, Araujo Júnior E, Drummond CL, Nardoza LM, Moron AF, Aldrighi JM. Prenatal diagnosis of Treacher-Collins syndrome using three-dimensional ultrasonography and differential diagnosis with other acrofacial dysostosis syndromes. *Case Rep Obstet Gynecol.* 2013;2013;2013:203976 [PMC free article: PMC3638565] [PubMed: 23653874]

Posnick JC. Treacher Collins syndrome: perspectives in evaluation and treatment. *J Oral Maxillofac Surg.* 1997;55:1120–33. [PubMed: 9331237]

Posnick JC, Ruiz RL. Treacher Collins syndrome: current evaluation, treatment, and future directions. *Cleft Palate Craniofac J.* 2000;37:434. [PubMed: 11034023]

Rotten D, Levailant JM, Martinez H, Ducou le Pointe H, Vicaut E. The fetal mandible: a 2D and 3D sonographic approach to the diagnosis of retrognathia and micrognathia. *Ultrasound Obstet Gynecol.* 2002;19:122–30. [PubMed: 11876802]

Sakai D, Trainor PA. Treacher Collins syndrome: unmasking the role of *Tcof1*/treacle. *Int J Biochem Cell Biol.* 2009;41:1229–32. [PMC free article: PMC3093759] [PubMed: 19027870]

Schaefer E, Collet C, Genevieve D, Vincent M, Lohmann DR, Sanchez E, Bolender C, Eliot MM, Nürnberg G, Passos-Bueno MR, Wieczorek D, van Maldergem L, Doray B. Autosomal recessive *POLR1D* mutation with decrease of *TCOF1* mRNA is responsible for Treacher Collins syndrome. *Genet Med.* 2014;16:720–4. [PubMed: 24603435]

Shoo BA, McPherson E, Jabs EW. Mosaicism of a *TCOF1* mutation in an individual clinically unaffected with Treacher Collins syndrome. *Am J Med Genet.* 2004;126A:84–8. [PubMed: 15039977]

Singh DJ, Bartlett SP. Congenital mandibular hypoplasia: analysis and classification. *J Craniofac Surg.* 2005;16:291–300. [PubMed: 15750428]

So RB, Gonzales B, Henning D, Dixon J, Dixon MJ, Valdez BC. Another face of the Treacher Collins syndrome (*TCOF1*) gene: identification of additional exons. *Gene.* 2004;328:49–57. [PubMed: 15019983]

Splendore A, Fanganiello RD, Masotti C, Morganti LS, Passos-Bueno MR. *TCOF1* mutation database: novel mutation in the alternatively spliced exon 6A and update in mutation nomenclature. *Hum Mutat.* 2005;25:429–34. [PubMed: 15832313]

Splendore A, Jabs EW, Passos-Bueno MR. Screening of *TCOF1* in patients from different populations: confirmation of mutational hot spots and identification of a novel missense mutation that suggests an important functional domain in the protein treacle. *J Med Genet.* 2002;39:493–5. [PMC free article: PMC1735178] [PubMed: 12114482]

Splendore A, Silva EO, Alonso LG, Richieri-Costa A, Alonso N, Rosa A, Carakushanky G, Cavalcanti DP, Brunoni D, Passos-Bueno MR. High mutation detection rate in *TCOF1* among Treacher Collins syndrome patients reveals clustering of mutations and 16 novel pathogenic changes. *Hum Mutat.* 2000;16:315–22. [PubMed: 11013442]

Teber OA, Gillessen-Kaesbach G, Fischer S, Bohringer S, Albrecht B, Albert A, Arslan-Kirchner M, Haan E, Hagedorn-Greife M, Hammans C, Henn W, Hinkel GK, König R, Kunstmann E, Kunze J, Neumann LM, Prott EC, Rauch A, Rott HD, Seidel H, Spranger S, Sprengel M, Zoll B, Lohmann DR, Wieczorek D. Genotyping in 46 patients with tentative diagnosis of Treacher Collins syndrome revealed unexpected phenotypic variation. *Eur J Hum Genet.* 2004;12:879–90. [PubMed: 15340364]

Thompson JT, Anderson PJ, David DJ. Treacher Collins syndrome: protocol management from birth to maturity. *J Craniofac Surg*. 2009;20:2028–35. [PubMed: 19881372]

Trainor PA, Andrews BT. Facial dysostoses: etiology, pathogenesis and management. *Am J Med Genet C Semin Med Genet*. 2013;163C:283–94. [PMC free article: PMC3870197] [PubMed: 24123981]

Trainor PA, Dixon J, Dixon MJ. Treacher Collins syndrome: etiology, pathogenesis and prevention. *Eur J Hum Genet*. 2009;17:275–83. [PMC free article: PMC2986179] [PubMed: 19107148]

Treacher Collins Syndrome Collaborative Group. Positional cloning of a gene involved in the pathogenesis of Treacher Collins syndrome. *Nat Genet*. 1996;12:130–6. [PubMed: 8563749]

Vincent M, Collet C, Verloes A, Lambert L, Herlin C, Blanchet C, Sanchez E, Drunat S, Vigneron J, Laplanche JL, Puechberty J, Sarda P, Geneviève D. Large deletions encompassing the TCOF1 and CAMK2A genes are responsible for Treacher Collins syndrome with intellectual disability. *Eur J Hum Genet*. 2014;22:52–6. [PMC free article: PMC3865420] [PubMed: 23695276]

Vincent M, Geneviève D, Ostertag A, Marlin S, Lacombe D, Martin-Coignard D, Coubes C, David A, Lyonnet S, Vilain C, Dieux-Coeslier A, Manouvrier S, Isidor B, Jacquemont ML, Julia S, Layet V, Naudion S, Odent S, Pasquier L, Pelras S, Philip N, Pierquin G, Prieur F, Aboussair N, Attie-Bitach T, Baujat G, Blanchet P, Blanchet C, Dollfus H, Doray B, Schaefer E, Edery P, Giuliano F, Goldenberg A, Goizet C, Guichet A, Herlin C, Lambert L, Leheup B, Martinovic J, Mercier S, Mignot C, Moutard ML, Perez MJ, Pinson L, Puechberty J, Willems M, Randrianaivo H, Szaskon K, Toutain A, Verloes A, Vigneron J, Sanchez E, Sarda P, Laplanche JL, Collet C. Treacher Collins syndrome: a clinical and molecular study based on a large series of patients. *Genet Med*. 2016;18:49–56. [PubMed: 25790162]

Warner RM, Fagan JM, Das-Gupta R. Treacher Collins syndrome: an undescribed characteristic of the condition and its management with botulinum toxin and surgery. *J Craniofac Surg*. 2008;19:1600–2. [PubMed: 19098560]

Winokur ST, Shiang R. The Treacher Collins syndrome (TCOF1) gene product, treacle, is targeted to the nucleolus by signals in its C-terminus. *Hum Mol Genet*. 1998;7:1947–52. [PubMed: 9811939]

Wise CA, Chiang LC, Paznekas WA, Sharma M, Musy MM, Ashley JA, Lovett M, Jabs EW. TCOF1 gene encodes a putative nucleolar phosphoprotein that exhibits mutations in Treacher Collins syndrome throughout its coding region. *Proc Natl Acad Sci U S A*. 1997;94:3110–5. [PMC free article: PMC20330] [PubMed: 9096354]

Chapter Notes

Acknowledgments

We acknowledge Mac Hays for his background research.

Author History

Garry R Cutting, MD; Johns Hopkins University (2004-2011)
Sara Huston Katsanis, MS (2004-present)

Ethylin Wang Jabs, MD (2011-present)

Revision History

- 27 September 2018 (bp) Comprehensive update posted live
- 30 August 2012 (cd) Revision: *TCOF1* and *POLRID* deletions reported in individuals with Treacher Collins syndrome; deletion/duplication analysis available clinically for *POLRIC* and *POLRID*
- 27 October 2011 (me) Comprehensive update posted live
- 27 October 2006 (me) Comprehensive update posted live
- 20 July 2004 (me) Review posted live
- 1 March 2004 (shk,gc) Original submission

Copyright © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2020 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the GeneReviews® Copyright Notice and Usage Disclaimer. No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the GeneReviews® Copyright Notice and Usage Disclaimer.

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.

Bookshelf ID: NBK1532 PMID: 20301704