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Treacher Collins Syndrome

Synonyms: Mandibulofacial Dysostosis, Treacher Collins-Franceschetti Syndrome

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Summary

Clinical characteristics

Treacher Collins syndrome (TCS) is characterized by lower eyelid abnormalities, malar hypoplasia, downslanted palpebral fissures, and micro- or retrognathia due to symmetric hypoplasia of the zygomatic bones, maxilla, and mandible. External ear anomalies include absent, small, malformed, and/or posteriorly rotated ears and atresia or stenosis of the external auditory canals. 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. Significant respiratory and feeding difficulties can be present in infancy. 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 a proband with characteristic clinical features and/or a heterozygous pathogenic variant in *TCOF1*, *POLR1D*, or *POLR1B*, biallelic pathogenic variants in *POLR1C*, or, rarely, biallelic pathogenic variants in *POLR1D* identified by molecular genetic testing.

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 airway management at delivery, special positioning, or tracheostomy to facilitate ventilation. Tube feeding may be needed for adequate caloric intake. Cleft palate repair (if needed) occurs at about age one year. Hearing loss is treated with bone conduction amplification, speech therapy, and educational intervention. Management of ocular issues is per ophthalmologist. Standard management for cardiac, gastrointestinal, renal, and limb anomalies. Craniofacial reconstruction is often necessary: zygomatic and orbital reconstruction at about age five to seven years, and

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bilateral microtia and/or narrow ear canal reconstruction after age six years. Botulinum toxin and subsequent surgery for coloboma of the lower eyelid. Eyelid reconstruction as needed for downslanted palpebral fissures. Orthodonture for misaligned teeth. The age of maxillomandibular reconstruction varies by severity; orthognathic therapies are typically before age 16 years.

Surveillance: Annual ophthalmology and audiology evaluations; assess for manifestations of obstructive sleep apnea, growth, and caloric intake at each visit; dental exams every six months with orthodontia exams as needed; assess speech development and educational progress annually or as needed.

Genetic counseling

TCS can be inherited in an autosomal dominant or autosomal recessive manner. Autosomal dominant inheritance accounts for most of TCS, most commonly heterozygous pathogenic variants in *TCOF1* and less commonly heterozygous pathogenic variants in *POLR1B* or *POLR1D*. Autosomal recessive inheritance (biallelic pathogenic variants in *POLR1C* or *POLR1D*) accounts for a minority of TCS. Significant intrafamilial clinical variability is common.

Autosomal dominant TCS: About 55%-61% of individuals with autosomal dominant TCS have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with autosomal dominant TCS has a 50% chance of inheriting the pathogenic variant.

Autosomal recessive TCS: The parents of a child with autosomal recessive TCS are presumed to be heterozygous for a *POLR1C* or *POLR1D* pathogenic variant. If both parents are known to be heterozygous for a TCS-causing pathogenic variant, each sib of an individual with autosomal recessive TCS has at conception 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. Carrier testing for at-risk relatives requires prior identification of the TCS-related pathogenic variants in the family.

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

Diagnosis

No consensus clinical diagnostic criteria for Treacher Collins syndrome (TCS) have been published.

Suggestive Findings

TCS **should be suspected** in probands with the following craniofacial features, conductive hearing loss, and radiographic features.

Craniofacial features

- Lower eyelid abnormalities including coloboma (notching) of the lower eyelid and sparse, partially absent, or totally absent eyelashes and tear ducts
- Malar hypoplasia due to hypoplasia of the zygomatic arch and lateral aspects of the orbits resulting in downward-slanted palpebral fissures, a bilaterally symmetric convex facial profile, and prominent nose
- Mandibular hypoplasia with micro- or retrognathia
- External ear abnormalities including absent, small, malformed, and/or posteriorly rotated ears and atresia or stenosis of the external auditory canals
- 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 occipitomental radiographs (Waters view) [Marszałek-Kruk et al 2021]
- Mandibular retrognathia, detected by orthopantomogram [Marszałek-Kruk et al 2021]

Establishing the Diagnosis

Clinical Diagnosis

The clinical diagnosis of TCS can be established in a proband with characteristic bilaterally symmetric abnormalities of the facial and mandibular structures, including downslanted palpebral fissures, hypoplasia of the zygomatic complex and mandible, and conductive hearing loss. Clinical features such as limb anomalies, microcephaly, and/or intellectual disability are rare in individuals with TCS and should prompt consideration of other disorders (see Differential Diagnosis).

Molecular Diagnosis

The molecular diagnosis of TCS **is established** in a proband with suggestive findings who has **one of the following** on molecular genetic testing (see Table 1):

- A heterozygous pathogenic (or likely pathogenic) variant in *TCOF1*, *POLR1D*, or *POLR1B*
- Biallelic pathogenic (or likely pathogenic) variants in *POLR1C*; rarely, biallelic pathogenic (or likely pathogenic) variants in *POLR1D*
- Heterozygous deletion of 5q32-q33.1 that includes *TCOF1*

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (serial single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Serial single-gene testing. Sequence analysis of *TCOF1* can be performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. If no *TCOF1* pathogenic variant is found, perform sequence analysis of *POLR1B*, *POLR1C*, and *POLR1D*. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis of *TCOF1* and *POLR1D* to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *TCOF1*, *POLR1B*, *POLR1C*, *POLR1D*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition 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, and/or other non-sequencing-based tests.

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

Option 2

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.

For an introduction to CMA click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of *TCOF1*, *POLR1B*, *POLR1C*, and *POLR1D* pathogenic variants reported (e.g., missense, nonsense, small deletions/insertions) are within the coding region and are likely to be identified by exome sequencing.

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] Identified by Method		
			Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]	CMA [6]
POLR1B	~1%-2% [7, 8]	AD	100% [7]	None reported	
POLR1C	~1% [7, 8]	AR	100% [7]	None reported	
POLR1D	6%-8% [7, 8]	AD AR [9]	~90% [7]	~10% [7]	No large deletions identified by CMA [7]
TCOF1	~60%-90% [7, 8]	AD	>97%	2%-3% [10]	<1% [10]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of TCS Attributed to Pathogenic Variants in Gene	MOI	Proportion of Pathogenic Variants [3] Identified by Method		
			Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]	CMA [6]
Unknown	3% [11]	NA			

AD = autosomal dominant; AR = autosomal recessive; CMA = chromosomal microarray; MOI = mode of inheritance; TCS = Treacher Collins syndrome

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. See Molecular Genetics for information on variants detected in this gene.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as 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.

6. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TCOF1* or *POLR1D*) 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.

7. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

8. Ulhaq et al [2023]

9. The same homozygous variant, c.163C>G (p.Leu55Val), was reported in three families [Schaefer et al 2014, Vincent et al 2016].

10. 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.

11. Vincent et al [2016]

Clinical Characteristics

Clinical Description

Treacher Collins syndrome (TCS) is characterized by bilateral and symmetric downslanted palpebral fissures, malar hypoplasia, and micro- or retrognathia. Hypoplasia of the zygomatic bones, maxilla, and mandible can cause significant respiratory and feeding 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. While some individuals may be so mildly affected as to go undiagnosed, others can have severe facial involvement and life-threatening airway compromise [Trainor & Andrews 2013]. To date, more than 5,000 individuals have been identified with a pathogenic variant in one of the genes listed in Table 1. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Treacher Collins Syndrome: Frequency of Select Features

Feature	Frequency
Downslanted palpebral fissures	Very frequent (>75%)
Malar hypoplasia / hypoplasia of zygomatic bones	
Conductive hearing loss	
Mandibular hypoplasia w/micro- or retrognathia	

Table 2. continued from previous page.

Feature	Frequency
Atresia of external ear canal	Frequent (30%-75%)
Microtia	
Coloboma (notching) of lower lid	
Delayed speech development	
Dental anomalies	
Preauricular hair displacement	
Cleft palate	Less common (10%-30%)
Choanal stenosis/atresia	
Cardiac malformation	
Rachis malformation	Rare (<10%)
Renal malformation	
Microcephaly	
Intellectual disability / delayed motor development	
Limb anomaly	

Splendore et al [2000], Teber et al [2004], Vincent et al [2016]

Ophthalmologic defects. The prevalence of ocular and adnexal anomalies was evaluated in 194 individuals with TCS [Rooijers et al 2022]. Primary ocular anomalies were described in almost all individuals, mostly consisting of downslanted palpebral fissures (93.8%), colobomata of the lower eyelids (69.6%), and (partial) absence of lower lid eyelashes (42.8%). The most prevalent secondary ocular anomalies were epiphora (24.2%) and exposure keratopathy (14.4%). Strabismus was reported in 27.3% and refractive errors in 49.5% [Rooijers et al 2022].

Ear anomalies and hearing. External ear anomalies including absent, small, malformed, and/or posteriorly rotated ears are typical. 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 [Marszałek-Kruk et al 2021]. The inner ear structures are typically normal. Conductive hearing loss is usually attributed to middle ear anomalies including hypoplasia or absence of the ossicles or middle ear cavities.

Airway/respiratory issues. Choanal atresia/stenosis or severe micrognathia with glossoptosis can obstruct the airway in an infant from the time of delivery [Trainor & Andrews 2013]. Prenatal ultrasound can identify a fetus at risk of severe airway obstruction at birth by assessment for micrognathia and abnormal fetal swallowing [Wang et al 2023]. Neonatal death in infants with TCS is usually associated with obstructive sleep apnea as a result of airway malformations. Management of the airway in a severely affected neonate with TCS typically includes special positioning of the infant to facilitate ex utero intrapartum treatment (EXIT) in order to perform oral intubation or tracheostomy during birth; Appropriate airway management can result in life expectancy that approximates that of the general population.

Feeding. Micrognathia and retrognathia can have variable effects on the temporomandibular joints and jaw muscles and can lead to cleft palate (typically U-shaped in the context of Pierre Robin sequence). These findings contribute to feeding issues including problems with chewing and swallowing.

Dental anomalies, reported in 60% of individuals with TCS, include tooth agenesis (33.3%), enamel opacities (20%), and ectopic eruption of the maxillary first molars (13.3%) [da Silva Dalben et al 2006]. Angle class II anterior open-bite malocclusion has been reported.

Additional craniofacial features. Preauricular hair displacement, in which hair growth extends in front of the ear to the lateral cheekbones, is common. Although craniosynostosis is not a feature of TCS, the cranium may have an abnormal shape (brachycephaly with bitemporal narrowing) [Marszałek-Kruk et al 2021]. Less frequently observed craniofacial features in individuals with TCS include hypertelorism, nasal deformity, high-arched palate, and macrostomia [Marszałek-Kruk et al 2021].

Cardiac manifestations are reported in some individuals with *TCOF1*- or *POLR1D*-related TCS. Congenital heart anomalies described to date include atrial septal defect, ventricular septal defect, patent ductus arteriosus, and patent foramen ovale; hypertrophic cardiomyopathy has also been rarely reported [Vincent et al 2016, Beaumont et al 2021].

Gastrointestinal manifestations. Altered function of the upper digestive tract including pyloric stenosis and esophageal atresia have also been reported [Beaumont et al 2021]. Abnormality of the lower digestive tract can include chronic intestinal pseudo-obstruction with abnormal innervation (enlarged ganglionic myenteric plexus has been histologically confirmed on a surgical rectal biopsy) [Giabicani et al 2017].

Musculoskeletal manifestations. Spine anomalies are observed in ~10% of individuals. Scoliosis is the most common; spina bifida occulta has also been reported. Other musculoskeletal manifestations include pectus excavatum or carinatum and pes planus [Beaumont et al 2021]. Congenital limb anomalies are rare but have been reported, including toe syndactyly, absent or hypoplastic thumbs, and carpal bone fusion [Beaumont et al 2021].

Renal malformations are rare but have been described, including congenital bilateral hydronephrosis and duplicated collecting system. One individual had a non-functioning left kidney [Beaumont et al 2021].

Development. Although intellectual disability and delayed motor development have been reported [Vincent et al 2014, Marszałek-Kruk et al 2021], intelligence is usually normal.

Phenotype Correlations by Gene

Individuals with *TCOF1*-related TCS may have more severe clinical features than individuals with *POLR1B*-, *POLR1C*-, and *POLR1D*-related TCS [Ulhaq et al 2023], although data is limited. Atresia of the external ear canal, downslanted palpebral fissures, and lower lid coloboma are more common in individuals with *TCOF1*-related TCS [Ulhaq et al 2023].

Genotype-Phenotype Correlations

TCOF1

- Individuals with *TCOF1* duplications tend to have a milder presentation than individuals with other *TCOF1* pathogenic variants [Ulhaq et al 2023].
- The most common 5-bp deletion in exon 24 (c.4369_4373delAAGAA) has been reported to have a higher severity than other exon 24 pathogenic variants [Teber et al 2004, Ulhaq et al 2023].
- Individuals with pathogenic variants in exon 15 have a significantly lower frequency of microtia, conductive deafness, and atresia of the external ear canal [Ulhaq et al 2023].

Penetrance

While the penetrance of pathogenic variants associated with TCS is high, reduced penetrance in *TCOF1* [Dixon et al 2004, Vincent et al 2016] and *POLR1D* [Dauwerse et al 2011, Vincent et al 2016] has also been reported.

Nomenclature

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

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], Treacher Collins syndrome is included in the craniofacial dysostoses group and referred to by the following gene-specific designations:

- *POLR1B*-related mandibulofacial dysostosis (Treacher-Collins, Franceschetti-Klein)
- *POLR1C*-related mandibulofacial dysostosis (Treacher-Collins, Franceschetti-Klein)
- *POLR1D*-related mandibulofacial dysostosis (Treacher-Collins, Franceschetti-Klein)
- *TCOF1*-related mandibulofacial dysostosis (Treacher-Collins, Franceschetti-Klein)

Prevalence

The prevalence of TCS is estimated at 1:80,000 [Reid & Carroll 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TCOF1*, *POLR1B*, or *POLR1D*.

POLR1C. Biallelic pathogenic variants in *POLR1C* are also known to be associated with hypomyelinating leukodystrophy (see *POLR3*-Related Leukodystrophy). Five missense variants in *POLR1C* have been identified in three individuals with Treacher Collins syndrome (TCS) [Dauwerse et al 2011]. Individuals with *POLR1C*-related TCS do not have evidence of demyelination.

Differential Diagnosis

Table 3a. Genes of Interest in the Differential Diagnosis of Treacher Collins Syndrome

Gene	Disorder	MOI	Features of Disorder	
			Overlapping w/TCS	Distinguishing from TCS
DHODH	Postaxial acrofacial dysostosis, *DHODH*-related (Miller syndrome) (OMIM 263750)	AR	• Mandibulofacial dysostosis • Eyelid coloboma • Micrognathia • Cleft lip/palate	• Limb deformities • Postaxial abnormalities (e.g., small or absent 5th digit incl 5th metacarpal, ulnar hypoplasia, absent 5th toe)
EDN1 *GNAI3* *HDAC9* *PLCB4*	Auriculocondylar syndrome (OMIM PS602483)	AD AR	• Mandibulofacial hypoplasia • Malformed ears • Micrognathia	• Prominent cheeks • Round face
EDNRA	Mandibulofacial dysostosis w/ alopecia, *EDNRA*-related (OMIM 616367)	AD	• Mandibulofacial dysostosis • Malformed ears • Eyelid coloboma	• Alopecia • Intact palate
EFTUD2	Mandibulofacial dysostosis w/ microcephaly, *EFTUD2*-related (Guion-Almeida type)	AD	• Mandibulofacial dysostosis • Microtia • Preauricular skin tags	• Microcephaly is present in most affected persons. • Intellectual disability • Asymmetry of facial features • Esophageal atresia / tracheoesophageal fistula in ~34% • Thumb abnormalities in ~33%

Table 3a. continued from previous page.

Gene	Disorder	MOI	Features of Disorder	
			Overlapping w/TCS	Distinguishing from TCS
FOXI3 [1] *SF3B2* [2]	Hemifacial microsomia (Goldenhar syndrome, Oculo-auriculo-vertebral spectrum) (OMIM PS164210)	AD AR	• Mandibulofacial dysostosis • Microtia • Preauricular skin tags • Cleft lip/palate	• Asymmetric • Ocular epibulbar dermoid cyst • Vertebral anomalies, Klippel-Feil anomaly
POLR1A [3]	Mandibulofacial dysostosis w/ limb deficiencies, *POLR1A*-related (Cincinnati type) (OMIM 616462)	AD	• Mandibulofacial dysostosis • Micrognathia • Eyelid coloboma • Cleft lip/palate • Microtia/anotia	• Abnormal neurodevelopment in ~78% (e.g., abnormal muscle tone, developmental delay, epilepsy) • Congenital heart defects in ~44% (e.g., septal defects) • Limb defects in ~33% (e.g., bowed long bones)
RPS28 *TSR2*	Diamond-Blackfan anemia w/ mandibulofacial dysostosis	AD XL	• Downslanted palpebral fissures • Micrognathia • Mandibulofacial dysostosis • Malformed ears	Macrocytic anemia
SF3B4	Acrofacial dysostosis, *SF3B4*-related (Nager syndrome) (OMIM 154400)	AD	• Downslanted palpebral fissures • Micrognathia • Mandibulofacial dysostosis	• Limb deformities • Preaxial abnormalities (e.g., small or absent thumbs, triphalangeal thumbs, radial hypoplasia or aplasia, radioulnar synostosis)

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; TCS = Treacher Collins syndrome; XL = X-linked
1. In a cohort of 670 individuals with craniofacial (hemifacial) microsomia, *FOXI3* pathogenic variants were identified in 3.1% of individuals [Mao et al 2023].
2. Genetic alterations involving *SF3B2* have been reported in ~3% of individuals with hemifacial microsomia and a negative family history and ~25% of individuals with a positive family history [Unger et al 2023].
3. Weaver et al [2015], Smallwood et al [2023]

Table 3b. Disorders of Unknown Genetic Cause with Mandibulofacial Dysostosis in the Differential Diagnosis of Treacher Collins Syndrome

Disorder	Features of This Disorder Distinguishing from TCS
Toriello-Carey syndrome (OMIM 217980)	• Growth failure • Microcephaly • Agenesis of corpus callosum • Intellectual disability • Urogenital anomalies in affected males • Facial dysmorphisms (hypertelorism, flattened nasal bridge, anteverted nares) • Short neck
Branchial arch syndrome (OMIM 301950)	• Microcephaly • Intellectual disability • High-arched palate • Webbed neck
Bauru syndrome (OMIM 604830)	• Upslanted palpebral fissures • Hypoplastic tragus & ear lobes
Hedera-Toriello-Petty syndrome (OMIM 608257)	Ptosis
Pierre Robin sequence (OMIM 261800) [1]	Micrognathia, glossoptosis, & airway obstruction w/cleft palate deformity may self-correct w/growth & w/o intervention. [2]

Table 3b. continued from previous page.

Disorder	Features of This Disorder Distinguishing from TCS
Nonsyndromic mandibular hypoplasia	• Severe mandibular deficiencies (e.g., temporomandibular joint, ankylosis, aglossia/microglossia, rare craniofacial cleft) • Progressive micrognathia or retrognathia [2, 3]

TCS = Treacher Collins syndrome
1. Disruption of a long-range *cis*-regulatory element leading to misregulation of *SOX9* has been reported in some individuals with Pierre Robin sequence.
2. Singh & Bartlett [2005]
3. In one study, 52 of 266 individuals with congenital mandibular hypoplasia had TCS [Singh & Bartlett 2005]. Molecular diagnosis was not confirmed in these individuals.

Management

No clinical practice guidelines for Treacher Collins syndrome (TCS) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with TCS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Treacher Collins Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval w/attention to extraocular movement, corneal exposure, & visual acuity	
Hearing	Formal audiology eval (See Genetic Hearing Loss Overview.)	In those w/conductive hearing loss identified at age <6 mos: craniofacial CT scan (axial & coronal slices) to assess anatomy of head & neck, external auditory canal, middle ear, & inner ear
Respiratory	Assess for choanal atresia/stenosis, micrognathia, & glossoptosis predisposing to obstruction of oropharynx.	If obstructive sleep apnea is suspected, consider sleep study.
Feeding/Nutrition	Assess for cleft palate & swallowing function.	
Dental	Assess for dental anomalies.	When teeth have erupted
Cardiac	Cardiology eval w/echocardiogram	To assess for structural heart defects
Gastrointestinal	In those w/persistent feeding issues, consider assessment for pyloric stenosis, esophageal abnormalities, & intestinal pseudo-obstruction.	
Musculoskeletal	Clinical assessment for spine & limb anomalies w/ radiographs as needed	
Renal	Renal ultrasound	To assess for structural renal defects
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of TCS to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

MOI = mode of inheritance; TCS = Treacher Collins syndrome
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

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-language 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

Airway. 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 for ex utero intrapartum treatment (EXIT), 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 [Lei et al 2023].

Feeding/nutrition. Assess nutrition and feeding support including nasogastric or gastrostomy tube feedings as needed to assure adequate caloric intake while protecting the airway [Trainor & Andrews 2013].

Cleft palate. Repair of cleft palate at age one to two years is recommended [Kobus & Wojcicki 2006].

Hearing. Bone conduction amplification, speech therapy, and educational intervention are indicated for treatment of hearing loss. Bone-anchored hearing aids are an alternative for individuals with ear anomalies [Trainor & Andrews 2013].

Eyes/vision. Management is per the treating ophthalmologist for eyelid coloboma, diminished tearing, and vision impairment. When present, corneal exposure keratitis should be medically treated.

Cardiac, gastrointestinal, renal, and limb anomalies are managed per standard practice.

Age Three to 12 Years

Craniofacial reconstruction is often necessary [Marszałek-Kruk et al 2021]. 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 (approximately age five to seven 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 downslanted palpebral fissures can use redundant upper eyelid skin [Trainor & Andrews 2013].
- Misaligned teeth often require orthodonture.

Educational support. Speech therapy and educational intervention as needed in those with hearing loss.

Age 13 to 18 Years

Orthognathic therapies are typically indicated before age 16 years. 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 (age ~16 years)
- Type III (severe) malformation at age six to ten years

Nasal reconstruction, if needed, should follow orthognathic surgeries.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with Treacher Collins Syndrome

System/Concern	Evaluation	Frequency
Eyes	Ophthalmology eval	Annually or as needed
Hearing	Audiology eval	
Airway	Assess for manifestations of obstructive sleep apnea.	At each visit
Feeding/Nutrition	Assess growth & caloric intake.	
Dental	Dental exam	Every 6 mos
	Orthodontia exam	As needed
Musculoskeletal manifestations	Clinical assessment for scoliosis & pes planus	Annually
Developmental	Assess speech development & educational progress.	Annually or as needed

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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

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

- Autosomal dominant inheritance accounts for most of TCS, most commonly caused by heterozygous pathogenic variants in *TCOF1* and less commonly by heterozygous pathogenic variants in *POLR1B* or *POLR1D* [Dauwerse et al 2011, Sanchez et al 2020].
- Autosomal recessive inheritance accounts for a minority of TCS, caused by 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 55%-61% of probands with autosomal dominant TCS have the disorder as the result of a *de novo* pathogenic variant [Trainor et al 2009, Vincent et al 2016, Sanchez et al 2020].
- About 40% of individuals diagnosed with autosomal dominant TCS have an affected parent.
- If the proband appears to be the only affected family member (i.e., a simplex case), recommended evaluations for both parents of a proband include:
  - Molecular genetic testing if a molecular diagnosis has been established in the proband;
  - If a molecular diagnosis has not been established in the proband, audiologic evaluation and occipitomental radiographic examination (Waters view). Radiographic examination may reveal mild zygomatic arch hypoplasia or even aplasia [Marres 2002].
- If a molecular diagnosis has been established in the proband, the pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Maternal and paternal somatic and germline mosaicism have been reported [Shoo et al 2004, Vincent et al 2016, Sanchez et al 2020]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

    * If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be unaffected or mildly/minimally affected [Shoo et al 2004, Sanchez et al 2020].
- 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. Therefore, an apparently negative family history cannot be

confirmed without appropriate clinical evaluation of the parents and molecular genetic testing if a molecular diagnosis has been established in the proband.

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 and their severity cannot be predicted in sibs who inherit a pathogenic variant because significant intrafamilial clinical variability is common in autosomal dominant forms of TCS [Posnick & Ruiz 2000, Teber et al 2004]. Reduced penetrance has also been reported.
- If the proband has a known *TCOF1*, *POLR1B*, 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, Sanchez et al 2020].
- 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 TCS 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 and their severity cannot be predicted in offspring who inherit a TCS-related pathogenic variant.

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, the parent's 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 presumed to be heterozygous for a *POLR1C* or *POLR1D* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a TCS-related pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- If both parents are known to be heterozygous for a TCS-causing pathogenic variant, each sib of an individual with autosomal recessive TCS has at conception 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.
- The specific malformations and their severity cannot be predicted in offspring who inherit biallelic TCS-related pathogenic variants.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with autosomal recessive TCS are obligate heterozygotes (carriers) for a TCS-related pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an autosomal recessive TCS-related pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the autosomal recessive TCS-related pathogenic variants in the family.

Related Genetic Counseling Issues

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. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

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 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 [Wang et al 2023]. 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. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  Treacher Collins syndrome
- **FACES: National Craniofacial Association**
  Phone: 800-332-2373
  Email: faces@faces-cranio.org
  Treacher Collins syndrome
- **Foundation for Faces of Children**
  Phone: 617-355-8299
  Email: info@facesofchildren.org
  Treacher Collins syndrome
- **MedlinePlus**
  Treacher Collins syndrome
- **National Organization for Rare Disorders (NORD)**
  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.
  babyhearing.org
- **Human Disease Gene Website Series - Registry**
  TCOF1-Related Treacher Collins Syndrome

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
POLR1B	2q14.1	DNA-directed RNA polymerase I subunit RPA2	POLR1B @ LOVD	POLR1B	POLR1B
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

Table A. continued from previous page.

TCOF1	5q32-q33.1	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
602000	POLYMERASE I, RNA, SUBUNIT B; POLR1B
606847	TREACLE RIBOSOME BIOGENESIS FACTOR 1; TCOF1
610060	POLYMERASE I, RNA, SUBUNIT C; POLR1C
613715	POLYMERASE I, RNA, SUBUNIT D; POLR1D
613717	TREACHER COLLINS SYNDROME 2; TCS2
618939	TREACHER COLLINS SYNDROME 4; TCS4

Molecular Pathogenesis

Cartilage and bone making up the craniofacial complex is primarily derived from neural crest cells [Trainor & Andrews 2013]. Thus, Treacher Collins syndrome (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, *POLR1B*, *POLR1C*, and *POLR1D* are all expressed in neural crest cells, and their gene products (treacle protein; RNA polymerase I subunit 2; RNA polymerases I and III subunit AC1; protein POLR1D, isoform 2) colocalize to the nucleolus and are involved in ribogenesis. It is hypothesized that the variants in the three key proteins disrupt 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].

Mechanism of disease causation. Loss of function

Gene-specific laboratory technical considerations. To date, only one *POLR1D* pathogenic variant, c.163C>G (p.Leu55Val), is associated with autosomal recessive inheritance and lack of clinical findings in heterozygous individuals [Schaefer et al 2014, Vincent et al 2016].

Table 6. Pathogenic Variants Referenced in This *GeneReview* by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
POLR1D	NM_015972.4 NP_057056.1	c.163C>G	p.Leu55Val	Assoc w/AR inheritance
TCOF1	NM_001135243.2 NP_001128715.1	c.4369_4373delAAGAA	p.Lys1457GlufsTer12	See Genotype-Phenotype Correlations.

AR = autosomal recessive
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. Genes from Table 1 are in alphabetic order.

Chapter Notes

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