A Newborn with Difficult Intubation Diagnosed with Treacher Collins Syndrome and Detection of a Novel Pathogenic Variant in TCOF1

Hua Wang, M.D., Ph.D., Enas Louzy, GC., MSc.

Abstract

*This case report highlights the challenges encountered during the intubation of a newborn presenting with distinctive features, prompting consideration of Treacher Collins syndrome (TSC). Subsequent genetic testing identified a novel heterozygous and pathogenic variant in TCOF1, specifically c.3671dup (p.Leu1225Alafx*16), conclusively confirming the diagnosis. Given the rarity of TSC, the significance of early diagnosis cannot be overstated, as it significantly enhances clinical management. Additionally, the unique nature of the TSC necessitates specialized intubation techniques.*

Introduction

Treacher Collins syndrome (TCS; OMIM #154500), also called mandibulofacial dysostosis (MFD), was described in 1900. it is a rare autosomal dominant disorder that profoundly impacts craniofacial development during early embryogenesis. This syndrome is distinguished by a characteristic array of bilaterally symmetric features, encompassing downward-slanting palpebral fissures, coloboma of the lower eyelids, hypoplasia of midfacial bones, cleft palate, and anomalous development of the external and middle ear structures, often resulting in conductive hearing loss (1). With an estimated incidence of 1 in 50,000 individuals, TCS predominantly emerges sporadically, affecting more than 60% of cases without any discernible familial antecedents, typically arising from de novo mutations (2). Here, we report a new case of Treacher Collins syndrome and the detection of a novel pathogenic variant.

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Case Description:

This Hispanic male, born only hours ago, was transferred to LLUH NICU due to a challenging intubation history and the presentation of distinctive facial features requiring further assessment and management. Delivered via Cesarean Section at 38 weeks due to maternal HELLP Syndrome, the 26-year-old primigravida mother experienced an uneventful pregnancy until the 38th week. Two ultrasound studies at the 20th and 30th weeks of gestation revealed no abnormalities. The newborn exhibited poor color/tone, absence of spontaneous cry, and heightened work of breathing. At the originating hospital, prior to transfer, the resuscitation process endured for about 25 minutes, culminating in successful intubation after two failed attempts and subsequent decompensation. Upon admission to LLUCH NICU, the infant remained ventilated and received nutrition through an OG tube. A genetic consultation was promptly initiated. Clinical examination revealed marked dysmorphic facies (see Fig.1), encompassing bilateral downslanting palpebral fissures, bilateral lower lid coloboma, bilateral ptosis, more pronounced lagophthalmos in the right eye, sparse eyelashes (Fig.1a.b.c.d.), severe malar hypoplasia, a prominent beak-like nose (Fig.1d.), bilateral microtia, malformed external ears with atresia of the external auditory canals (Fig.1 e.f.), zygomatic bone hypoplasia, micrognathia, retrognathia, sparse and faint eyebrows, a large mouth with thin lips, and a short neck (Fig.1e.). Ophthalmologic examination unveiled a right exposure keratopathy with a small healing defect and mature retina. The discernible dysmorphism and the history of challenging intubation raise high suspicion of Treacher Collins syndrome (TCS). Family history provides no contributory information. An Invitae Facial Dysostosis and Facial Dysplasia Panel were ordered. Subsequent investigations, including head Echo and spine ultrasound, yielded unremarkable results.

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A 2D Echo displayed a foramen ovale with a small shunt. Florescent Swallow and Upper GI studies confirmed the infant's ability to initiate swallowing without obstruction. Multiple Chest X-rays showed no anomalies. A CT Maxillofacial examination demonstrated a constellation of findings consistent with TCS (see Fig 2), including non-visualization of the vomer, soft tissue opacification of the bilateral choana consistent with choanal atresia, micrognathia, irregular/hypoplastic zygomatic arches, aplasia of the external auditory canals, hypoplasia of the middle ear canals with absent middle ear ossicles, hypoplastic mastoid air cells, unremarkable soft tissues of the face, and microtia. Micro-laryngoscopy and Bronchoscopy yielded normal results, while Nasopharyngoscopy revealed bilateral choanal atresia without clefting. A Brainstem Auditory Evoked Response (BAER) study and limited audiometric examination displayed normal findings. An extubation attempt on the seventh day of life failed, leading to tracheostomy two days later due to decompensation with non-invasive ventilation. Due to recurrent removal of the NG tube, poor feeding, and failure to

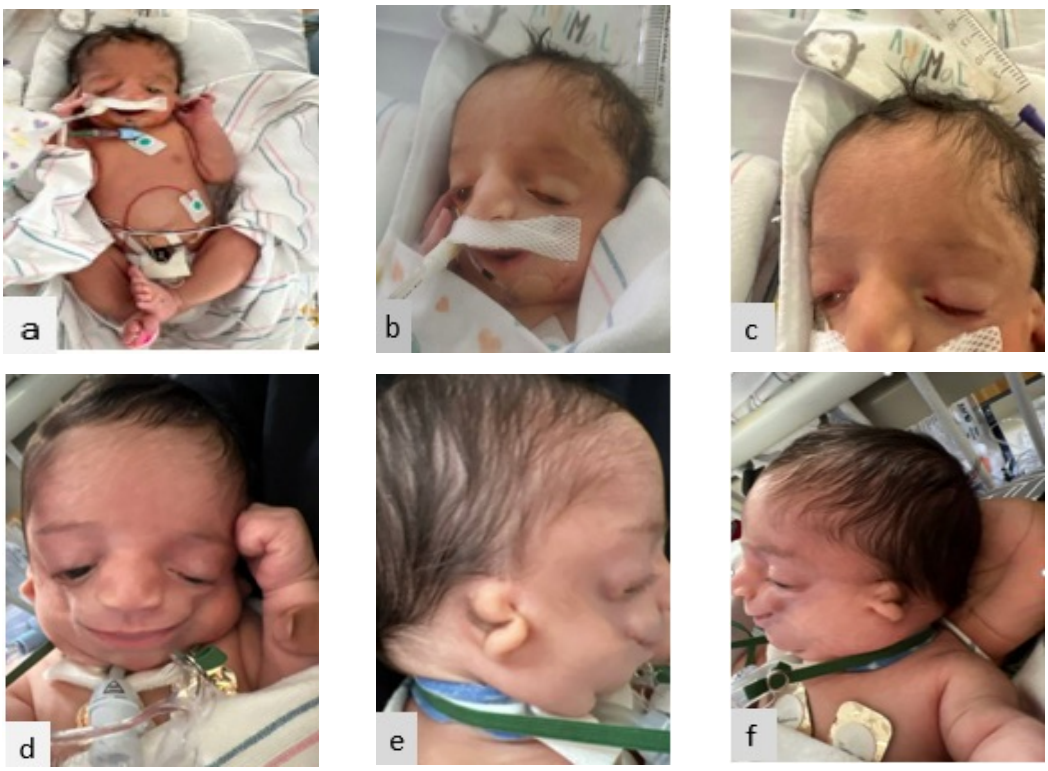

Figure 1.

*Bilateral down-slanting palpebral fissures, bilateral lower lid coloboma, bilateral ptosis, bilateral lagophthalmos more evident on the right eye, sparse eyelashes (Fig.1 a.b.c.d.), severe malar hypoplasia, large prominent beak-like nose (Fig.1 d.), bilateral microtia, malformed external ear with atresia of the **external** auditory canals (Fig. 1 e.f.), hypoplasia of the zygomatic bones, micrognathia, and retrognathia, sparse and faint eyebrows, large mouth with thin lips and short neck (Fig.1e.).*

Note: Fig.1d.e. f photos were taken two weeks later when the patient was off ventilation with tracheotomy only.

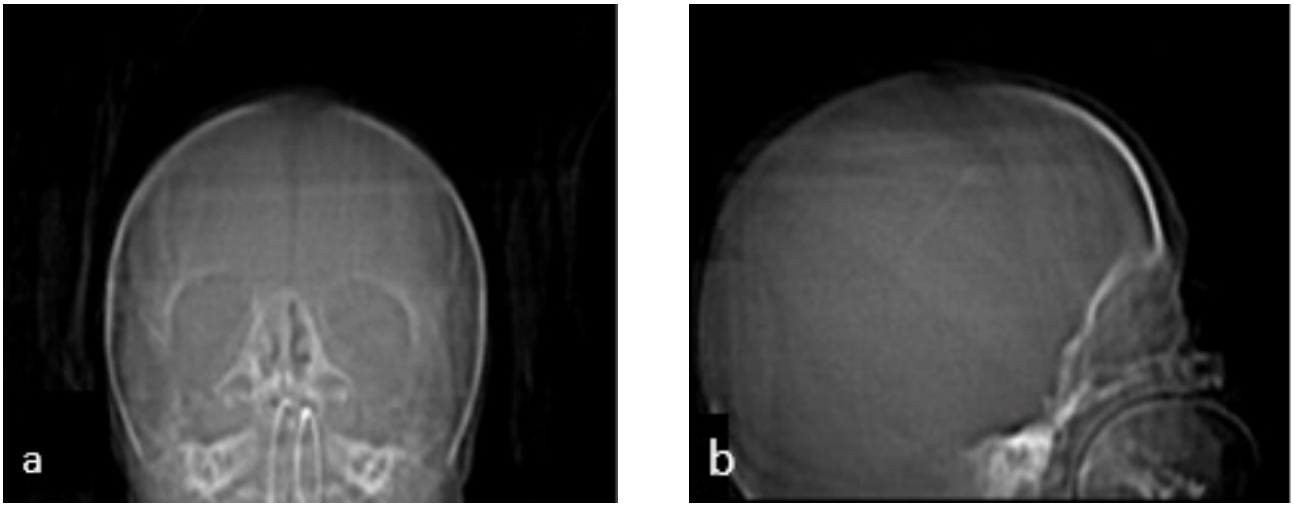

***Figure 2.** A CT Maxillofacial demonstrated a constellation of findings consistent with TCS including non-visualization of the vomer, soft tissue opacification of the bilateral choana consistent with choanal atresia, micrognathia, irregular/hypoplastic zygomatic arches, aplasia of the external auditory canals, and hypoplasia of the middle ear canals with absent middle ear ossicles, hypoplastic mastoid air cells, unremarkable soft tissues of the face and microtia (fig.2 a.b.)*

thrive, a percutaneous endoscopic gastrostomy (PEG) tube was placed at four weeks. Plastic surgery opted not to proceed with mandibular distraction due to ongoing central apnea, recommending a re-evaluation at six months. The multidisciplinary management involves teams in Speech Therapy, Occupational Therapy, and Respiratory Therapy.

Genetic test result

The result of the Invitae Facial Dysostosis and Facial Dysplasia Panel was returned two weeks after admission, which showed a frameshift pathogenic heterozygous variant in TCOF1 gene c3671dup (p.leu1225alafs*16) (see Fig 3). TCOF1 is associated with autosomal dominant Treacher-Collins Syndrome (TCS). This pathogenic variant establishes a molecular diagnosis of TCS in the patient.

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The variant is localized on the 23rd exon of TCOFI. This is a known hotspot on TCOF1. It creates a premature translational stop signal, expected to result in an absent or disrupted protein product. This variant is not present in the population database (gnomAD, no frequency). Based on the above evidence, this variant has been classified as pathogenic. The variant has not been reported in the literature in individuals affected with TCOF1-related conditions. This means it is a new pathogenic variant detected for the first time in our patient, as per the laboratory report. We searched the CLinVar database, and there was no entry of the variant, which confirms that this is a newly detected TCOF1 pathogenic variant. We searched to find out if there has been evidence of genotype-phenotype correlation, but such correlation still needs to be established. However, the severity of the condition is related to the type of the mutation.

Discussion:

TCS exhibits a range of prominent characteristics, collectively giving rise to a distinct facial appearance often described as "fish-like." These features encompass a slant of the palpebral fissure, eyelid abnormalities, facial underdevelopment (notably affecting the mandibular and zygomatic regions), outer and middle ear malformations, conductive hearing impairment, cleft palate, and macrostomia. TCS typically exhibits high penetrance, yet there can be considerable variations in the phenotypic expression. Franceschetti and Klein (4) classified TCS into five clinical forms: (1) the complete form (displaying all recognized features), (2) the incomplete form (exhibiting varying degrees of ear, eye, zygoma, and mandibular abnormalities), (3) the abortive form (characterized by lower lid pseudo coloboma and zygoma hypoplasia), (4) the unilateral form (with anomalies confined to one side of the face), and (5) the atypical form (accompanied by additional abnormalities not typically associated with the syndrome) as outlined in Table 1. Mild phenotypes may not exhibit overt clinical characteristics.

"Individuals with a severe phenotype may face life-threatening complications such as ventilation obstruction arising from conditions like posterior nasal foramen atresia. Consequently, the exploration of genetic testing becomes especially crucial, serving as a valuable tool in the auxiliary diagnosis and guiding intervention treatments."

Additionally, TCS shares overlapping clinical traits with other conditions, such as Nager syndrome, Miller syndrome, Goldenhar syndrome, and Burn-McKeown syndrome, posing diagnostic challenges (5). Individuals with a severe phenotype may face life-threatening complications such as ventilation obstruction arising from conditions like posterior nasal foramen atresia. Consequently, the exploration of genetic testing becomes especially crucial, serving as a valuable tool in the auxiliary diagnosis and guiding intervention treatments.

The existing literature delineates four distinct clinical subtypes of Treacher Collins syndrome (TCS): TCS1 (OMIM 154500), which arises from mutations in the TCOF1 gene (OMIM 606847); TCS2 (OMIM 613717), attributable to mutations in the POLR1D gene (OMIM 613715); TCS3 (OMIM 248390), resulting from mutations in the POLR1C gene (OMIM 610060); and TCS4 (OMIM 618939), linked to mutations in the POLR1B gene (OMIM 602000). Variants within TCOF1 and POLR1B follow an autosomal dominant inheritance pattern, whereas POLR1C variants exhibit autosomal recessive inheritance. Variants in the POLR1D gene can mani-

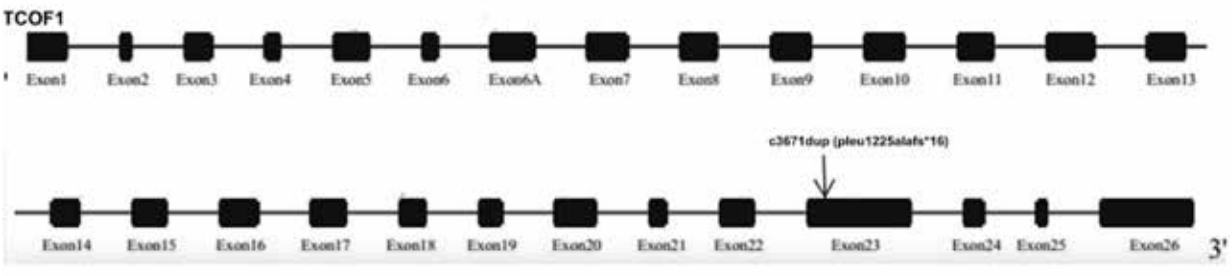

Fig 3. Illustration of the structure of the TCOF1 gene (NM_001135243.1), black boxes proportionately represent coding exons, and introns are not scaled (3). Our patient's causative mutation is in exon 23. Mutation is marked with an arrow.

fest as either autosomal dominant or autosomal recessive in their inheritance patterns. Approximately 86% of all documented TCS cases stem from mutations in the TCOF1 gene, with POLR1C mutations accounting for roughly 1.2%, POLR1D mutations representing 6%, and POLR1B mutations contributing to 1.3% of cases (6). The scientific literature has documented over 200 mutations within the TCOF1 gene. A significant proportion of these mutations consist of small deletions that lead to the generation of a premature termination codon, resulting in either a truncated protein or triggering nonsense-mediated mRNA decay. This collective evidence strongly indicates that the developmental anomalies associated with these mutations stem from the haploinsufficiency (or loss of function) of TCOF1 (7). The penetrance of genetic mutations associated with TCS is commonly regarded as high; nevertheless, this could be one of the reasons causing notable variability in phenotypic expressions, both within and among families (8). Pathologically, TCS arises due to the underdevelopment of the first and second branchial arches. The inhibition of ribosome synthesis in neural crest cells and neuroepithelial cells precipitates a reduction in the quantity of migrating neural crest cells towards the maxillofacial region, serving as the primary pathogenic mechanism (9).

"If the global incidence of CCHD reported by Quiroz et al. (16), which is 6 to 8 cases per 1000 live births, is taken, the cases of CCHD in Ciudad Juarez would range from 92.52 to 177.19 cases per year."

As outlined by Chang et al. (Chang & Steinbacher, 2012) and Trainor (Trainor & Andrews, 2013), TCS treatment spans neonatal, infancy, childhood, and adolescence. The neonatal phase focuses on symptom relief, addressing airway obstruction and eyelid issues. Infancy centers on feeding, growth, and early interventions like cleft palate repair. Childhood involves airway monitoring, possible interventions, and otoplasty, while adolescence focuses on skeletal and soft tissue reconstruction and occlusal corrections. The comprehensive approach integrates various medical disciplines, such as oral surgery, orthodontics, ophthalmology, ear-nose-throat care, speech pathology, pediatrics, nursing, genetics, psychology, and social work. Of note, TSC poses significant challenges for anesthetists due to the combination of maxillary, zygomatic, and mandibular hypoplasia and a small oral aperture, high-arched palate, and temporomandibular joint abnormalities. These anatomical features contribute to difficulties in performing direct laryngoscopy and endotracheal intubation, with the former becoming increasingly challenging as patients age. In cases where endotracheal intubation is unnecessary, the laryngeal mask airway emerges as a favorable choice for maintaining a secure airway (10).

"This is cross-sectional, analytical, and exploratory research. The main unit of analysis is the newborn in apparent good health. Similarly, information is collected from the mother of the newborn."

Conclusion:

Our presented case exhibits typical TSC manifestations. Given its rarity, encountering difficult intubation alongside distinctive facial dysmorphism necessitates heightened awareness for prompt recognition and appropriate management. The broad clinical phenotype spectrum requires thorough differential diagnosis, with genetic testing pivotal in confirmation. While genotype-phenotype correlation remains unestablished, loss-of-function mutations are predominant, leading to typical clinical presentations. The novel variant identified here contributes to the TCOF1 mutation bank, offering potential utility in future genetic testing. Comprehensive genetic counseling was provided, with a pending parental targeted test. Ongoing follow-up in our genetics clinic will guide the family in managing, monitoring, and future pregnancies.

Practical Application:

- Treacher-Collins syndrome (TCS) is an uncommon genetic disorder.
- Evaluation for TCS is advisable in neonates presenting with challenging intubation and distinctive dysmorphic features.
- Despite the diversity in clinical phenotypes, a clinically recognizable typical feature exists, though with some overlap with other syndromes.
- Genetic testing plays a critical role in confirming a definitive diagnosis.
- De novo mutations are frequently observed, and most mutations entail loss of function.
- The multidisciplinary treatment approach necessitates specialized attention and techniques for effective intubation management.

References:

Table 1. Franceshetti-TCS Clinical Forms

Type	Clinical features
Complete form	Having all known features
Incomplete form	Presenting variably with less severe ear, eye, zygoma, and mandibular abnormalities
Abortive form	Only the lower lid pseudo coloboma and zygoma hypoplasia are present
Unilateral form	Anomalies limited to one side of the face
Atypical form	Combined with other abnormalities not usually part of the typical syndrome

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Corresponding Author

Hua Wang, MD, PhD
Assistant Professor, Pediatrics
Loma Linda University School of Medicine
Division of Genetics
Department of Pediatrics
Loma Linda, CA
Email: HUAWang@llu.edu

Enas Louzy, GC., MSc.
Loma Linda University School of Medicine
Division of Genetics
Department of Pediatrics
Loma Linda, CA