

## Cardiovascular Malformations in Patients with Treacher Collins Syndrome: A Systematic Review

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**Background:** Cardiovascular malformation is an uncommon extra-craniofacial presentation in a patient with Treacher Collins syndrome [TCS], however, a systematic review of this manifestation is lacking.

**Objective:** To systematically review of prevalence and type of cardiovascular malformations in patients with TCS.

**Materials and Methods:** A systematic literature search was conducted through PubMed, Google Scholar, Cochrane central data bases, and OMIM using the medical subject heading “Treacher Collins syndrome” for articles published between 1996 and March 2018.

**Results:** Of the 15 studies included, there were 159 patients who had a clinical diagnosis of TCS and 144 (91%) of these patients had documented gene mutations [i.e., *TCOF1* (114 patients), *POLRIC* (3 patients), or *POLRID* (27 patients)]. Of the 144 patients who had been documented gene mutations, eight (6%) patients had cardiovascular malformations. All 8 patients with cardiovascular malformations had only the *TCOF1* gene mutations. The type of cardiovascular malformations were atrial septal defect [ASD] (5 cases), patent ductus arteriosus [PDA] (2 cases) and ASD + PDA (1 case).

**Conclusion:** The prevalence of cardiovascular malformation significantly increases in patients with TCS compared with the general population. Cardiovascular malformation found in a patient with TCS is likely to present as a simple lesion.

**Keywords:** Treacher Collins syndrome, Treacher Collins-Franceschetti syndrome, Cardiovascular malformations, Congenital heart diseases, Prevalence, Type, *TCOF1*, *POLRIC*, *POLRID*, Gene

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Treacher Collins syndrome [TCS] [Online Mendelian Inheritance in Man (OMIM): TCS-1: 154500, TCS-2: 613717, TCS-3: 248390], sometimes known as Treacher Collins-Franceschetti syndrome, is a craniofacial malformation syndrome resulting from developmental disorders of the first and second pharyngeal arches<sup>(1)</sup>, and it is the most common mandibulofacial dysostosis, occurring in ~1 in 50,000 live births in the general population<sup>(1,2)</sup>. The syndrome is named after Dr. Edward Treacher Collins<sup>(3)</sup> and Dr. Adolphe Franceschetti<sup>(4)</sup> who first described the syndrome. Its major craniofacial abnormalities include

downward slanting of the palpebral fissures (eyelids) (anti-mongoloid slant eyes), malar and mandibular hypoplasia, coloboma (notch) of the lower eyelid, microtia (small ear) and conductive hearing loss<sup>(5-7)</sup>. Associated malformations frequently include dental abnormalities, projection of the scalp hair into the lateral cheek area, and cleft palate<sup>(1,5)</sup>.

Previously, diagnosis of TCS was based on the typical craniofacial anomalies<sup>(3,4)</sup>. Recently, mutation abnormalities of three genes (*TCOF1* [cytogenetic location: 5q32-q33], *POLRIC* [cytogenetic location: 6p21.1], and *POLRID* [cytogenetic location: 13q12.2]) have been identified in the majority of patients with craniofacial features compatible with TCS<sup>(6-10)</sup>. In the case of *TCOF1* mutation [TCS-1], the mode of inheritance is autosomal dominant, while for the *POLRIC* mutation (TCS-3), it is autosomal

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recessive<sup>(6-9)</sup>. Medially, the *POLR1D* mutation (TCS-2) can be either autosomal dominant or autosomal recessive<sup>(6-9)</sup>. The *TCOF1*, *POLR1C*, and *POLR1D* genes are responsible for ribosome biogenesis, which is a general mechanism for cell proliferation and cell growth<sup>(7-10)</sup>. Mutations of these genes result in defects to RNA biogenesis and abnormal ribosome functions<sup>(1,6-9)</sup>. The spectrum of clinical presentations of TCS can be accurately determined with a molecular assessment as a patient with an uncommon presentation can be included in the spectrum of the syndrome if they have *TCOF1*, *POLR1C*, and/or *POLR1D* gene mutations<sup>(6-10)</sup>.

Although craniofacial presentations is a major concern for this syndrome, cardiovascular abnormalities have rarely been reported<sup>(5,8,11-27)</sup>. Since there has been no previous systematic review of cardiovascular involvement of the syndrome, the authors of the current study summarized the respective frequencies and types of cardiovascular malformations in cohorts of patients with genetically documented TCS in order to improve awareness of cardiovascular malformations in patients with the syndrome.

## Materials and Methods

### Data sources

A systematic literature search was conducted using electronic databases (viz., PubMed, Google Scholar, Cochrane central data bases, and OMIM), using the medical subject heading “Treacher Collins syndrome” for articles published between January 1996 and March 2018. The eligible articles in all languages were included and screened. The titles and abstracts of the relevant articles were assessed independently by the two authors (MP and OP) to identify potential articles for which full text publications were retrieved. Reference lists of included articles were examined for additional relevant articles that may have been missed in the search.

### Definitions

Cardiovascular malformation was defined as a defect in the structure and function of the heart or great vessel presented at birth.

Treacher Collins syndrome was defined as typical clinical findings, including downward slanting of the palpebral fissures (eyelids), (anti-mongoloid slant eyes), malar and mandibular hypoplasia, coloboma (notch) of the lower eyelid, microtia (small ear), and conductive hearing loss. In these cases, a molecular genetic assessment was used

to confirm the diagnosis of TCS (i.e., a mutation in the *TCOF1*, *POLR1C* and *POLR1D* genes).

### Study selection

All published articles and case reports of patients with TCS who had a molecular diagnosis of the *TCOF1*, *POLR1C* and *POLR1D* genes were considered for inclusion. When a study was eligible for inclusion, the authors (MP and OP) independently verified the frequencies and types of cardiovascular malformations or congenital heart diseases to check for accuracy. Any reports that presented only clinical features without gene confirmations data were excluded. Disagreements were resolved by consensus.

### Data extraction

The data extracted from each research article included (a) total number of patients with clinical diagnosis of TCS, (b) number of patients with gene mutation identified, (c) number of cases with cardiovascular malformations, and (d) types of cardiovascular malformations.

### Quality assessment

Studies were assessed on completeness of data. The molecular assessment for each study was determined as patients with cardiovascular malformations were included within the spectrum of the syndrome if gene mutations were confirmed.

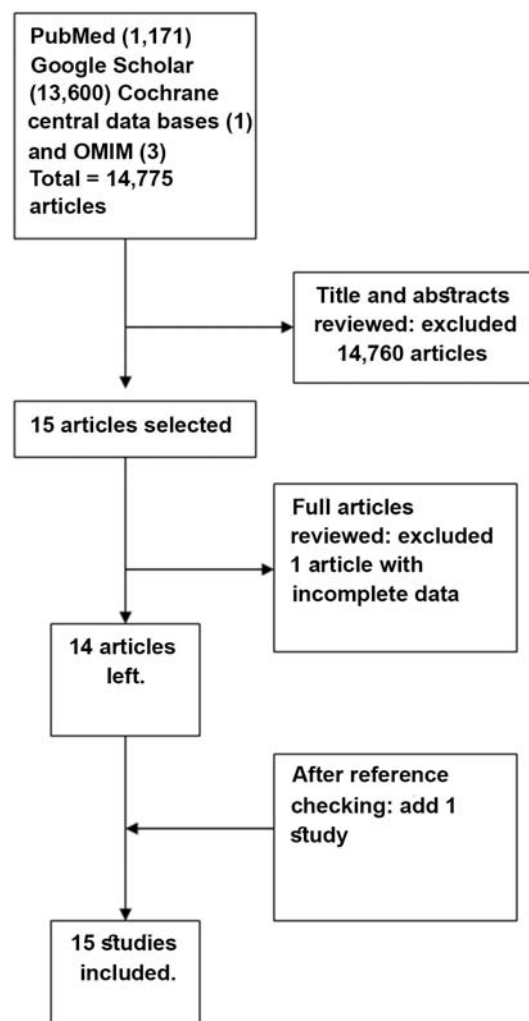
### Statistical analyses

The frequencies of cardiovascular malformations in TCS were reported as a percentage.

## Results

The database search revealed 14,775 relevant articles. After applying the study selection criteria, 14,760 articles were excluded, so only 15 articles met the selection criteria and were extensively reviewed. After the critical review, 1 article was excluded due to incomplete data. After reference checking of the included 14 articles, an additional study was found. This additional study was not initially retrieved because it had not been indexed in the searched databases. Ultimately, 15 articles were eligible for inclusion in this systematic review (Figure 1).

From among the 15 studies included, there were 159 patients who had a clinical diagnosis of TCS and 144 (91%) of these patients had documented gene mutations [i.e., *TCOF1* (114 patients), *POLR1C* (3 patients), or *POLR1D* (27 patients)]. Of the 144



**Figure 1.** Flow diagram of the articles included into this systematic review.

patients who had documented gene mutations, eight (6%) patients had cardiovascular malformations (Table 1). All 8 patients with cardiovascular malformations had only the *TCOF1* gene mutation. The types of cardiovascular malformations included atrial septal defect [ASD] (5 cases), patent ductus arteriosus [PDA] (2 cases), and ASD + PDA (1 case) (Table 1).

## Discussion

In this systematic review, the pooled average frequency of cardiovascular malformations was found in 6% of patients with TCS whose diagnoses were confirmed by molecular gene studies. In the general population, it is estimated that ~1% of live birth infants have congenital cardiovascular malformations<sup>(28-30)</sup>. The

significance of this finding is that patients with TCS have higher prevalence of cardiovascular malformations than the general population. Although cardiovascular malformation is an uncommon presentation in a patient with TCS, this malformation should be carefully evaluated in each patient with a confirmed diagnosis of TCS. Physicians providing care to patients with TCS should, thus, be aware of the potential for cardiovascular malformation association of this syndrome.

The type of cardiac malformations in genetically-unconfirmed case reports of TCS has been documented to be atrial and ventricular septal defects, patent ductus arteriosus, coarctation of the aorta, and sinus of Valsalva aneurysm<sup>(23-27)</sup> (Table 2). The present review including gene-mutation confirmed TCS had similar findings regarding the types of cardiovascular malformations (i.e., atrial septal defect and patent ductus arteriosus). Cardiovascular malformation in a patient with TCS is most likely to present as a simple lesion that is not difficult to manage during patient care or craniofacial surgery.

TCS results from mutations in the *TCOF1*, *POLR1C* or *POLR1D* genes, resulting in abnormal craniofacial developments. According to molecular studies of the 8 patients with cardiovascular malformations, 7 had frame shift mutations and 1 had a non-sense mutation of *TCOF1* gene (Table 1). *TCOF1* gene is responsible for encoding treacle protein which involved in mRNA formation in neural crest cells during embryogenesis<sup>(7,24)</sup>. Abnormalities in this pathway are hypothesized to lead to early neural crest cell apoptosis and neural crest cell depletion in pharyngeal arches 1 and 2<sup>(1,7)</sup>. These events result in cartilage, bone, and connective tissue hypoplasia, which leads to the characteristic craniofacial abnormalities associated with TCS and is also involved in the etiology of cardiovascular malformation<sup>(23-26)</sup>.

With respect to pathogenesis, the most important finding may be that there are relatively fewer frequencies of cardiovascular malformation found in TCS in comparison with other syndromes with abnormal development of neural crest cells (i.e., the 22q11.2 deletion syndrome or Goldenhar syndrome)<sup>(28,29)</sup>. A better understanding of the pathogenesis of the syndrome could help identify the etiologies of the various cardiovascular malformations involved. Although some TCS patients may show apparent cardiovascular malformations or congenital heart diseases, such presentations are sometimes overlooked and under-reported.

**Table 1.** Frequency and type of cardiovascular malformations in 144 patients with gene-mutation confirmed Treacher Collins syndrome.

Authors/Years	Number of patients with gene mutation identified/Total number of patients with clinical diagnosis of TCS	Number of cases with cardiovascular malformations (N)			Number of cases with cardiovascular malformations (N)/Total numbers of patients with gene-mutation confirmed TCS (%)	Types of cardiovascular malformations (N)
		N/Number of patients with <i>TCOF1</i> gene mutation	N/Number of patients with <i>POLRIC</i> gene mutation	N/Number of patients with <i>POLRID</i> gene mutation		
Giabicani et al <sup>(11)</sup> /2017	1/1	0/1	ND	ND	0/1 (0)	NA
Vincent et al <sup>(5)*</sup> /2016	65/70	7 <sup>a</sup> /60	ND	0/5	7 <sup>a</sup> /65 (11)	ASD (4), PDA (2), ASD with hypertrophic cardiomyopathy (1)
Hao et al <sup>(12)</sup> /2016	3/3	0/3	ND	ND	0/3 (0)	NA
Wang et al <sup>(13)</sup> /2014	3/3	0/3	ND	ND	0/3 (0)	NA
Schaefer et al <sup>(9)</sup> /2014	2/2	0/0	ND	0/2	0/2 (0)	NA
Zhang et al <sup>(14)</sup> /2013	2/2	0/2	ND	ND	0/2 (0)	NA
Bauer et al <sup>(15)</sup> /2013	2/2	0/2	ND	ND	0/2 (0)	NA
Ulusal et al <sup>(16)</sup> /2013	1/1	0/1	ND	ND	0/1 (0)	NA
Marszalek-Kruk et al <sup>(17)</sup> /2012	2/2	0/2	ND	ND	0/2 (0)	NA
Dauwerse et al <sup>(8)*</sup> /2011	23/23	ND	0/3	0/20	0/23 (0)	NA
Li et al <sup>(18)</sup> /2009	1/1	1 <sup>b</sup> /1	ND	ND	1 <sup>b</sup> /1 (100)	ASD + PDA + mesocardia (1)
Writzl et al <sup>(19)</sup> /2008	1/1	0/1	ND	ND	0/1 (0)	NA
Horiuchi et al <sup>(20)</sup> /2005	9/11	0/9	ND	ND	0/9 (0)	NA
Teber et al <sup>(21)*</sup> /2004	28/36	0/28 <sup>c</sup>	ND	ND	0/28 <sup>c</sup> (0)	NA
Horiuchi et al <sup>(22)</sup> /2004	1/1	0/1	ND	ND	0/1 (0)	NA
Total	144/159	8 <sup>d</sup> /114	0/3	0/27	8 <sup>d</sup> /144 (6)	ASD (4), PDA (2), ASD with hypertrophic cardiomyopathy (1), ASD + PDA + mesocardia (1)

TCS = Treacher Collins syndrome; N = number of cases with cardiovascular malformations; ND = not determined; NA = not available; ASD = atrial septal defect, secundum type; PDA = patent ductus arteriosus

<sup>a</sup> Among the seven patients with cardiovascular malformations, six had a frame shift mutation and one had a non-sense mutation of the *TCOF1* gene.

<sup>b</sup> A patient with a cardiovascular malformation had a frame shift mutation of the *TCOF1* gene.

<sup>c</sup> The sister of a patient's father had clinical features of TCS (not molecular proved) with cardiac insufficiency.

<sup>d</sup> Overall the eight patients with cardiovascular malformations, seven had a frame shift mutation and one had a non-sense mutation of *TCOF1* gene.

<sup>e</sup> Prospective studies

**Table 2.** Cardiovascular malformations associated with genetically unconfirmed Treacher Collins syndrome

Authors/Years	Types of cardiovascular malformations (numbers)
Dinlen et al <sup>(23)</sup> /2014	ASD + VSD + PA + persistence of LSVC (1) <sup>ab</sup>
Dobrilovic et al <sup>(24)</sup> /2013	Sinus of Valsalva aneurysm + AR (1)
Albarran et al <sup>(25)</sup> /2013	Sinus of Valsalva aneurysm (1)
Tsitouridis et al <sup>(26)</sup> /2007	ASD + VSD + Coarctation of aorta (1)
Gottsegen et al <sup>(27)</sup> /1956	VSD (1)

ASD = atrial septal defect, secundum type; VSD = ventricular septal defect; PA = pulmonary valve atresia; LSVC = left superior vena cava; AR= aortic regurgitation.

<sup>a</sup> Modified Blalock-Taussig shunt at 6<sup>th</sup> day of life and sudden cardiac arrest at 30<sup>th</sup> day of life.

<sup>b</sup> It was not clear whether cardiovascular malformations were parts of the TSC or caused by paroxetine exposure

Limitations of this study lie in its methodology. The available studies were mostly retrospective case series and case reports with few patients and sometimes a lack of screening for extra-craniofacial features (e.g., cardiovascular malformations). The methodology used to diagnose cardiovascular malformation or congenital heart disease is not always presented; nevertheless, the current literature review provides comprehensive data suggesting that cardiovascular malformation is occurring with a significantly increased frequency in TCS patients.

In conclusion, although cardiovascular malformation is an uncommon clinical presentation in TCS, the prevalence of cardiovascular malformation significantly increases in TCS patients compared with the general population. The current systematic literature review suggests that the cardiovascular malformation found in patients with TCS is likely to present with a simple lesion and a low operative risk.

#### What is already known on this topic?

The prevalence of cardiovascular malformations in patients with TCS is low.

#### What this study adds?

1) Patients with TCS have a higher prevalence of cardiovascular malformations than the general population.

2) Cardiovascular malformation in a patient with TCS is most likely to present as a simple lesion such as atrial septal defect and patent ductus arteriosus.

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#### Potential conflicts of interest

The authors declare no conflicts of interest.

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