Erciyes Med J 2019; 41(1): 111–3 • DOI: 10.14744/etd.2019.62144

Treacher Collins Syndrome with a Novel Deletion in the *TCOF1* Gene

CASE REPORT

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

ABSTRACT

Treacher Collins syndrome (TCS) is a rare autosomal dominant congenital disorder characterized by various craniofacial malformations. The estimated incidence is 1 in 50000 live births. Bilaterally symmetric anomalies of the structure are present within the first and second branchial arches. Characteristic facial findings includes 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 prevalance of this syndrome is approximately 1 in 50000 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

Cite this article as:
Eser Çavdartepe B, Koçak N, Nafiz Yaşa, Çora T. Treacher Collins Syndrome with a Novel Deletion in the *TCOF1* Gene. Erciyes Med J 2019; 41(1): 111-3.

Department of Medical Genetics, Selçuk University Faculty of Medicine, Konya, Turkey

Submitted
11.12.2018

Accepted
30.01.2019

Available Online Date
01.02.2019

Correspondence
Büşra Eser Çavdartepe, Department of Medical Genetics, Selçuk University Faculty of Medicine, Konya, Turkey
Phone: +90 332 224 39 34
e.mail: bsraesr@gmail.com

Figure 1. Phenotype of the patient with TCS

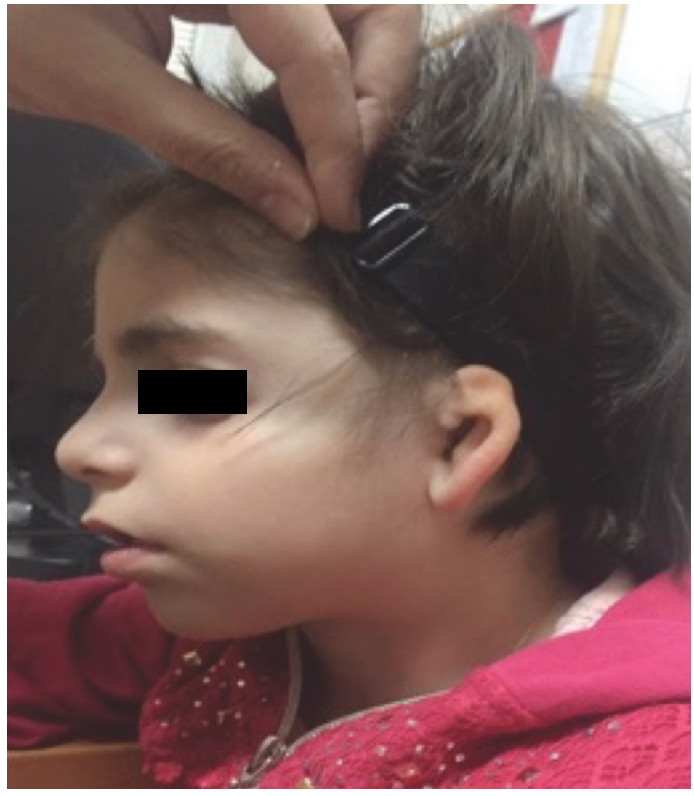

Figure 2. Microtia, micrognathia and malar hypoplasia

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

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

TCS: Treacher Collins Syndrome

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 patientts 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.

We planned to perform a mutation analysis of the *TCOF1* gene from the parents of the patient. However, the parents did not agree to mutation analysis. For this reason, we do not know whether the mutation is de novo or familial.

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.

Acknowledgments: We would like to thank the family for their participation in this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: BEÇ, NY. Performed the experiments or case: BEÇ, TÇ. Analyzed the data: BEÇ, NK. Wrote the paper: BEÇ. All authors have read and approved the final manuscript.

Conflict of Interest: There is no conflict of interest in this study.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Online Mendelian Inheritance in Man, OMIM. Johns Hopkins University, Baltimore. Available at: http://www.ncbi.nlm.nih.gov/omim/. Accessed February 18, 2019.
2. Dauwerse JG, Dixon J, Seland S, Ruivenkamp CA, van Haeringen A, Hoefsloot LH, et al. Mutations in genes encoding subunits of RNA polymerases I and III cause Treacher Collins syndrome. Nat Genet 2011; 43(1): 20–2. [CrossRef]
3. Conte C, D'Apice MR, Rinaldi F, Gambardella S, Sangiuolo F, Novelli G. Novel mutations of TCOF1 gene in European patients with Treacher Collins syndrome. BMC Med Genet 2011; 12: 125. [CrossRef]
4. Trainor PA, Dixon J, Dixon MJ. Treacher Collins syndrome: etiology, pathogenesis and prevention. Eur J Hum Genet 2009; 17(3): 275–83.
5. Weiner AM, Scampoli NL, Calcaterra NB. Fishing the molecular bases of Treacher Collins syndrome. PLoS One 2012; 7(1): e29574.
6. Valdez BC, Henning D, So RB, Dixon J, Dixon MJ. The Treacher Collins syndrome (TCOF1) gene product is involved in ribosomal DNA gene transcription by interacting with upstream binding factor. Proc Natl Acad Sci U S A 2004; 101(29): 10709–14. [CrossRef]
7. Gonzales B, Henning D, So RB, Dixon J, Dixon MJ, Valdez BC. The Treacher Collins syndrome (TCOF1) gene product is involved in pre-rRNA methylation. Hum Mol Genet 2005; 14(14): 2035–43.
8. Dai J, Si J, Wang M, Huang L, Fang B, Shi J, et al. Tcof1-Related Molecular Networks in Treacher Collins Syndrome. J Craniofac Surg 2016; 27(6): 1420–6. [CrossRef]
9. Bowman M, Oldridge M, Archer C, O'Rourke A, McParland J, Brekelmans R, et al. Gross deletions in TCOF1 are a cause of Treacher-Collins-Franceschetti syndrome. Eur J Hum Genet 2012; 20(7): 769–77.
10. Giabicani E, Lemale J, Dainese L, Boudjemaa S, Coulomb A, Tounian P, et al. Chronic intestinal pseudo-obstruction in a child with TreacherCollins syndrome. Arch Pediatr 2017; 24(10): 1000–4.
11. Jones KL, Jones MC, Campo MD. Smith's Recognizable Patterns of Human Malformation E-Book. 7th edition. Amsterdam: Elsevier Health Sciences; 2013.
12. Chen Y, Guo L, Li CL, Shan J, Xu HS, Li JY, et al. Mutation screening of Chinese Treacher Collins syndromepatients identified novel TCOF1 mutations. Mol Genet Genomics 2018; 293(2): 569–77. [CrossRef]