Treacher Collins Syndrome with a de Novo 5-bp Deletion in the TCOF1 Gene

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Treacher Collins syndrome (TCS) is an autosomal dominant disorder of craniofacial development with features including malar hypoplasia, micrognathia, microtia, downward slanting palpebral fissures, lower eyelid coloboma, conductive hearing loss, and cleft palate. TCS is caused by mutations in the TCOF1 gene, which encodes the nuclear phosphoprotein treacle. Here, we describe a 1-day-old male infant with classical TCS presentation. A 5-bp deletion in exon 22 of the TCOF1 gene (3469delACTCT) was found to cause a premature stop codon. This is the first report of TCOF1 gene mutation in the Taiwanese population. [J Formos Med Assoc 2006;105(6):518–521]

**Key Words:** mutation, TCOF1 gene, Treacher Collins syndrome

Treacher Collins syndrome (TCS), also known as Franceschetti-Zwahlen-Klein syndrome and mandibulofacial dysostosis, OMIM 154500, is an autosomal dominant craniofacial disorder affecting the development of structures derived from the first and second branchial arches during the 5th–8th week of embryonic development.¹ It has an estimated incidence of 1 in 50,000 live births.² The major diagnostic criteria of TCS include bilaterally symmetric midface hypoplasia, downward slant of palpebral fissures, lower eyelid coloboma, micrognathia, microtia, and other deformities of the ear often leading to conductive hearing loss. The phenotype is so variable that it may range from perinatal death due to a compromised airway at one end of the spectrum, to cases that go undetected under clinical examination.³ This marked variability can make diagnosis difficult, especially in cases that do not show all the canonical signs of the syndrome.

The gene underlying this syndrome, TCOF1, was cloned in 1996 by the Treacher Collins Syndrome Collaborative Group and designated treacle.⁴ The TCOF1 gene contains 26 exons and encodes a 1411-amino acid protein. More than 105 pathogenic mutations have been described.⁵ Most of these mutations are insertions or deletions that result in an introduction of a premature termination codon into the reading frame. Mutational spectra support the hypothesis that TCS results from haploinsufficiency of treacle,⁶ because of the increased level of apoptosis in the prefusion neural fold and severe defects in craniofacial development in mouse embryos with one allele of TCOF1 gene ablated.⁷ Here, we report a case of TCS with a de novo deletion in the TCOF1 gene.

**Case Report**

This male neonate was transferred to the neonatal intensive care unit immediately after birth because of congenital facial anomalies and respiratory distress. He had downward slanting palpebral fissures, sunken cheek bones, receding chin, micrognathia, bilateral microtia, absent eyelashes...
of the right lower eyelid, epicanthus inversus, ptosis, external ear canal defect, and cleft palate (Figure 1). Head computed tomography demonstrated maxillary and mandibular hypoplasia, bilateral auditory canal atresia, and poorly pneumatized mastoid. Bronchoscopy demonstrated laryngomalacia. Brainstem auditory evoked potentials (BAEP) showed conductive deafness. Cytogenetic analysis revealed a normal 46,XY karyotype.

Genomic DNA was isolated from the whole blood of the patient and his parents. Exon 1 to exon 26 of the TCOF1 gene were amplified by polymerase chain reaction (PCR) under optimal conditions, using specific primers. Sequencing analysis of the PCR products revealed six polymorphisms; five were silent and one caused an alanine to valine change (A810V) (Table). A 5-bp deletion in exon 22 (3469del ACTCT), which caused a premature stop codon, was also found. This deletion was not present in the patient’s parents and normal controls. Therefore, it is a de novo mutation (Figure 2).

Because of the compromised airway, the patient had frequent episodes of respiratory distress, and died of respiratory and heart failure at the age of 60 days. One year later, under close prenatal three-dimensional (3D) sonographic surveillance, the mother delivered a normal female baby.

Discussion

Differential diagnosis of TCS includes Goldenhar syndrome (oculoauriculo-vertebral dysplasia), which has the characteristic features of unilateral notching of the upper rather than the lower eyelid and epibulbar dermoids, and Nager acrofacial dysostosis, which presents with mandibulofacial dysostosis with preaxial reduction defects of the upper limbs.

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**Figure 1.** The patient at age 12 days: (A) downward slanting palpebral fissures, sunken cheekbones, micrognathia; (B) microtia and malformation of the auricles.

**Figure 2.** The partial sequence of exons 16 and 22 of the: (A) patient; (B) patient’s father; (C) patient’s mother; (D) normal control.
Mutations and polymorphisms found in this study

<table>
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<th>Exon</th>
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<th>Amino acid</th>
<th>Effect</th>
<th>Protein product</th>
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<td>9</td>
<td>1247 A→G</td>
<td>E419E</td>
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<td>Polymorphism</td>
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<tr>
<td>22</td>
<td>3469del ACTCT</td>
<td>T1146G</td>
<td>Frameshift</td>
<td>Aborted translocation</td>
<td>This study</td>
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TCS is considered a neonatal emergency because the tongue may obstruct the airway. Antenatal diagnosis of TCS using conventional two-dimensional (2D) sonography depends on the midsagittal scan of the fetal face. However, in 1997, Merz et al reported that the facial profile shown in the 2D image represented the true midsagittal profile in only 69.6% of cases studied, while surface rendering using 3D sonography was able to provide more useful striking images of the fetal face. In 2002, Tanaka et al reported the antenatal sonographic features in the case of a Japanese woman at 36 weeks of gestation referred for polyhydramnios. Hsu et al reported a Taiwanese woman at 34 weeks of gestation referred for polyhydramnios and fetal anomaly. These cases suggest the value of 3D imaging in monitoring at-risk pregnancies. Without specific past histories, this congenital anomaly will not be detected by routine antenatal examination.

Mutations detected previously in TCS indicate that: (1) the majority of pathogenic mutations are small deletions and insertions causing frameshifts that lead to truncation of the protein; (2) mutations (both polymorphic and pathogenic) can be found throughout the 25 coding exons of the gene; (3) most mutations are family-specific, with the exception of a commonly occurring 5-bp deletion in exon 24 (found in approximately 16% of families); and (4) there is no correlation between type and/or localization of the mutation and phenotypic expression. More than 50% of all described pathogenic known mutations are clustered in five exons (10, 15, 16, 23, 24) in different populations. The 5-bp deletion in exon 22, 3469del ACTCT (T1146G), that was found in our patient has not been reported previously, and is not located within the mutational hot spots.

Because of the marked phenotypic variability in TCS, antenatal 3D sonography is very important to confirm the diagnosis, especially in the presence of craniofacial dysostosis in previous pregnancies. DNA analysis is also very helpful in confirming the diagnosis.

References


