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Syndromes of the First and Second Pharyngeal Arches: A Review

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Our aim in this review is to discuss currently known mechanisms associated with three important syndromes of the first and second pharyngeal arches: Treacher Collins syndrome (TCS), Oculo-auriculo-vertebral syndrome (AOVS) and Auriculo-Condylar syndrome (ACS) or question mark ear syndrome. TCS and ACS are autosomal dominant diseases, with nearly complete penetrance and wide spectrum of clinical variability. The phenotype of the latter has several overlapping features with OAVS, but OAVS may exist in both sporadic and autosomal dominant forms. Mutations in the *TCOF1* gene are predicted to cause premature termination codons, leading to haploinsuficiency of the protein treacle and causing TCS. Low amount of treacle leads ultimately to a reduction in the number of cranial neural crest cells migrating to the first and second pharyngeal arches. Other than TCS, the genes associated with ACS and OAVS are still unknown. The first locus for ACS was mapped by our group to 1p21-23 but there is genetic heretogeneity. Genetic heterogeneity is also present in OAVS. Based on the molecular analysis of balanced translocation in an OAVS patient, it has been suggested that abnormal expression of *BAPX1* possibly due to epigenetic disregulation might be involved with the etiology of OAVS. Involvement of environmental events has also been linked to the causation of OAVS. Identification of factors leading to these disorders are important for a comprehensive delineation of the molecular pathways underlying the craniofacial development from the first and the second pharyngeal arches, for genetic counseling and to open alternative strategies for patient treatment. © 2009 Wiley-Liss, Inc.

Key words: Treacher Collins syndrome; Auriculo-Condylar syndrome; oculo-auriculo-vertebral syndrome; *TCOF1*; cranial neural crest; epigenetic; genetic heterogeneity

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INTRODUCTION

First and second pharyngeal arches, which are composed of mesenchymal cells derived from mesodermal and cranial neural crest cells, give rise to a wide variety of facial structures including skeletal, muscular and neural elements (Figs. 1 and 2) through a complex signaling network still poorly characterized. Disregulation of these signaling pathways triggered by genetic or environmental factors constitute a potential source of facial maldevelopment. Manifestation and severity of the defect will thus depend on how the expression and activation of genes and proteins have been shifted during facial development. The list of syndromes involving structures derived from the first and second pharyngeal arches is extensive [Gorlin, 2001] (Table I), but they are often associated with malformations derived from other embryological origins than these arches. Understanding the molecular basis of these syndromes, which has not yet been fully elucidated, contributes to the identification of critical genes for facial development and provides tools for diagnosis and genetic counseling. In this review, we will focus on the currently known molecular mechanisms associated with Treacher Collins, oculo-auriculo-vertebral spectrum syndromes and Auriculo-Condylar syndrome.

Treacher Collins Syndrome (TCS; OMIM# 154500), also known as Franceschetti-Zwahlen-Klein Mandibulofacial Dysostosis (MFD1), is a typical autosomal dominant craniofacial disorder of the first and second pharyngeal arches (Figs. 1 and 2). The resulting clinical features comprise downslanting palpebral fissures with lower eyelid coloboma, malar and maxillary hypoplasia, microtia, and other malformations of the ears, and conductive hearing loss due to atresia of the external ear canal. Cleft palate and absence of the zygomatic arch may occur in severe cases. Birth prevalence has been estimated as 1:50,000 newborns and approximately 60% are caused by new mutations. Penetrance seems to be nearly complete.

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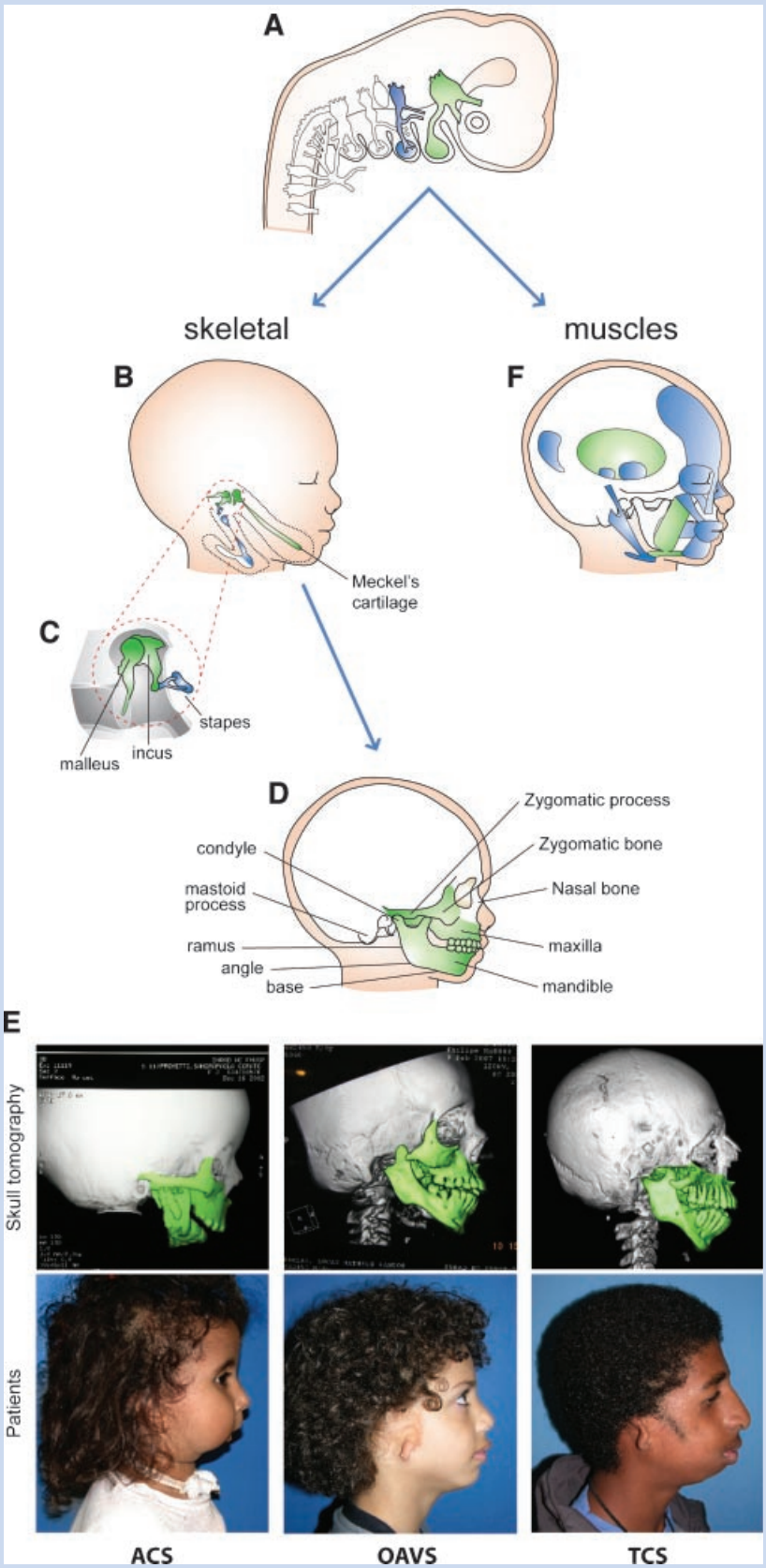

FIG. 1. Scheme illustrating the clinical consequences that might result from genetic alterations in the first (green) and second (blue) pharyngeal arches. A: First and second pharyngeal arches. B,C: Derived skeletal structures of these pharyngeal arches, which will give rise to maxilla, mandible, and ossicles of the middle ear. D: Newborn cranial bone structures derived from first and second pharyngeal arches. E: Skull tomography and pictures of patients with ACS, OAVS, and TCS showing alterations of maxilla and mandible as a possible result of genetic disturbance in the cranial neural crest and/or cells of the first and second pharyngeal arches. F: Adult muscle derivatives of the first and second pharyngeal arches. Adapted from Carlson [2005].

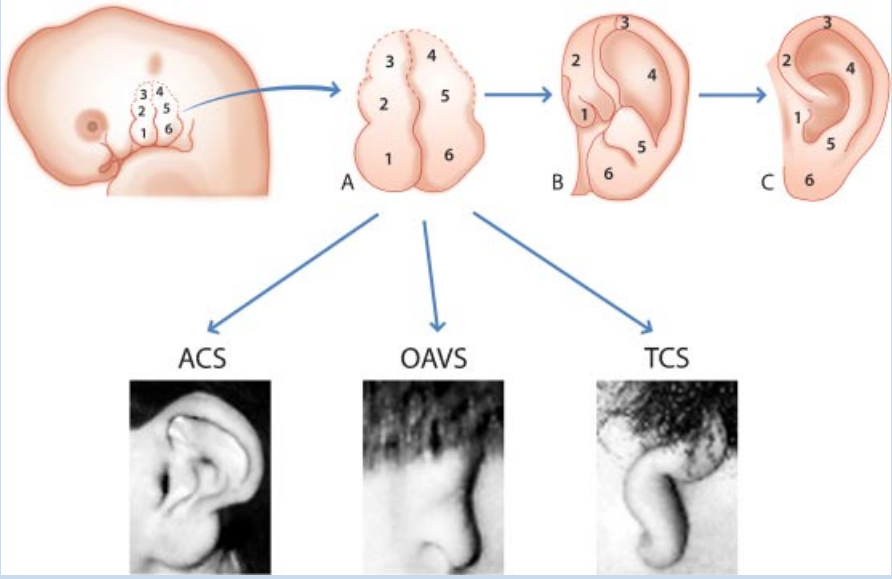

FIG. 2. The exter nal ear is derived from mesenchymal tissue of the first and second pharyngeal arches that flank the first pharyngeal cleft. A: During the second month, three nodular masses of mesenchyme (auricular hillocks) take shape along each side of the first pharyngeal cleft. B, C: The auricular hillocks enlarge asymmetrically and ultimately coalesce to form the external ear. Alteration in these cells or in pharyngeal arches' cells might lead to misshapen ears, which is often present in patients with ACS, OAVS, and TCS. Ear abnormalities in patients affected by one of these syndromes present a wide spectrum of variability. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Clinical features are usually bilateral, but there is markedly broad phenotypic variability among patients, ranging from perinatal death due to a compromised airway to cases that undergo undetected by medical examination. The extent of clinical variability sometimes makes it difficult to differentiate a case of nonpenetrance from one with minimal expression of the syndrome. Mutations in the *Treacher Collins-Franceschetti syndrome 1* (*TCOF1*) gene, mapped to 5q32-q33.1, are responsible for the phenotype in most of the cases. Genetic heterogeneity for TCS remains a possibility, because some patients still have no identified mutation even after screening for large deletions [Splendore et al., 2005]. Except for a recurrent deletion in exon 24 (c.4366_4370delGAAAA) that accounts for approximately 17% of the cases, the mutations are distributed along its 26 coding exons and are usually family-specific (www.genoma.ib.usp.br/TCOF1_database). Most of the 120 *TCOF1* pathogenic mutations, mainly deletions, so far described are predicted to cause premature termination codons (PTC). The mechanism of the disease is haploinsufficiency of treacle, the *TCOF1* protein product [Gladwin et al., 1996; Edwards et al., 1997; Wise et al., 1997]. Null *TCOF1* heterozygous mutations should have a higher functional impact at early developmental stages (days 8, 9, and 10 of mouse development) when *Tcof1* is highly expressed. Treacle is a serine/alanine rich nucleolar phosphoprotein. It is involved in ribosomal DNA gene transcription as well as in processing of the pre-ribosomal RNA. Deficiency of treacle leads to insufficient ribosome biogenesis, which is associated with diminished cell proliferation, increased neuroepithelial apoptosis and deficient formation of migrating cranial neural crest cells. Haploinsufficiency of *Tcof1* thus leads to a depletion of neural crest cell precursors, which results in a reduced number of neural crest cells migrating into the core of the first and second pharyngeal arches. No correlation between type, location of mutation and phenotype has been found [Dixon et al., 2004]; and there is yet no molecular mechanism to explain the remarkable clinical variability of the disease. We have hypothesized that lower levels of the normal allele could modulate the phenotype, but we did not identify any SNP in the promoter region of the *TCOF1* that could account for this effect [Masotti et al., 2005]. TCS overlaps with some other conditions of the 1st and 2nd pharyngeal arches, most particularly Nager, Miller and OAVS. However, *TCOF1* null mutations have been excluded as causative for these conditions. Nager and Miller syndromes are very rare and their underlying molecular mechanism is unknown. On the other hand recently, as detailed below, new insights have been brought through molecular analysis about OAVS.

OAVS (OMIM 144210), in contrast to TCS, represents a very heterogeneous and complex group of disorders and includes those conditions previously known as hemifacial microsomia and Goldenhar syndrome [Gorlin, 2001]. The disorder involves primarily ocular and aural anomalies (Figs. 1 and 2), but some patients may also have vertebral malformations and renal defects. Most patients have hemifacial microssomia with a wide spectrum of clinical variability, but bilateral involvement also occurs. Epibulbar dermoids and upper eyelid colobomas are found often associated with macrostomia or facial celfts [Tasse et al., 2005; Wieczorek et al., 2007]. There is no agreement about minimal diagnostic criteria, but isolated microtia or hemifacial microsomia together with mild ear malformations, such as preauricular tags and nodes, may represent the mildest manifestations of OAVS [Gorlin et al., 2001]. Tasse et al. [2005] suggested that relatives of typically affected patients with

TABLE I. Malformations, Inheritance, and Mechanisms of Some Syndromes Involving Structures Derived From the First and Second Pharyngeal Arches

Disease	Malformations of first and second pharyngeal arches	Other malformations	Inheritance	Mechanisms
Oculo-auriculo-vertebral spectrum	Ocular and aural anomalies, hemifacial microssomia, epibulbar dermoids, upper eyelid colobomas, macrostomia, facial clefts, ear malformations	Vertebral malformations, cardiac and renal defects	Most cases are sporadic; but there are reports of autosomal dominant and autosomal recessive inheritance	Non-genetic factors (diabetes, thalidomide, primidone, retinoic acid). Chromosome alterations (5, 18, 22, X). Locus at 14q32.1; epigenetic changes
Treacher Collins syndrome	Hypoplasia of the zigomata, maxilla, mandible, downslanting palpebral fissures, absence of the medial lower eyelashes with coloboma of the lower lid, microtia, cleft palate, conductive hearing loss	—	Autosomal dominant	Haploinsufficiency of treacle, the *TCOF1* protein product
Auriculo-Condylar syndrome (Question Mark Ear syndrome)	Prominent and malformed ears, microstomia, abnormal temporomandibular joint, mandibular condyle hipoplasia; facial asymmetry, cleft palate, hypoplastic tongue	Developmental delay in few cases	Autosomal dominant	Heterogeneity, ACS1 locus mapped at 1p21-q23
Oculoauriculofrontonasal spectrum	Ocular hypertelorism, wide nasal bridge, microtia, epibulbar dermoids, cleft lip, macrostomia	Congenital heart anomalies, encephaloceles, fusion of C2-C3	Sporadic and autosomal dominant	Unknown
Acrofacial dysostosis, type Nager	Hypoplasia of the zigomata, maxilla, mandible, downslanting palpebral fissures, absence of the medial lower eyelashes with coloboma of the lower lid, cup-shaped ears, cleft palate	Asymmetric thumb hyploplasia or aplasia, radial hyploplasia or aplasia with radioulnar synostosis, missing phalanges and syndactyly	Most cases are sporadic; but there are reports of autosomal dominant and autosomal recessive inheritance	Alterations in chromosomes 1q, 3p and 9q
Miller syndrome	Malar hipoplasia, lower lid ectropion, downslanting palpebral fissures, coloboma of the eyelid, micrognathia, cleft lip and/or cleft palate, long philtrum, malformed ears	Bilateral absence of the fifth finger and fifth metacarapal, hipoplasia of the thumbs and syndactyly, forearm anomalies, hyploplasia or absence of the third and fourth toes	Sporadic. Autosomal recessive inheritance is possible	Unknown
Branchio-oto-renal syndrome (BOR syndrome)	Long and narrow facial shape, facial nerve paralysis, aplasia or stenosis of the lacrimal duct, anomalies of the external and inner ears, preauricular pits	Anomalies of the renal system, neck branchial cleft cysts or fistulas	Autosomal dominant	Heterogeneity: haploinsufficiency of *EYA1* and *SIX5*; and a locus mapped at 1q31
Wildervanck syndrome	Abducens palsy with retracted globe, facial asymmetry, hearing loss (sensorineural and conductive)	Fused cervical vertebrae, short and thick neck, spina bifida occulta, fusion or absent ribs	Multifactorial	Unknown
Townes–Brocks syndrome	Malformed ears ("satyr" ears) with sensorineural hearing loss, preauricular skin tags	Imperforate anus, triphalangeal thumbs, renal and cardiac defects	Autosomal dominant	Mutations in *SALL1*

Moebius syndrome	Palsies of the sixth and seventh cranial nerves, hipoplasia or absence of the facial muscles, mask-like facies, micrognathia, defective ocular rotation, ptosis, nystagmus or strabismus	Reductive limb anomalies, defects of the chest wall, mental retardation	Most cases are sporadic; but there are reports of autosomal dominant and autosomal recessive inheritance	Heterogeneity; possible disease gene locations: chromosomes1, 2 and 13q12.2-q13
Oral-facial-digital syndromes (types I to X) (OFD)	Minor facial anomalies, oral findings (cleft or lobulated tongue, oral frenula, cleft palate)	Digital anomalies (brachydactyly, syndactyly, clinodactyly and polydactyly)	X-linked dominant (OFD1, OFD7); X-linked recessive (OFD8, OFD9); autosomal recessive (OFD2, OFD3, OFD4, OFD5, OFD6, OFD9); autosomal dominant (OFD7)	OFD1 is the only mapped locus (*CXORF5* gene)
Otopalatodigital syndrome, type I (OPD1)	Overhanging brow, prominent supraorbital ridge, wide nasal bridge, downslanting palpebral fissures, hypertelorism, cleft palate (only in affected males), conductive hearing loss	Retarded skeletal growth, small trunk, pectus excavatum, digital anomalies (syndactyly and clinodactyly, short big toes), mushroom-like appearance of the skull	X-linked semidominant condition	Gain-of-function mutations in the gene encoding filamin A (*FLNA*)
Otopalatodigital syndrome, type II (OPD2)	Hypertelorism, frontal bossing, midface hipoplasia, broad nasal bridge, downslanting palpebral fissures, low set ears, microstomia, mandibular micrognathia	Thin and wavy clavicles, narrow thorax, malformed ribs, flattened vertebrae, scoliosis, bowed humeri, radii, femora and tibiae, digital anomalies, rocker-bottom or equinovarus feet	X-linked semidominant condition	Allelic variant of OPD1

OAVS with minor signs of the syndrome, such as preauricular tags/pits, should represent milder forms of the disorder.

The birth prevalence was estimated to be 1/5,600 [Grabb, 1965], but others suggested a much lower birth prevalence in the range of 1/20,000 [Melnick, 1980; Stoll et al., 1984]. The etiological mechanism for OAVS, which might affect the embryo at approximately 30–45 days of gestation, is still unknown. There are several evidences based both on animal models [Poswillo, 1975] and human case reports [Gorlin et al., 2001] that early vascular disruption is associated with this phenotype. The OAVS phenotype has also been noted in infants born to diabetic mothers [Grix, 1982; Ewart-Toland et al., 2000; Wang et al., 2002], woman living in high altitude regions [Castilla et al., 1999] or to pregnant women exposed to thalidomide [Brancato, 1969; Smithells and Newman, 1992; Jacobsson and Granstrom, 1997], primidone [Gustavson and Chen, 1985] and retinoic acid [Lammer et al., 1985; Johnston and Bronsky, 1995] providing evidence that nongenetic factors also play a role in its causation.

Several cytogenetic alterations have been associated with OAVS. Most of the chromosome alterations were patient-specific, but involvement of chromossomes 5, 18, 22 and X were reported more than once. A 1p21-23 deletion was identified through CGH array in a patient with a complex phenotype that included OAVS [Schell-Apacik et al., 2008]. It is thus possible that microchromosomal rearrangenments might be an important etiological mechanism for OAVS, particularly in those cases associated with abnormal development, as we have recently shown for syndromic craniosynostosis [Jehee et al., 2008]. Most cases are sporadic, but familial instances usually compatible with autosomal dominant inheritance have been observed in about 2–10% of the cases [Gabbett et al., 2008; Vendramini-Pittoli and Kokitsu-Nakata, 2009]. Wide clinical variability is also observed within families. Discordance in monozygotic and dizygotic twins has been reported frequently but there are rare reports of concordance with variable expression in monozygotic twins [Gomez Garcia et al., 1984; Stoll et al., 1984]. The rarity of reports of concordance of the defect in twins supports the suggestion that the condition is sporadic in most families. Indeed, a low recurrence risk (about 2–3%) has been estimated [Gorlin et al., 2001]. Thus etiologic heterogeneity including genetic and nongenetic factors seems to be the most likely explanation for OAVS.

New insights into the understanding of OAVS have come through linkage analysis in two large families with an inheritance pattern compatible with autosomal dominant model [Kelberman et al., 2001]: an OAVS locus was mapped at 14q32.1 through linkage analysis and genetic heterogeneity was also shown. *Goosecoid*, mapped to the 14q32 region, was considered the best candidate gene. However, no pathogenic mutation has yet been found. Studies of additional families are of utmost importance to help in the identification of the causational gene. Furthermore, cloning of the breakpoint of a translocation involving chromosomes 4 and 8 (46, XX, t(4;8)(p15.3;q24.1) in a patient with OAVS and multiple exostoses showed that the disruption of *EXT* at chromosome 8 is possibly responsible for the multiple exostoses phenotype. On the other hand, the break in chromosome 4 is very close to the human *BAPX1* gene. Although the gene is not disrupted, they found abnormal *BAPX1* expression in a significant number of patients with OAVS [Fischer et al., 2006]. A new hypothesis has emerged in

which epigenetic disregulation of *BAPX1* and other genes might play a role in the etiology of OAVS. Such a mechanism can explain many of the genetic and phenotypic manifestations of OAVS, including the high proportion of discordant monozygotic twins, the increased proportion of twins and high correlation of use of in vitro fertilization and incidence of OAVS [Wieczorek et al., 2007]. Although still incompletely understood, it is possible that epigenetic changes in the ovum or in the zygote could be related to the higher incidence of twining and related to OAVS [Fischer et al., 2006; Wieczorek et al., 2007].

Auriculo-Condylar syndrome (ACS OMIM 602483), first described by [Jampol et al., 1998], is another autosomal dominant disorder of the first and second pharyngeal arches in which the spectrum of clinical variability overlap with OAVS (Figs. 1 and 2). The syndrome is characterized by the presence of prominent and malformed ears, microstomia, abnormal temporomandibular joint, and hypoplasia of the mandibular condyle. This condition is also known as question mark ear syndrome due to the unusual shape of the ear, which characteristically has marked constriction at the junction between the lower and middle thirds of the pinna, with a cleft separating the lobule from the helix giving them an appearance of a ''question mark.'' Facial asymmetry is not rare. Penetrance seems to be complete, but there is high inter- and intra-familial clinical variability. The phenotype variation is not only defined by the severity of the malformations, but also by the presence/absence of less-frequent clinical findings such as cleft palate, hypoplastic tongue, hypotonia, and developmental delay. We have mapped the first locus to 1p21-q23 and showed that there is genetic heterogeneity [Masotti et al., 2008]. ACS has several overlapping clinical signs with other disorders of the first and second pharyngeal arches, but most markedly with oculoauriculo-vertebral spectrum (OAVS). Identification of the ACS gene will be important not only to better understand the molecular pathways underlying the development of the first and second pharyngeal arches but also for genetic counseling.

Treatment of these conditions is mainly corrective through surgical interventions. New hope has been given with pharmacological and genetic inhibition of p53 function, which has rescued the phenotype of the TCS mouse model through decrease in apoptosis of cranial neural crest cells during early embryogenesis [Jones et al., 2008]. Considering the phenotypic overlap among these three conditions (Figs. 1 and 2), it is possible that genes involved in these conditions belong to a common molecular pathway. Therefore, identification and characterization of the primary and indirect factors leading to this group of disorders will have an important impact on the delineation of the molecular pathways involved in craniofacial development from the first and second pharyngeal arches or even from cranial neural crest cells. In addition, it will open new strategies for treatment and rehabilitation of these patients.

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