GENEReviews

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Treacher Collins Syndrome

[*Mandibulofacial Dysostosis, Treacher Collins-Franceschetti Syndrome*]

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Summary

Disease characteristics. Treacher Collins syndrome (TCS) is characterized by hypoplasia of the zygomatic bones and mandible, external ear abnormalities, coloboma (notching) of the lower eyelid, absence of the lower eyelid cilia, and preauricular hair displacement. About 40%-50% of individuals have conductive hearing loss attributed most commonly to malformation (including ankylosis, hypoplasia, or absence) of the ossicles and hypoplasia of the middle ear cavities. Inner ear structures tend to be normal. Other less common abnormalities include cleft palate with or without cleft lip and unilateral or bilateral choanal stenosis or atresia.

Diagnosis/testing. *TCOF1* is the only gene currently known to be associated with TCS. Direct sequencing of the coding and flanking intronic regions of *TCOF1* detects mutations in about 90%-95% of individuals.

Management. Treatment should be tailored to the specific needs of each individual, preferably by a multidisciplinary craniofacial management team. Neonates may require special positioning or tracheostomy to manage the airway. Hearing loss is treated with bone conduction amplification, speech therapy, and educational intervention. Craniofacial reconstruction is often necessary. Cleft palate, if present, is repaired at age one to two years, zygomatic and orbital reconstruction about age five to seven years, and external ear reconstruction after age six years. The age of maxillomandibular reconstruction varies by severity; orthognathic procedures are typically before age 16 years. Bilateral microtia and/or narrow ear canals require reconstruction.

Genetic counseling. TCS is inherited in an autosomal dominant manner. About 60% of probands with TCS have the disorder as the result of a *de novo* gene mutation. Each child of an individual with TCS has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk for TCS is possible.

Diagnosis

Clinical Diagnosis

Diagnosis of Treacher Collins syndrome (TCS) relies upon clinical and radiographic findings.

Distinguishing clinical features [Hertle et al 1993, Posnick & Ruiz 2000, Marszalek et al 2002, Teber et al 2004]

- Individuals with TCS having an identified *TCOF1* mutation (see Figure 1); for additional photos and further details on the individuals in Figure 1, see Figure 2.
- Three of eight individuals with a clinical unequivocal diagnosis of TCS without a detected *TCOF1* mutation; see Figure 3.
- Intrafamilial variation of TCS features; see Figure 4.

Major clinical features

- **Hypoplasia of the zygomatic bones and mandible** [Posnick 1997] resulting in the following:
  - Midface hypoplasia (89%) with a bilaterally symmetrical convex facial profile, prominent nose, and characteristic downward slant of the eyes secondary to hypoplasia of the lateral aspects of the orbits
  - Micrognathia and retrognathia (78%) with variable effects on the temporomandibular joints and jaw muscles
- **External ear abnormalities** (77%) including absent, small, and malformed ears (microtia) or rotated ears
- **Lower eyelid abnormalities** including the following:
  - Coloboma (notching) (69%)
  - Sparse, partially absent, or totally absent cilia (lashes) (53%)
- **Family history** consistent with autosomal dominant inheritance (40%)

Minor clinical features

- **External ear abnormalities** including atresia or stenosis of the external auditory canals (36%)
- **Conductive hearing loss** (40%-50%) attributed most commonly to ankylosis, hypoplasia, or absence of the ossicles and hypoplasia of the middle ear cavities. Inner ear structures tend to be normal.
- **Ophthalmalogic defects**
  - Vision loss (37%)
  - Amblyopia (33%)
  - Refractive errors (58%)
  - Anisometropia (17%)
  - Strabismus (37%)
- **Cleft palate** with or without cleft lip (28%)
- **Preauricular hair displacement** (26%), in which hair growth extends in front of the ear to the lateral cheekbones
- **Airway abnormalities** including the following:
  - Tracheostoma
  - Uni- or bilateral choanal stenosis or atresia
- **Delayed motor or speech development**

Distinguishing radiographic features

- **Hypoplasia or aplasia (discontinuity) of the zygomatic arch** detected by occipitomental radiographs. These radiographs include an occipitomental projection of the skull (Waters' view) and orthopantogram to identify mandibular hypoplasia or other abnormalities.
- **Malar hypoplasia** confirmed by intraorbital measurements by CT that are at the mean, with zygomatic measurements less than normal [Posnick & Ruiz 2000]
- **Mandibular retrognathia** caused by facial convexity, the extent of which is established by cephalometric radiographic measurements [Posnick & Ruiz 2000]

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *TCOF1* is the only gene currently known to be associated with TCS.

Other loci. While no direct evidence exists for locus heterogeneity, mutations in *TCOF1* have not been identified in some individuals with typical clinical signs of TCS [Dixon et al 1994, Splendore et al 2000]. Specifically, Splendore et al (2000) failed to identify *TCOF1* mutations in two of 28 (7%) probands using mutation scanning by SSCP followed by sequence analysis; one of the two probands had evidence of linkage to 5q31-q34.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Molecular genetic testing: Clinical methods

- **Sequence analysis.** Direct sequencing of the coding and flanking intronic regions of *TCOF1* should detect all of the mutations reported to date, including frameshifts and missense, nonsense, and splice-site mutations. This assay does not detect intronic mutations, 5'UTR or 3'UTR mutations, or genomic rearrangements.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Treacher Collins Syndrome

Test Methods	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	*TCOF1* sequence alterations	100% of reported mutations [1]	Clinical Testing

1. Teber et al (2004) reported a 78% clinical sensitivity with 8/36 individuals who had unequivocal features of TCS and no mutation in *TCOF1*.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

Molecular testing should be considered for any individual presenting with at least two major features or three minor features of TCS.

Because of the varying degree of presentation of clinical features of TCS, molecular testing is indicated for individuals with any degree of severity of TCS features for confirmation of a diagnosis.

Genetically Related (Allelic) Disorders

TCOF1 mutations have not been associated with any other phenotypes.

Clinical Description

Natural History

Significant clinical variability is common in Treacher Collins syndrome (TCS), both among affected families and among individuals in the same family [Posnick & Ruiz 2000, Teber et al 2004]. While some individuals may be so mildly affected as to go undiagnosed, others can have severe facial involvement and life-threatening airway compromise [Edwards et al 1996].

Classic features of TCS are bilaterally symmetric and evident at birth.

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, choanal 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.

Conductive hearing loss in individuals with TCS is usually attributed to middle ear anomalies including hypoplasia or absence of the ossicles or middle ear cavities. The inner ear structures are typically normal. External ear anomalies including absent, small or rotated ears are typical of individuals with TCS, and some may also present with atresia or stenosis of the external auditory canals.

Ophthalmologic defects, including coloboma of the lower eyelid, are present in the majority of individuals with TCS and should be addressed to protect the cornea. Vision loss can occur and may be associated with refractive errors, anisometropia, and/or strabismus.

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

Da Silva Dalben et al (2006) found dental anomalies in 60% of individuals with TCS, with one to eight anomalies per individual. Anomalies identified included tooth agenesis (33.3%), enamel opacities (20%), and ectopic eruption of the maxillary first molars (13.3%).

Less frequently observed features in individuals with TCS:

- Nasal deformity
- High-arched palate
- Angle class II anterior open-bite malocclusion
- Vision loss (37%)

Abnormalities occasionally observed in individuals with TCS:

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

- Choanal atresia
- Macrostomia

The presence and severity of external auditory canal defects correlates highly with the presence and severity of middle ear defects [Posnick 1997].

Although mild developmental delay has been reported, intelligence is usually normal.

Fertility is normal.

Genotype-Phenotype Correlations

The phenotype cannot be predicted by the genotype [Edwards et al 1997, Splendore et al 2000, Teber et al 2004].

Data presented by Teber et al (2004) suggest preliminary evidence that conductive hearing loss is significantly less common in individuals with mutations in the 3' ORF.

Penetrance

Until recently, penetrance in TCS was believed to be complete.

- Reduced penetrance (i.e., absence of clinical or radiographic findings of TCS in individuals with a pathogenic *TCOF1* mutation), suspected in mapping studies, was confirmed by Marres et al (1995) who detected, by clinical findings and linkage analysis, the first convincing case of an individual who must have the gene mutation but did not express the phenotype.
- Katsanis et al (2003) identified the recurrent 4369_4373delAAGAA mutation in an affected mother and son; prenatal testing confirmed the mutation in a subsequent pregnancy, which resulted in the birth of a child who did not have at birth the clinical features of TCS present in the mother or half-sibling, including downward-slanting eyes with lower eyelid coloboma, mandibular hypoplasia, and microtia. It is now evident that, although incomplete penetrance is rare, both variable expressivity and reduced penetrance must be considered, particularly in the prenatal setting.
- Incomplete penetrance in parents of an affected child has since been reported by Dixon et al (2004) for mutations 2490delA (exon 15) and 2853_2854insT (exon 16).
- Suspected germline mosaicism of the mutation 1639_1640delAG was reported by Shoo et al (2004), whereby the mutation was detected in the peripheral blood but not in skin fibroblasts of an unaffected mother of a child diagnosed with TCS.
- It is unknown if the previous reports of two affected individuals born of normal parents represent genetic heterogeneity or an undetected alteration in *TCOF1* [Splendore et al 2000].

Anticipation

An apparent increased severity in successive generations is attributed to ascertainment bias. Splendore, Jabs et al (2002) noted that probands were more likely to have ear malformations than their parents and concluded that ear abnormalities seemed to be an important factor in seeking medical evaluation.

Nomenclature

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

Prevalence

The prevalence of TCS is estimated to be between 1:10,000 and 1:50,000 [Fazen et al 1967, Argenta & Iacobucci 1989, Gorlin et al 2001].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Features of Treacher Collins syndrome (TCS) are also associated with Goldenhar syndrome, Nager syndrome, Miller syndrome, Pierre Robin sequence, and nonsyndromic mandibular hypoplasia.

In TCS, coloboma is present in the lower eyelid, rather than in the upper eyelid as in Goldenhar syndrome.

In Nager and Miller syndromes, individuals present with limb deformities in addition to mandibular dysostosis.

Unlike TCS, the features associated with Pierre Robin sequence, including micrognathia, glossoptosis, and airway obstruction with or without cleft palate deformity, tend to self-correct without intervention [Singh & Bartlett 2005].

Individuals with nonsyndromic mandibular hypoplasia have severe mandibular deficiencies (including TMJ ankylosis, aglossia/microglossia, and rare craniofacial cleft) and progressive micrognathia or retrognathia [Singh & Bartlett 2005]. In one study, 52 of 266 individuals with congenital mandibular hypoplasia presented with TCS [Singh & Bartlett 2005]. Molecular diagnosis was not confirmed on these individuals.

The *TCOF1* alterations 4096_4098delAAG and 4329_4331delGAA have been associated with Goldenhar syndrome and Nager syndrome, respectively [Ellis et al 2002; Splendore, Passos-Bueno et al 2002].

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

In infants, evaluation should include assessment of the following:

- 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 Deafness and Hereditary Hearing Loss Overview)
- Ophthalmologic evaluation with attention to extraocular movement, corneal exposure, and visual acuity

During the first six months of life, a craniofacial CT scan (axial and coronal slices) is indicated to document the anatomy of the head and neck and the external auditory canal, middle ear, and inner ear.

Assessment for dental anomalies should be made when teeth have erupted.

Treatment of Manifestations

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

Procedures for surgical intervention for the airway, if needed, are standard, primarily for improving the respiratory function or restoring patency of the nostrils and distraction of the mandible [Kobus & Wojcicki 2006]. Management of the airway in neonates usually includes special positioning of the infant or tracheostomy. With proper management, life expectancy approximates that of the general population.

Gastrostomy may be needed to assure adequate caloric intake while protecting the airway [Marszalek et al 2002].

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 [Marres 2002].

Craniofacial reconstruction is often necessary [Posnick 1997]. Generally, bone reconstruction precedes soft tissue corrections. Reconstruction can prevent the progression of facial asymmetry. Recommendations by Posnick (1997) for reconstruction include the following:

- Repair of cleft palate, if present, at age one to two years [Kobus & Wojcicki 2006]
- Zygomatic and orbital reconstruction when the cranio-orbitozygomatic bony development is complete (~5-7 years)
- Maxillomandibular reconstruction
  - Type I (mild) and type IIA (moderate) malformation: between age 13 and 16 years
  - Type IIB (moderate to severe malformation): at skeletal maturity
  - Type III (severe malformation): between age six and ten years

Orthognathic procedures are typically indicated before age 16 years.

Misaligned teeth often require orthodonture.

Nasal reconstruction, if needed, should follow orthognathic surgeries.

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 affected individuals with bilateral microtia and/or narrow ear canals.

Therapies Under Investigation

Search ClinicalTrials.gov for access to 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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Treacher Collins syndrome (TCS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 40% of individuals diagnosed with TCS have an affected parent.
- About 60% of probands with TCS have the disorder as the result of a *de novo* gene mutation [Jones et al 1975, Splendore et al 2000].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include molecular genetic testing for the mutation found in the proband and, if no mutation is found, radiographic examination by Waters' view, which may reveal mild zygomatic arch hypoplasia or even aplasia [Marres 2002].

Note: Although 40% of individuals diagnosed with TCS have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members or the rare occurrence of incomplete penetrance in a parent.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%. The specific malformations or their severity cannot be predicted.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If a pathogenic mutation cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. One instance of germline mosaicism has been reported [Shoo et al 2004]; it is unknown if the reports of clinically affected sibs born to clinically normal parents represent other examples of germline mosaicism or genetic heterogeneity.

Offspring of a proband

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

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected or to have a *TCOF1* mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible

non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk for TCS is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed. The presence of a *TCOF1* mutation detected by prenatal testing does not predict the specific malformation(s) or their severity. The possibility of incomplete penetrance of the common 4369_4373delAAGAA mutation must be considered in providing counseling and interpretation of prenatal diagnostic test results to parents.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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 (slanting forehead, microphthalmos, micrognathia), and abnormal fetal swallowing is possible [Rotten et al 2002, Tanaka et al 2002]. Diagnostic features in a mildly affected fetus are likely to be missed.

Requests for prenatal testing for conditions such as TCS that do not affect intellect and have treatment available are not common. 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. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Treacher Collins Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
TCOF1	5q32-q33.1	Treacle protein

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Treacher Collins Syndrome

154500	TREACHER COLLINS-FRANCESCHETTI SYNDROME; TCOF
606847	TCOF1 GENE

Table C. Genomic Databases for Treacher Collins Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD
TCOF1	TCOF1	6949 (MIM No. 606847)	TCOF1

For a description of the genomic databases listed, click here.

Normal allelic variants: *TCOF1* contains 27 coding exons, three of which are alternatively spliced in-frame (6A, 16A, and 19), and an additional exon containing the 3'UTR [So et al 2004]. The longest transcript 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) followed by a 507-bp 3' UTR [Dixon, Edwards et al 1997]. A number of apparently non-pathogenic polymorphisms (≥18) and rare variants (≥17) have been identified [Splendore et al 2000; Ellis et al 2002; Splendore, Jabs et al 2002; Dixon et al 2004]. See TCOF1 Mutation Database [Splendore et al 2005].

Pathologic allelic variants: More than 100 disease-causing mutations in *TCOF1* have been documented in individuals with Treacher Collins syndrome (TCS) [Gladwin et al 1996; TCSCG 1996; Edwards et al 1997; Wise et al 1997; Splendore et al 2000; Ellis et al 2002; Splendore, Jabs et al 2002; Dixon et al 2004; Horiuchi et al 2005]. The majority of mutations found to date are frameshift mutations leading to a premature termination of the transcript caused by an insertion or deletion. Mutations span the entire gene. Although several mutations have occurred more than once, only one mutation, 4369_4373delAAGAA, has been identified as commonly recurrent. This mutation is present in 16% of individuals with an identifiable mutation. The majority of the mutations found to date in *TCOF1* are small deletions or insertions (66%), though splice site (16%), nonsense (13%) and missense (5%) mutations have also been identified. However, the number of nucleotide substitutions may be underestimated as a result of the methodology of detecting the known mutations.

Normal gene product: The 144-kd treacle protein comprises 1488 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, Hovanes et al 1997; 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 may also be involved in rDNA transcription, nucleologenesis, or trafficking of proteins or ribosomal subunits between the nucleolus and cytoplasm [Winokur & Shiang 1998].

Abnormal gene product: Mutations in *TCOF1* lead to haploinsufficiency of the treacle protein [Isaac et al 2000]. Because the majority of mutations lead to the introduction of a premature termination codon, it is likely that RNA transcripts from the abnormal gene are lost as a result of nonsense-mediated RNA degradation leading to loss of protein from the abnormal gene and haploinsufficiency in the affected individual. Missense mutations 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 [Marsh et al 1998, Jones et al 1999, Dixon et al 2000, Isaac et al 2000].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Treacher Collins syndrome

The Treacher Collins Foundation
P.O. Box 683
Norwich VT 05055-0683

AboutFace International
123 Edward Street Suite 1003
Toronto Ontario
Canada M5G 1E2
Phone: 800-665-FACE (800-665-3223)
Fax: 416-597-8494
Email: info@aboutfaceinternational.org
www.aboutfaceinternational.org

my baby's hearing
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

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

Marsh KL, Dixon MJ. Treacher Collins syndrome. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 246. www.ommbid.com. modified 2002

Chapter Notes

Revision History

- 27 October 2006 (me) Comprehensive update posted to live Web site
- 20 July 2004 (me) Review posted to live Web site
- 1 March 2004 (shk,gc) Original submission

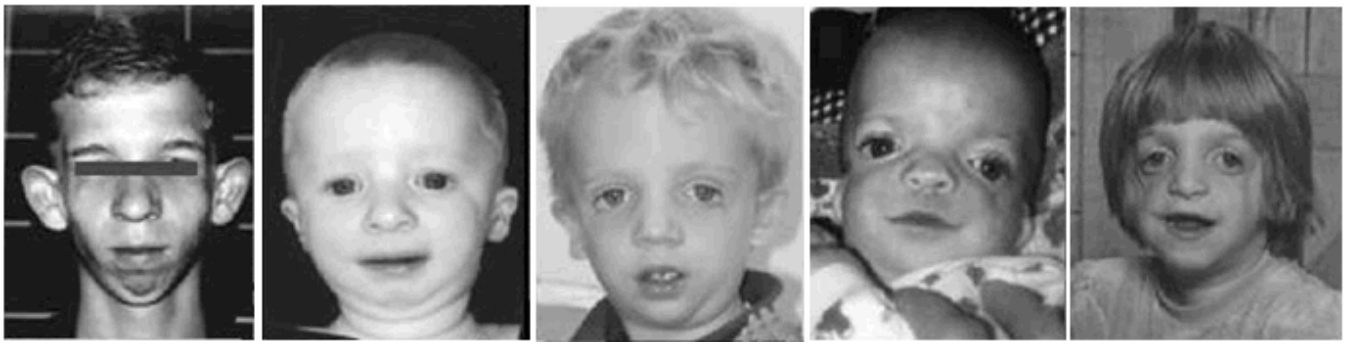

Figure 1. Individuals with TCS and detected *TCOF1* mutation
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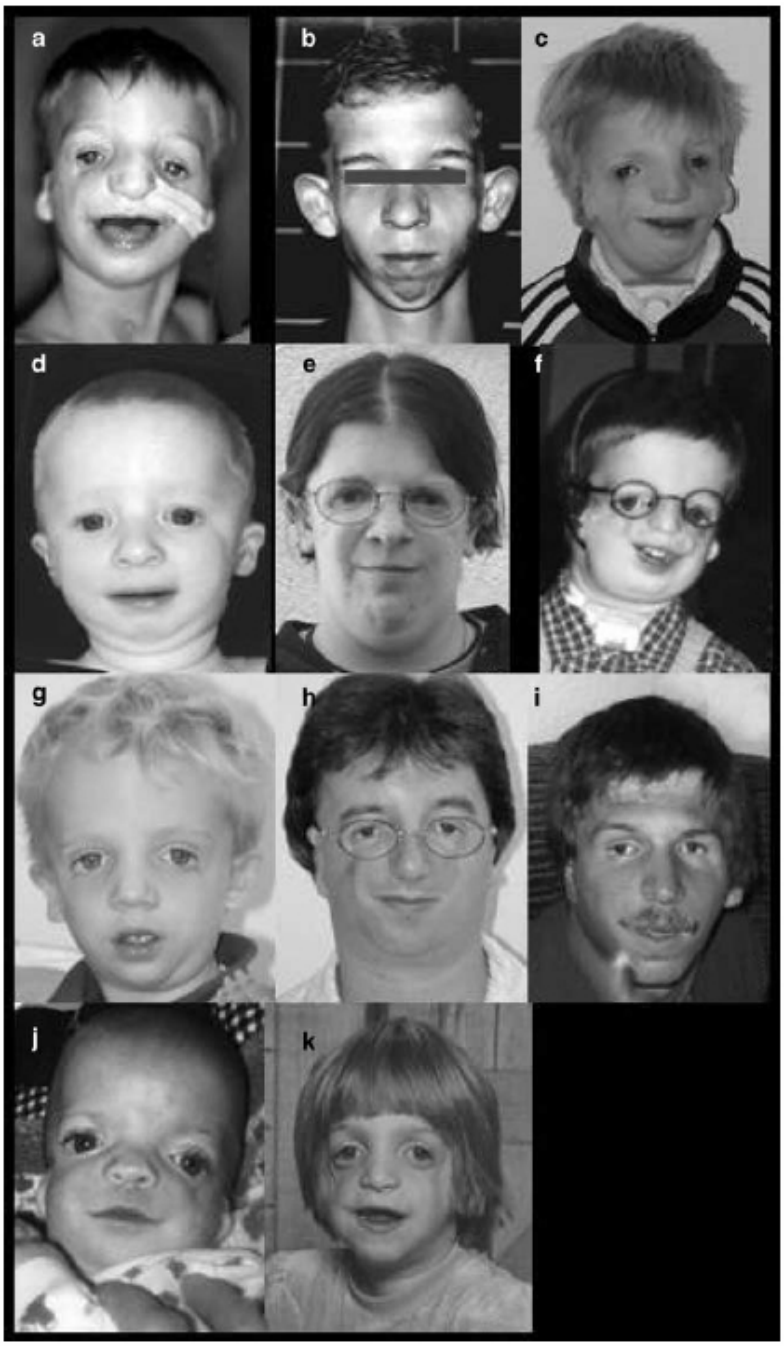

Figure 2. Patients with TCS and detected *TCOF1* mutation, (a-k) are arranged according to the location of the mutation in the *TCOF1* gene.
a) Patient M17639 with M1I
b) Patient M17807 with 121X
c) Patient M20194 with 209X
d) Patient M19731 with K367X
e) Patient M18982 with Q563X
f) Patient M18923 with 795X
g) Patient M17629 with Q818X

h) Patient M18013 with 854X
i) Patient M18774 with G848X
j) Patient M17995 with c.2629-3A>G
k) Patient M18293 with 1392X

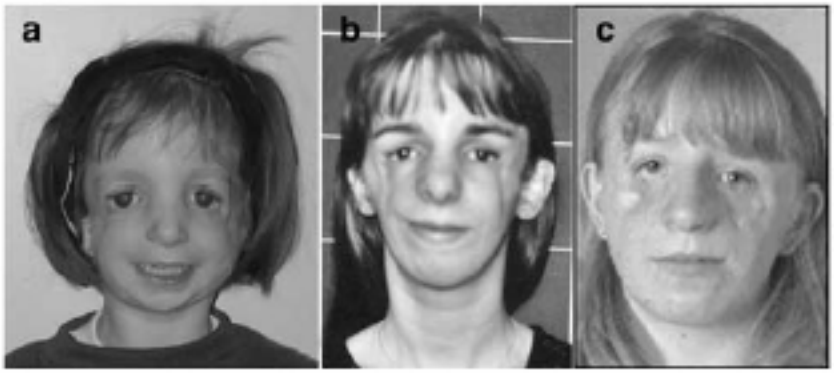

Figure 3. Three of the eight patients with a clinical unequivocal diagnosis of TCS without detected *TCOF1* mutation
a) Patient M17739
b) Patient M18662
c) Patient M17652

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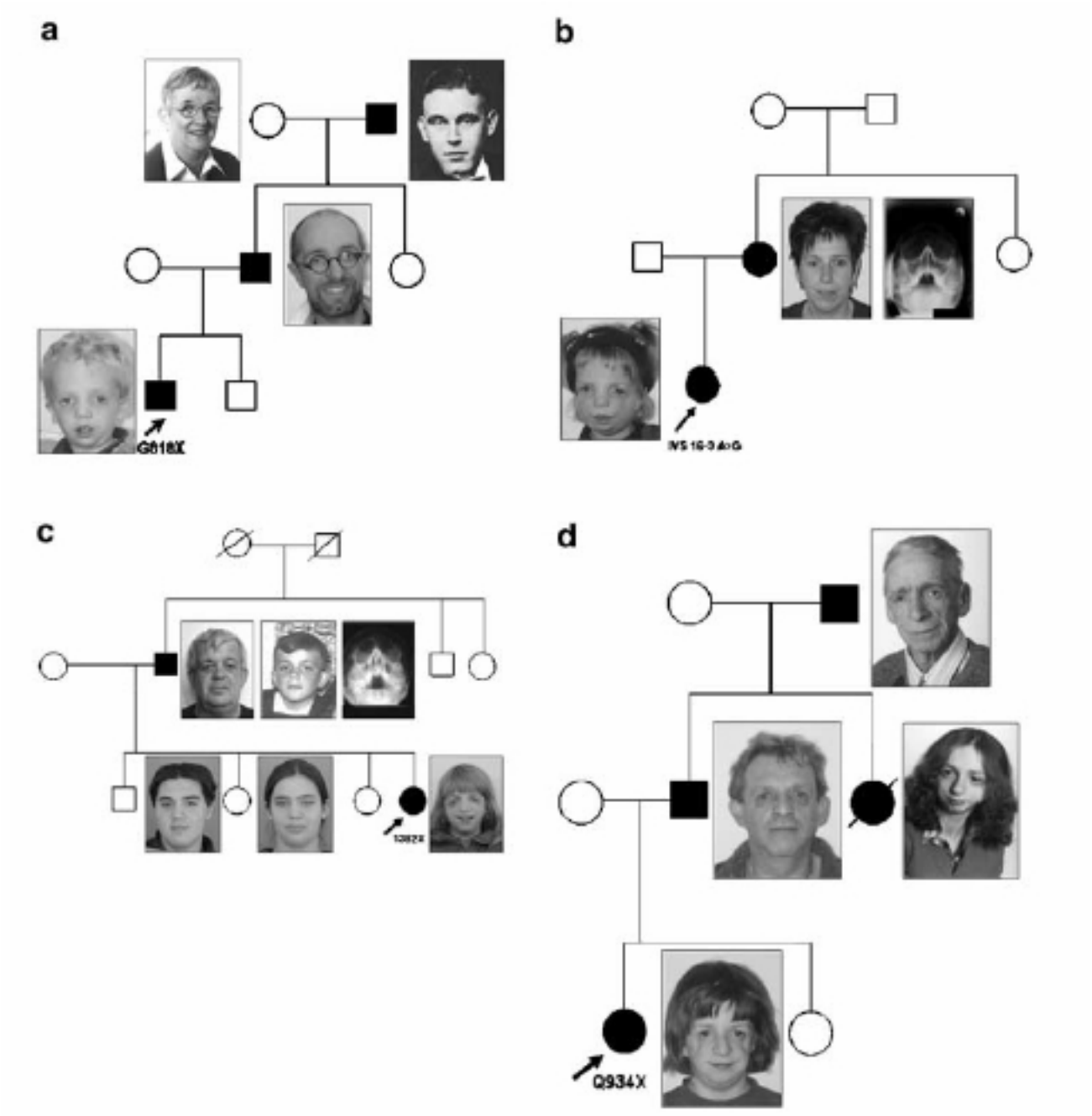

Figure 4. Intrafamilial variation

a. Pedigree of family M17629. The proband shows the characteristic facial phenotype with downward slanting palpebral fissures, hypoplastic zygomatic complex, slightly dysplastic ears, conductive hearing loss, and hypoplasia of mandibula. A stop mutation (G818X) was identified to be the causative mutation. The proband's father was much more mildly affected and his beard and his glasses mask the phenotype: conductive hearing loss was lacking and his ears were surgically corrected. The paternal grandmother has a facial phenotype similar to her son and a positive family history for dysplastic ears. Surprisingly, the paternal grandfather, who has no facial characteristics for TCS, carries the mutation. He might be an example of non-penetrance, although he denied personal investigation and radiographs.

b. Pedigree of family M17995. The proband is severely affected with hypoplasia of the zygomatic complex, bilateral microtia with atresia of the external auditory canal, cleft palate, and bilateral choanal atresia. A splice mutation (c.2629-3A>G) seems to be causative in this patient. The mother has a hypoplasia of the mandible and clinical suspicion of hypoplasia of right zygomatic complex, although she has a normal slant of palpebral fissures. Radiographic examination (Waters' projection) clearly shows the hypoplasia of the zygomatic complex. We consider that the mother is mildly affected.

c. Family M18293. The propositus is severely affected with bilateral microtia, hypoplastic zygomatic complex, and antimongoloid slant of palpebral fissures. We received some photographs of the father and suggested that he was not affected. After molecular investigation and knowing him as a mutation carrier, we were able to personally investigate him. The only abnormal facial findings were his slightly downward slanting palpebral fissures. It is much easier to recognize the mild facial phenotype in childhood. Waters' projection showed bilateral hypoplasia of zygomatic complex with unilateral left-sided aplastic zygomatic arch. The brother and the elder sister of the propositus do not carry the mutation.

d. Family M22186. The propositus is severely affected. Her father only shows mild hypoplasia of the zygomatic complex. He himself believed that he was unaffected; diagnosis was established after birth of his affected daughter. His sister was severely affected (not molecularly proved) and died at the age of 20 years due to cardiac insufficiency. The paternal grandfather has a mild hearing loss and downward slanting palpebral fissures. He is most likely mildly affected, but DNA was not available.