*Special Article*

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

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

***Objective:*** Our aim was to systematically review the prevalence and type of GI malformations in patients with TCS.

***Materials and Methods:*** A systematic literature search was conducted for articles published on "Treacher Collins syndrome" between 1996 and March 2018 using PubMed, Google scholar, Cochrane central data bases, and OMIM.

***Results:*** Of the 15 studies included, we found 159 patients who had a clinical diagnosis of TCS; 144 (91%) of whom had documented gene mutations [i.e., *TCOF1* (114 patients), *POLR1C* (3 patients), or *POLR1D* (27 patients)]. Of the 144 patients who had been documented gene mutations, 2 (1.4%) patients had GI malformations; both of which had only the *TCOF1* gene mutation. The types of GI malformations included chronic intestinal pseudo-obstruction [CIPO] (1 case) and esophageal regurgitation (1 case).

***Conclusion:*** A GI malformation is an uncommon clinical presentation in a patient with TCS but this type of malformation should be looked for and managed during a craniofacial care.

***Keywords:*** Treacher Collins syndrome, Treacher Collins-Franceschetti syndrome, Gastrointestinal malformations, Frequency, Type, *TCOF1*, *POLR1C*, *POLR1D*, Gene

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Treacher Collins syndrome [TCS], sometimes known as Treacher Collins-Franceschetti syndrome, (Online Mendelian Inheritance in Man [OMIM] TCS1: 154500, TCS2: 613717, TCS3: 248390), is a craniofacial malformation syndrome resulting from developmental disorders of the first and second pharyngeal arches[1], and it is the most common type of mandibulofacial dysostosis occurring in approximately 1 in 50,000 live births[1,2]. The syndrome was described by Dr. Edward Treacher Collins[3] and Dr. Adolphe Franceschetti[4]. The most frequent craniofacial abnormalities include downward slanting of palpebral fissures (anti-mongoloid slant eyes), malar and mandibular hypoplasia, coloboma of lower eyelids, microtia and conductive hearing loss. Frequently associated malformations include dental abnormalities, projection of the scalp hair into the lateral cheek area, and cleft palate[1,5].

Clinically, a diagnosis of TCS is based on the characteristic craniofacial anomalies[3,4]. Since 1996, mutation abnormalities of three genes [*TCOF1* (TCS1, location: 5q32-q33, autosomal dominant inheritance), *POLR1D* (TCS2, location: 13q12.2, autosomal dominant or autosomal recessive inheritances) and *POLR1C* (TCS3, location: 6p21.1, autosomal recessive)]

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have been identified in the majority of patients with craniofacial features compatible with TCS[6-10]. *TCOF1*, *POLR1C*, and *POLR1D* genes have functions for ribosomal biogenesis, which are responsible for cell proliferation and cell growth[7-10]. Mutations of these genes result in defects in RNA biogenesis and abnormal ribosomal functions[1,6-9]. The spectrum of clinical presentations of TCS can be precisely determined using a molecular assessment because patients with an atypical presentation can be included in the spectrum of this syndrome if they have *TCOF1*, *POLR1C*, and *POLR1D* gene mutations[6-10].

Although craniofacial abnormalities are the most frequent presentations of this syndrome, gastrointestinal [GI] malformations have been reported albeit rarely[5,8,9,11-22]. Since there has been no previous systematic review of GI malformations in TCS, the authors summarized the frequencies of GI malformations in cohorts of patients with genetically-documented TCS.

## Materials and Methods

### *Data sources*

Molecular diagnosis of TCS genes has started since 1996[7], so a systematic literature search was conducted for articles using the medical subject heading "Treacher Collins syndrome" published between January 1996 and March 2018. The electronic databases searched included PubMed, Google scholar, Cochrane central data bases, and OMIM. The eligible papers in all languages were included and screened. The titles and abstracts of the relevant articles were assessed independently by two authors (BC and MP) 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. This review protocol followed the PRISMA guideline.

### *Definitions*

Gastrointestinal (alimentary canal or digestive tract) malformations were defined as defects in the structure and function of the mouth, pharynx, esophagus, stomach, small intestine, large intestine, and anus, and included the solid organs of the digestive system (i.e. the liver, pancreas, and gallbladder).

Treacher Collins syndrome was defined as the most frequent craniofacial abnormality; including downward slanting of the palpebral fissures (eyelids), malar and mandibular hypoplasia, coloboma of the lower eyelids, microtia, and conductive hearing loss. Additionally, 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*

The authors (BC and MP) independently verified the prevalence and types of GI malformations to check for accuracy. All published papers and case reports of patients with TCS, who had a molecular diagnosis of the *TCOF1*, *POLR1C* and *POLR1D* genes were considered for inclusion. Any reports that presented only clinical features without gene confirmations data were excluded. Dental and oral cavity malformations were excluded from GI malformations in the current study because they were too closely related to the craniofacial malformation of TCS. Diagnostic disagreements were resolved by consensus.

### *Data extraction*

From each research article, we extracted data on the total number of patients with a clinical diagnosis of TCS, number of patients identified with a gene mutation, number of cases with GI malformations, and types of GI malformations.

### *Quality assessment*

The studies were assessed for completeness of data. Each study was assessed for its documentation of molecular detail, and the type of GI malformation was included in the spectrum of this syndrome if gene mutations were confirmed.

### *Statistical analyses*

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

## Results

The search combination in the databases revealed 14,775 relevant articles. After thorough evaluations—using the study selection criteria—of the titles and abstracts, the authors excluded 14,760 articles. After all, only 15 articles met the study selection criteria and were extensively reviewed. After critical reviews of the full texts, one article was excluded due to incomplete data. From the reference lists of the 14 included articles, an additional study was found. This additional study was not initially retrieved by the original search because it was not indexed in the searched databases. Overall, 15 articles were eligible for inclusion in the systematic

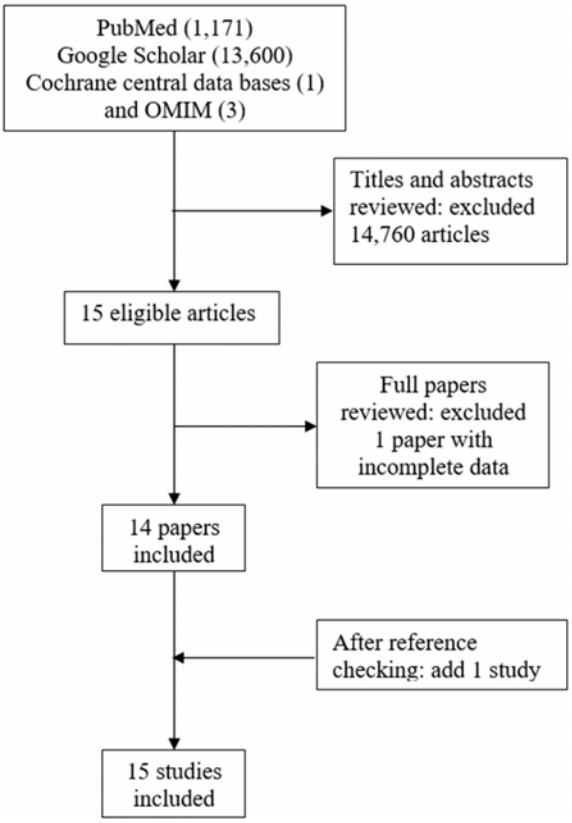


**Figure 1.** Flow diagram of the articles included in the systematic review.

review (Figure 1).

From the 15 studies included, there were 159 patients who had a clinical diagnosis of TCS; among whom 144 (91%) had documented gene mutations [including, *TCOF1* (114 patients), *POLR1C* (3 patients), or *POLR1D* (27 patients)]. Of the 144 patients, 2 (1.4%) had GI malformations (Table 1); both of whom had only the *TCOF1* gene mutation. The types of GI malformations included chronic intestinal pseudo-obstruction [CIPO] (1 case), and esophageal regurgitation (1 case) (Table 1).

## Discussion

In this systematic review, the pool averaged prevalence of GI malformation was 1.4% of patients with TCS whose diagnoses were confirmed by molecular gene studies. In a large population based study, it was estimated that 0.07% of infants are born with GI malformations[21]. Due to differences in methodology among the studies, it cannot be concluded that patients with TCS have a higher prevalence of GI malformations than the general population. Although GI malformation is uncommon in a patient with TCS, each patient with a confirmed diagnosis of TCS should be carefully evaluated to rule out any GI malformations. Physicians providing care to patients with TCS should be aware of the potential for GI disorders associated with this syndrome.

The type of GI malformations in genetically-unconfirmed case reports of TCS have been documented to be tracheoesophageal fistula, rectovaginal fistula, anal atresia, and achalasia[22,23] (Table 2). The present review of gene-confirmed cases of TCS revealed milder involvements of gastrointestinal malformations (i.e., CIPO and esophageal regurgitation) (Table 1). GI malformations found in a patient with TCS should, however, be managed during a patient care or a craniofacial surgery.

A better understanding of the pathogenesis of the syndrome could help to identify the development of various GI malformations encountered in TCS. Although some TCS patients may show apparent GI malformations, such presentations are sometimes overlooked.

Limitations of the current study lie in its methodology. The available studies were mostly retrospective case series and case reports with small numbers of patients and sometimes lacked screening for extra-craniofacial features (i.e., GI malformations). The methodology used to diagnose GI malformation was not always presented. Notwithstanding, this literature review suggests that GI malformations can occur in TCS patients.

In conclusion, although GI malformation is an uncommon presentation in a patient with TCS, the systematic review of literatures suggests that the GI malformation may have to be managed during craniofacial managements.

## What is already known on this topic?

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

## What this study adds?

GI malformation is found in 1.4% in patients with TCS, and this abnormality may have to be managed during a craniofacial care.

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**Table 1.** Prevalence and type of gastrointestinal [GI] malformations in 144 patients with gene-mutation confirmed Treacher Collins syndrome

| Authors/Years | Patients with gene mutation identified/ Total with clinical diagnosis of TCS | Number of cases with GI malformations (N) | | | Cases with GI malformations (N)/ Total with gene-mutation confirmed TCS (%) | Types of GI malformations (N) |
|---|---|---|---|---|---|---|
| | | N/ Patients with TCOF1 gene mutation | N/ Patients with POLR1C gene mutation | N/ Patients with POLR1D gene mutation | | |
| Giabicani et al.[11]/2017 | 1/1 | 1/1 | ND | ND | 1/1 (100) | CIPO (1) |
| Vincent et al.[5]/2016[a] | 65/70 | 0/60 | ND | 0/5 | 0/65 (0) | NA |
| Hao et al.[12]/2016 | 3/3 | 0/3 | ND | ND | 0/3 (0) | NA |
| Wang et al.[13]/ 2014 | 3/3 | 0/3 | ND | ND | 0/3 (0) | NA |
| Schaefer et al.[9]/ 2014 | 2/2 | 0/0 | ND | 0/2 | 0/2 (0) | NA |
| Zhang et al.[14]/ 2013 | 2/2 | 0/2 | ND | ND | 0/2 (0) | NA |
| Bauer et al.[15]/ 2013 | 2/2 | 0/2 | ND | ND | 0/2 (0) | NA |
| Ulusal et al.[16]/ 2013 | 1/1 | 0/1 | ND | ND | 0/1 (0) | NA |
| Marszalek-Kruk et al.[17]/ 2012 | 2/2 | 0/2 | ND | ND | 0/2 (0) | NA |
| Dauwerse et al.[8]/2011[a] | 23/23 | ND | 0/3 | 0/20 | 0/23 (0) | NA |
| Li et al.[18]/2009 | 1/1 | 0/1 | ND | ND | 0/1 (0) | NA |
| Writzl et al.[19]/2008 | 1/1 | 0/1 | ND | ND | 0/1 (0) | NA |
| Horiuchi et al.[20]/2005 | 9/11 | 1/9 | ND | ND | 1/9 (11) | Esophageal regurgitation (1) |
| Teber et al.[21]/2004[a] | 28/36 | 0/28 | ND | ND | 0/28 (0) | NA |
| Horiuchi et al.[22]/ 2004 | 1/1 | 0/1 | ND | ND | 0/1 (0) | NA |
| Total | 144/159 | 2/114 | 0/3 | 0/27 | 2/144 (1.4) | CIPO (1), Esophageal regurgitation (1) |

GI = Gastrointestinal, TCS = Treacher Collins syndrome, N = numbers of cases, ND = not determined, NA = not available, CIPO = chronic intestinal pseudo-obstruction

[a] Prospective studies

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

| Authors/Years | Types of gastrointestinal malformations (numbers) |
|---|---|
| Robb et al[22]/1991 | Tracheoesophageal fistula, rectovaginal fistula, and anal atresia (1) |
| Schneider et al[23]/1987 | Achalasia (1) |

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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