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Review Article

Treacher Collins Syndrome: The genetics of a craniofacial disease

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ABSTRACT

Objectives: The molecular underpinnings of Treacher Collins Syndrome (TCS) are diverse. This article codifies the most recent findings in this complex area of research to further current understanding of the disease process. Elucidating the genetic causes of the disorder can be useful in earlier detection and better treatment planning.
Design: Articles from 1991 to 2013 were selected and reviewed by five researchers utilizing the most recent literature of the genetics and pathophysiology of TCS.
Results: Mutations in TCOF1, POLR1C and POLR1D have all been implicated in causing TCS. The association of the *TCOF1* gene product, Treacle, and gene products of POLR1C and POLR1D with ribosome biosynthesis suggests that a loss of function mutation in these genes disrupts ribosome biosynthesis in constituent neural crest cells and neuroepithelium leading to apoptosis. However, recent data illustrating that P53 heterozygosity is protective against TCS, and that P53 and TCOF1 hemizygous embryos do not affect ribosomal function, implicates P53 or elements downstream of P53 as playing a role in TCS pathogenesis.
Conclusion: Our study codified nascent findings of the molecular determinants of TCS. These findings add to a burgeoning database of TCS-associated mutations, and as such, can be used to establish TCS diagnosis and further clarify TCS pathogenesis.

Contents

1. Introduction

Treacher Collins Syndrome (TCS;OMIM #154500) is a rare autosomal dominant (AD) mandibulofacial dysostosis occurring in 1 in 10,000–50,000 births, that ensues subsequent to mutations in

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the *TCOF1* (78–93%) and *POLR1C* or *POLR1D* genes (8%) [1–5]. A small proportion (1%) of TCS cases are also inherited in a recessive fashion due to mutations in *POLR1C*. In these patients, carrier status can be obtained; however, TCS often occurs due to *de novo* mutation (60%) in the *TCOF1* gene (5q32-33.1) of which well over 100 distinct mutations have been identified [2,6]. TCOF1 encodes for a 1411-amino acid protein, treacle, a nucleolar phosphoprotein that shuttles between the nucleolus and the cytoplasm [2]. Treacher Collins Syndrome was first introduced and examined by George Andreas Berry in 1889, then by Treacher Collins in 1900 [7]. Franceschetti and Klein provided a comprehensive overview of the syndrome in 1949, and hence TCS is often called Franceschetti–Klein syndrome in German-speaking countries [2]. Affecting the proper formation of the first and second branchial arches, this syndrome occurs during the fifth to eighth week of fetal development [8], and leads to profound facial dysmorphism. This disordered craniofacial development seen in TCS has implicated *treacle* as pivotal for craniofacial development, and additionally studies have illustrated that proper *treacle* expression is essential for the survival and migration of craniofacial neural crest cells [2].

TCS patients have normal intelligence. As a result of distorted physical appearance, patients often experience significant psychosocial challenges and social stigma [9]. TCS has a variable phenotype with major clinical characteristics including bimaxillary micrognathia and retrognathia (78% of patients), coloboma of the lower eyelids (69%) with associated loss of medial eyelashes (53%), external ear aplasia or microtia (78%), downward slant of palpebral fissure secondary to hypoplasia of the lateral orbit, a large or protruding nose, and zygomatic bone hypoplasia (89%) [4,10]. Minor clinical characteristics include cleft lip with or without concomitant cleft palate (28%), hair displacement anterior to the auricle (26%), airway dysfunction such as tracheostoma or choanal stenosis/atresia, external ear atresia, stenosis of the external auditory canal (35%) and approximately 50% of patients have conductive hearing loss due to ear malformations including microtia, ossicular chain malformation, ankylosis, and meatal atresia [4,10,11]. In a large cohort, downward slanting palpebral fissures and a hypoplastic zygomatic complex where observed to be the most commonly-occurring features [2].

Despite extensive malformation and hypoplasia of the middle ear cavity, inner ear structures are typically unaffected [4,11]. Interestingly, conductive hearing loss occurs at a significantly lower frequency in patients with mutations of the 3′ open reading frame of *TCOF1* [2]. Other minor characteristics include ophthalmologic complaints including refraction error (58%), strabismus (37%), amblyopia (33%), and anisometropia (17%). In one sample, dental anomalies were identified in 60% of TCS patients, with an average of 1–8 anomalies per patient. The most frequent dental anomalies were tooth agenesis (33.3%) predominantly affecting the mandibular second premolars, and enamel opacities (20%) [12]. Together, these features contribute to speech and language difficulties, visual impairment or loss (37%), conductive hearing loss, breathing difficulty, and obstructive sleep apnea [11,13].

1.1. Diagnosis

Diagnosis of TCS is usually made at birth and is primarily a clinical diagnosis supported by radiographic data and molecular studies. However, diagnosis can also occur prenatally if molecular analysis is performed by amniocentesis (~15–18 weeks gestation) or chorionic villous sampling (~10–12 weeks gestation) [14]. In affected families, subsequent pregnancies can be monitored with transvaginal and abdominal ultrasound. Sonographic imaging combined with linkage analysis can identify the disease as early as the first trimester [15]. Anomalies commonly observed by ultrasound include polyhydramnios, abnormal fetal swallowing, microcephaly, distorted facial characteristics such as antimongoloid slanting palpebral fissures, malformation of the auricles, microphthalmos, micrognathia [16–18]. Occipitomental radiographs are useful in identifying aplasia or hypoplasia of the zygomatic arch, and Occipitomental X-ray view (Water's view) and orthopantogram films are helpful in identifying mandibular hypoplasia. Computed tomography (CT) scans can establish malar hypoplasia and cephalometric radiographs can determine the extent of mandibular retrognathia [19].

Genetic testing, which should be considered in patients with at least two of the major features or three minor features, utilizes a broad range of diagnostic modalities to determine mutations in *TCOF1*, *POLR1C* and *POLR1D* [4]. In general, whole gene or whole exon deletions are not detected in TCS. The strategy for testing first utilizes sequence and deletion/duplication analysis in patients with a family history consistent with AD inheritance (40% of TCS cases have a positive family history) and in cases that are the first occurrence of TCS in a family. If this approach is not effective, *POLR1D* should be utilized. *POLR1C* sequence analysis should be utilized in families with multiple affected siblings, consanguinity, or in patients in whom *TCOF1* and *POLR1D* testing was negative. Families with a known history of TCS may opt for pre-implantation genetic diagnosis or *in utero* testing.

Although penetrance of the disorder is high, there is a considerable amount of phenotypic variation ranging from perinatal airway obstruction to milder variants with minimal dysmorphism [20–22]. For example, the common *TCOF1* 4369_4373delAAGAA mutation is known for its incomplete penetrance and patients should be counseled regarding the inability to provide comprehensive insight into the extent of facial malformation or disease severity [4]. Therefore, despite the availability of genetic testing modalities, the phenotype cannot be readily predicted by the patient's genotype [2]. The differential diagnosis for TCS is broad and includes other mandibulofacial dysostoses including Toriello syndrome, Bauru syndrome, Hedera-Toriello-Petty syndrome, and Guion-Almeida syndrome. There are phenotypic features of TCS in addition to mandibular dysostosis that are seen in other diseases. Limb deformities are found within Nagar and Miller syndrome. Colobomas, which in TCS occur symmetrically on the lower eyelids, are found also in Goldenhar syndrome – albeit asymmetrically on the upper lids. Some permanent features of TCS, namely micrognathia, glossoptosis, and cleft palate, are found to self-correct without intervention in Pierre Robin syndrome. Finally patients with nonsyndromic mandibular hypoplasia also have similar mandibular deformities such as temporomandibualr joint ankylosis, aglossia, and microglossia [4].

1.2. Management

An extensive range of surgical interventions is utilized to secure respiratory function, ensure proper feeding, improve hearing, and reconstruct profound periorbital and craniofacial defects. Extent of airway compromise is diverse, with some infants requiring immediate tracheostomy. TCS management is a multidisciplinary affair, as interventions range from reconstructive to psychosocial. Satisfaction with reconstructive surgery varies, and a recently published cross-sectional cohort study of 58 TCS patients illustrated patient dissatisfaction with physical characteristics of their ears, facial profile, eyelids, chin, and teeth. Patients were also distressed by functional challenges of hearing, nasal patency, eye tearing, altered smell, and eyelid closure. Despite challenges in the surgical management of TCS, there is a relatively extensive armamentarium to address the profound dysmorphism seen in this disease.

Complaints concerning the eyelids were most frequently managed by lateral canthopexy and lower eyelid reconstruction.