Treacher Collins Syndrome with a Novel Deletion in the TCOF1 Gene

Buşra Eser Çavdartepe, Nadir Koçak, Nafiz Yaşa, Tülin Çora

Treacher Collins syndrome (TCS) is a rare autosomal dominant congenital disorder characterized by various craniofacial malformations. The estimated incidence is 1 in 50,000 live births. Bilaterally symmetric anomalies of the structure are present within the first and second branchial arches. Characteristic facial findings include bilateral hypoplasia of the malar bones and mandible. This syndrome most commonly results from mutations in the TCOF1 gene. Here we present a five-year-old female patient with syndromic appearance and hearing loss. The patient had various facial dysmorphic features and malformed bilateral pinnae and left ear microtia. According to the clinical features, we suspected TCS and sequence analysis of TCOF1 gene was performed. A heterozygous new mutation c.1722_1731delCATCCTCCAG in exon 12 of the TCOF1 gene was detected. It has been determined that this mutation is pathogenic according to the in silico prediction tools. The current study further expands the TCOF1 mutation spectrum.

Keywords: Mutation, TCOF1 gene, Treacher Collins syndrome, hearing loss

INTRODUCTION

Treacher Collins syndrome (TCS) is a disorder of craniofacial development that affects differentiation of the first and the second pharyngeal arches (1, 2). The estimated prevalence of this syndrome is approximately 1 in 50,000 live births (3). Approximately 54%–60% of probands have the disorder as a result of de novo mutations, the rest of the cases are hereditary (4).

TCS occurs as a result of mutations in one of the following three genes: TCOF1, POLR1C, and POLR1D (2). Mutations in the TCOF1 gene, have been found to be responsible for most of the cases. Treacle protein is a protein that in humans is encoded by the TCOF1 gene. Most mutations in the TCOF1 gene result in the truncation of encoded treacle protein, which leads to TCOF1 haploinsufficiency (4, 5). Mutations in the TCOF1 gene lead to a reduction in the amount of treacle protein in cells. This protein is active in the early embryonic development of bone and other tissues in the face. A loss of treacle decreases the production of rRNA in embryonic facial bone and tissue precursors (6). Consequently, the apoptosis of particular cells involved in the early development of facial bones and tissues is triggered. This cell death may lead to specific problems with facial development found in TCS (7).

We have identified a novel mutation in the TCOF1 gene in a patient with clinical features compatible with TCS.

CASE REPORT

A five-year-old girl was referred to our clinic from an ear, nose, and throat clinic because of syndromic appearances. The patient was the second child of a 28-year-old mother and 30-year-old father. She was born of a non-consanguinous marriage and the pedigree analysis revealed no other affected member in the family. No apparent craniofacial abnormalities were observed in the parents. She was born via normal vaginal delivery at term. Developmental milestones were age appropriate except for hearing deficit as she said her first words at the age of three years. The height of the child was 98 cm (<3p) and the body weight was 14.6 kg (<3p). The facial characteristics were bilaterally symmetrical but abnormal.

Physical and diagnostic examinations revealed various facial dysmorphic features including downward-slanting palpebral fissures, malar hypoplasia, hypoplasia of mandible, micrognathia, fishlike mouth with a high arched palate, absent lower eyelid eyelashes, and preauricular hair displacement (Fig. 1). The child had malformed bilateral pinnae and left ear microtia (Fig. 2). The patient had bilateral external auditory canal atresia. Audiometry revealed bilateral profound mixed-type hearing loss. Temporal bone CT revealed significant reduction in airflow in the
The middle ear cavity, mastoid antrum and air cells. The ossicular chain sizes in both middle ears were deformed and smaller than normal. No other abnormality was observed in the patient. Brain magnetic resonance imaging and abdominal ultrasound were normal.

On the basis of clinical symptoms, TCS was considered at preliminary diagnosis. Sequence analysis of TCOF1 gene was performed. Informed consent forms were obtained for genetic analysis.

### DISCUSSION

Sequence analysis detected a novel, heterozygous c.1722_1731 delCATCCTCCAG mutation in exon 12 of TCOF1 gene. The deletion causes a frameshift mutation and a premature stop codon (p.Asn574LysfsTer19; NM_001135243) of the treacle protein. This mutation has not been previously reported. In silico tools predict this mutation as potentially deleterious.

Pathogenic variants in TCOF1 gene lead to haploinsufficiency of the treacle protein (8). The majority of pathogenic variants cause the premature stop codon. It is probable that RNA transcripts from the mutant gene were missing as a result of nonsense mediated RNA decay and this caused the loss of protein.

Many mutations in the TCOF1 gene responsible for TCS have been identified up to now (9). No genotype/phenotype relations have been found. No significant clinical presentation has been identified due to the relevant gene (10). The phenotype is so variable that it may extend from perinatal death to cases that go undetected under clinical examination (11). This prominent variability can make diagnosis challenging, particularly in cases where patients do not exhibit all the standard clinical signs of the syndrome.

Diagnostic features of TCS include abnormalities in eyes, ears, nose/mouth, and facial bone. Majority (Table 1) of these features were present in our case.

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### Table 1. The features of Treacher Collins syndrome along with correlation with the present case

<table>
<thead>
<tr>
<th>Clinical features of TCS</th>
<th>For the Our Case</th>
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<tbody>
<tr>
<td>Absent (−)/Present (+)</td>
<td></td>
</tr>
<tr>
<td>Hypoplasia of the zygomatic bones</td>
<td>+</td>
</tr>
<tr>
<td>Hypoplasia of the mandible</td>
<td>+</td>
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<tr>
<td>Microtia</td>
<td>+</td>
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<tr>
<td>Conductive hearing loss</td>
<td>+</td>
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<tr>
<td>External auditory canal atresia/stenosis</td>
<td>+</td>
</tr>
<tr>
<td>Hypoplasia of middle ear ossicles</td>
<td>+</td>
</tr>
<tr>
<td>Cleft palate with or without cleft lip</td>
<td>−</td>
</tr>
<tr>
<td>Preauricular hair displacement</td>
<td>−</td>
</tr>
<tr>
<td>Antimongoloid slant of palpebral fissures</td>
<td>+</td>
</tr>
<tr>
<td>Lower eyelid abnormalities</td>
<td>−</td>
</tr>
<tr>
<td>Coloboma</td>
<td>−</td>
</tr>
<tr>
<td>Sparse or absent eyelashes</td>
<td>+</td>
</tr>
<tr>
<td>Ophthalmologic defects</td>
<td>−</td>
</tr>
</tbody>
</table>

TCS: Treacher Collins Syndrome

![Figure 1. Phenotype of the patient with TCS](image1.png)

![Figure 2. Microtia, micrognathia and malar hypoplasia](image2.png)
We assume that these findings facilitated a correct diagnosis of the patient. For the treatment of patients with TCS, multidisciplinary collaboration requiring reconstructive surgery, otolaryngology, speech rehabilitation, and psychological consultation is necessary (12). Molecular diagnosis of this syndrome is necessary and has great importance for genetic counseling. The current study further expands the TCOF1 mutation spectrum.

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REFERENCES