Original Article

Molecular Syndromology

Mol Syndromol 2018;9:15–21
DOI: 10.1159/000484427

Accepted: September 18, 2017
by M. Schmid
Published online: November 29, 2017

Proximal Deletion of 6q Overlapping with Toriello-Carey Facial Phenotype: Prenatal Findings, Clinical Course, Differential Diagnosis, and Review

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Keywords
Deletion of 6q · Facial dysmorphism · Toriello-Carey syndrome

Abstract
Proximal deletion of 6q is a relatively rare chromosomal abnormality. Reported patients have deletions of different sizes but share partial overlap and present with similar clinical features, and some of them were described prior to the introduction of chromosome microarrays. We describe a male patient with prenatal sonographic findings of nuchal edema, intrauterine growth restriction, renal pelvis dilatation, and oligohydramnios. At birth, facial dysmorphism, retro/micrognathia, a short and wide neck as well as cardiovascular and renal anomalies were noted. His clinical evolution has been marked by failure to thrive, severe developmental delay, and cognitive impairment. The diagnosis of Toriello-Carey syndrome (TCS) was based on his "gestalt." aCGH identified a de novo proximal deletion of 17 Mb in 6q (6q12q14.3). Deletion 6q13q14 seems to be responsible for the main facial features and should be considered within the differential diagnosis of TCS.

Proximal 6q deletion is relatively uncommon. Prior to the introduction of chromosome microarrays, 9 cases were described with deletions between 6q11 and 6q16 [Kumar et al., 1997]. The authors stated a variable degree of cognitive impairment associated with a recurrent distinctive facial phenotype, including upslanting palpebral fissures with epicanthal folds, a short nose with anteverted nares, long philtrum, thin lips, and large ears. Joint hypermobility and hernias were frequent.

In this study, we describe a patient with a large deletion of the long arm in chromosome 6 (6q12q14.3), who has a phenotype consistent with Toriello-Carey syndrome (TCS). TCS is a genetically heterogeneous disorder originally described in 1988 in 4 patients [Toriello and Carey, 1988]. Key features include postnatal growth failure, hypotonia, developmental delay, intellectual disability, a short neck, and characteristic facial anomalies (hypertelorism/telecanthus, blepharophimosis, abnormal ears, small nose, full cheeks, thin lips, and micrognathia). Abnormal corpus callosum, laryngeal/tracheal anomalies, cardiovascular disease, herniae, genital anomalies in males, and skeletal defects have also been reported features [Toriello et al., 2003]. Prenatal sonographic findings

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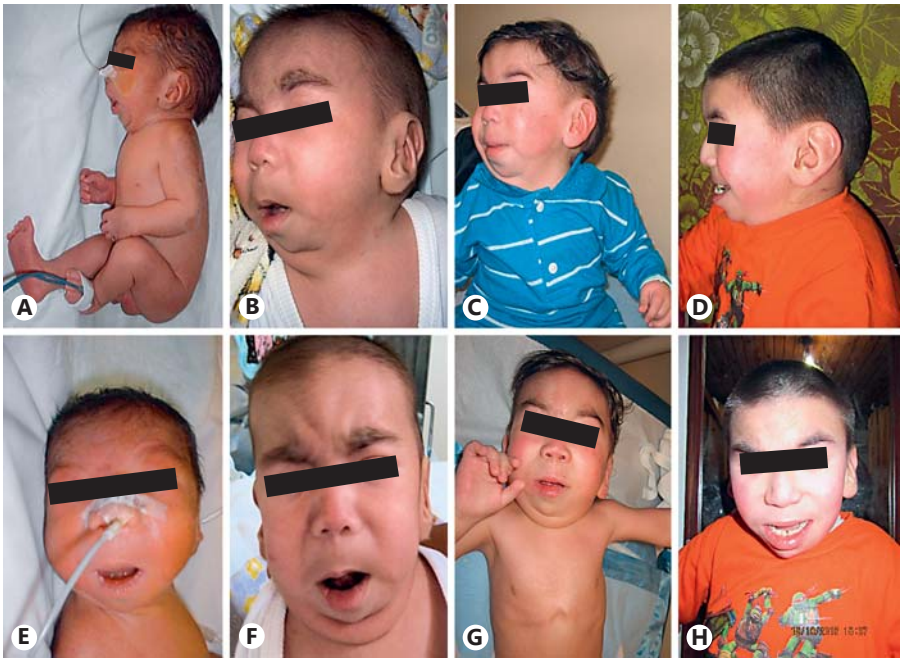

Fig. 1. Evolving facial phenotype. Profile and frontal views of the patient. **A**, **E** At birth. **B**, **F** 6 months old. **C**, **G** 14 months old. **D**, **H** 9 years old. Note the blepharophimosis, epicanthal fold and telecanthus, medially flared eyebrows, low-set posteriorly rotated ears, long philtrum, full cheeks, microretrognathia, and a short, wide neck.

and clinical follow-up examinations up to age 9 years and 4 months are reported. The common clinical findings of proximal deletion of 6q are compared and reviewed with those of TCS.

Clinical Report and Results

The patient is the first child of a Chilean nonconsanguineous couple. The mother, who was 41 years old, had 2 previous children who were healthy. The father also was a healthy 36-year-old man. Family history was unremarkable. Prenatal gestational diabetes was reported at the end of the second trimester and was controlled by diet. No other prenatal teratogen exposure was reported. At 22 weeks of gestation, ultrasound findings revealed marked nuchal edema, ventricular septal defect, intrauterine growth restriction as well as bilateral renal pelvis dilatation and oligohydramnios. The parents declined prenatal cytogenetic analysis.

The boy was born at 36 weeks by cesarean section due to fetal distress. His birth weight was 2,500 g (10–25th percentile), length 44 cm (below 10th percentile), and his head circumference was 34 cm (50–90th percentile), according to national charts [Milad et al., 2010]. Apgar scores were 8/9 at 1 and 5 min.

On physical examination, hypotonia and dysmorphic features were evident at birth. Facial anomalies included blepharophimosis, epicanthic folds, telecanthus, thick eyebrows, depressed nasal bridge, posteriorly rotated large ears, long philtrum, high-arched palate, full cheeks, retro/micrognathia, downturned corners of the mouth, thick lower lip, and a short, wide neck with redundant skin (Fig. 1). Other physical findings include a broad thorax with wide-spaced nipples, mild pectus carinatum, and right undescended testis. His hands and feet showed mild camptodactyly and brachydactyly.

Flexible endoscopy confirmed a mild laryngomalacia. Fundoscopic examination was normal. Skull and cervical radiographs were also normal. A brain CT scan did not show abnormalities.

An echocardiogram revealed a small ventricular septal defect, patent ductus arteriosus, and aortic coarctation, which were subsequently corrected by surgery.

An abdominal ultrasound scan showed a left duplex collecting system and nephrolithiasis in the right kidney. Ureterocystography revealed a grade IV-V left and grade III right vesicoureteral reflux. Renal scintigraphy (99mTc-DMSA) revealed exclusion of the left kidney (lower pole); therefore, a left lower-pole hemine-phrectomy was performed.

TCS was proposed based on the facial phenotype and congenital anomalies. Peripheral blood chromosome analysis revealed a normal karyotype (46,XY), and FISH analysis for 22q11.2 microdeletion was negative. In addition, subtelomeric screening using FISH multiplex did not show abnormalities.

During his first 2 years of life, he had recurrent and prolonged hospitalizations due to life-threatening bronchial and urinary tract infections. From ages 2 to 9, there were no follow-up examinations, and the patient had not received medical care and rehabilitation therapy.

At the age of 9 years and 4 months, his mother resumed his medical checkups. At that time, his height was 110 cm (–3.96 SD for age), weight 16.6 kg (–4.07 SD for age), and his head circumference was 51 cm (10th percentile for age). During his physical examination, he had some eye contact but near absence of speech. He did not walk alone and remained lying or sitting down most of the time. Joint hypermobility and thoracic scoliosis were noted. So far, he did not attend kindergarten or any other type of school education.

In order to discard cryptic chromosomal alterations, molecular karyotyping (Cytoscan HD, Affymetrix, Santa Clara, CA, USA)

was performed. A genomic loss at 6q12q14.3 (68,809,340–86,346,689) with a deletion size >17 Mb was identified, arr[hg19] 6q12q14.3(68,809,340–86,346,698)×1 (Fig. 2). According to the OMIM database, the 6q12q14.3 region contains 46 genes. No additional relevant copy number variation was detected.

Parental chromosome analyses and a new prometaphase karyotype of the patient are pending for further characterization.

Discussion

The etiology of TCS is not fully understood; 20% of the cases reported have chromosomal abnormalities [Toriello and Hatchwell, 2008]. In this study, we describe the clinical features of a patient with a TCS facial phenotype who also was found to have a 6q12q14.3 deletion. Other patients with proximal 6q deletion have been reported with varying phenotypes as shown in Table 1.

Common clinical manifestations of patients with 6q13q14 deletion syndrome include developmental delay, hypotonia, and characteristic facial dysmorphism defined by upslanting palpebral fissures, short nose/anteverted narines, a thin upper lip, smooth long philtrum, and large earlobes. Other common features are joint laxity and loose connective tissue. The majority of patients described in the literature have urogenital anomalies as well [Van Esch et al., 2010].

We performed a literature review of clinical findings of proximal 6q deletion cases overlapping with our case [McNeal et al., 1977; Young et al., 1985; Yamamoto et al., 1986; Lonardo et al., 1988; Slater et al., 1988; Turleau et al., 1988; Valtat et al., 1992; Gershoni-Baruch et al., 1996; Romie et al., 1996; Hopkin et al., 1997; Kumar et al., 1997; Myers and Challman, 2005; Lespinasse et al., 2009; Van Esch et al., 2010; Wentzel et al., 2010; Woo et al., 2010; Becker et al., 2012; Quintela et al., 2015; Duarte et al., 2016]. In the majority of the cases, developmental delay and craniofacial features were common and variable. None of the authors mentioned the differential diagnosis of TCS syndrome for their patients.

Our patient had severe global developmental delay that could be attributed to the relatively large size of the deletion. In addition, he suffered 2 episodes of cardiac arrest during his hospitalizations; early intervention and multidisciplinary care were limited.

The facial features present in our case are similar to the patients reported by McNeal et al. [1977]; Young et al. [1985], patient 1; Slater et al. [1988]; Romie et al. [1996]; Gershoni-Baruch et al. [1996]; Kumar et al. [1997]; Lespinasse et al. [2009], and Van Esch et al. [2010], patient 4. These patients have a common region of overlap between

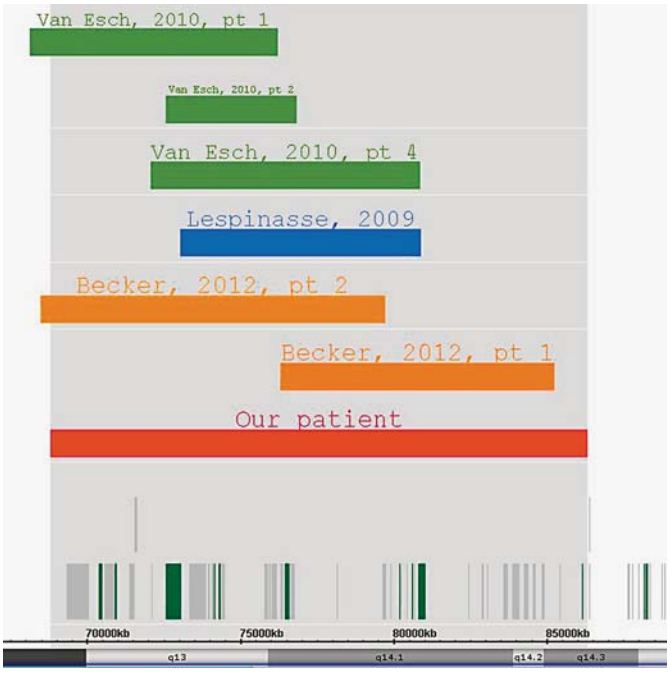

Fig. 2. Schematic diagram of the 6q arm. Our patient's deletion (marked in red) and previously reported similar deletions with cytogenomic data within the 6q12q14.3 region are depicted (Figure prepared using Affymetrix® Chromosome Analysis Suite 3.1).

6q13 and 6q14.1, but only the latter 2 provide cytogenomic data as depicted in Figure 1. Patients reported by Becker et al. [2012] also have a deletion which overlaps in this region; however, there was only a photograph of one patient available who presented with mild dysmorphism. In general, patients with deletions encompassing at least 6q14.1 had short palpebral fissures, ear anomalies, full cheeks, and a short neck (Table 1).

To date, no gene has been identified as the main cause of TCS, and the diagnosis remains mainly clinical, even though no clinical criteria have been established. In our case, the facial phenotype with redundant neck skin, growth failure, hypotonia, developmental delay, and the associated malformations resembled TCS. Although our patient does not have corpus callosum abnormalities, not all TCS patients have callosal anomalies [Toriello and Carey, 1988]. In addition, it is well recognized that up to 20% of the patients with a TCS phenotype [Martin-Denavit et al., 2004; Toriello and Hatchwell, 2008; Tegay et al., 2009] have been found to have different chromosome anomalies.

Our patient had short stature with prenatal onset, and his head circumference always remained consistent. Ear-

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Table 1. Phenotypic overlap between patients with 6q proximal deletions involving the 6q12q14 region and Toriello-Carey syndrome

Features	McNeal et al., 1977	Young et al., 1985; patient 1	Yamamoto et al., 1986	Lonardo et al., 1988	Turleau et al., 1988	Slater et al., 1988	Valtat et al., 1992		Gershoni-Baruch et al., 1996	Romie et al., 1996	Kumar et al., 1997	Hopkin et al., 1997; patient 1	Lespinasse et al., 2009	Woo et al., 2010
							patient 1	patient 2						
Cytogenetic or cytogenomic abnormality	6q13q15	6q14q15	6q13q15	6q12q14	6q14q16.2	6q11q15	6q14q16	6q14q16	6q13q15	6q13q14.2	6q13q14.2	6q13q14.2	arr[hg19] 6q13-6q14.1 (73,055,279–80,931,281) × 1	arr[hg19] 6q13q16.2 (73,378,824–99,824,130) × 1
Respiratory distress	+	–			–	–		+						+
Feeding abnormalities	–	+			–	+								+
Postnatal growth failure	+	+	–	–	–	+	+	–	+	–	–		–	
Global delay	+	+	+		+	+			+	+	+	+	+	
Intellectual disability		+	+		+		+	+					+	
Large anterior fontanelle		–												
Microcephaly	+	–	–	–	+	+	+	–	–					
Abnormal eyebrows	+	+	+	+	+				+					
Telecanthus, hypertelorism		–			–	–						+		
Short ascendent palpebral fissures	+	+	+	+	+	–	+	+	+	+	+	+	+	
Short nose/anteverted nares	+	+	–	+	+			+	+	+	+		+	
Full cheeks	+	+	+	+	+									
Cleft or highly arched palate		–	+		–	+		+	+				–	+
Long/smooth philtrum	+	+	+	+	+	+			+					
Thin upper lips	–	–	–		–					+	+	+	–	
Micrognathia, retrognathia	+	–			–	+		+	+				+	
Ear anomalies	+	+	–		+	+	–	+	+	+	+	+	+	+
Short neck/nuchal fold	+	+	+	–	+	+		+	+					
Abnormal corpus callosum			–		–		–		–	–	–	–	–	–
Other brain anomaly			–		–		–		+	+	+	–	–	+
Spinal/vertebral anomaly	+	+	+		–				–					
Hypotonia		+			+				+	+	+	+	+	
Joint laxity		–							+	+	+		+	+
Hearing loss	–								–					
Laryngeal/tracheal anomaly	+	–			–			+						
Cardiac defect	+	–	+	+	–				–	+	+	–	–	–
Urogenital anomaly	+	–	+		–	+			+	+	+	–		–
Hernia	+	+	+	+	+	+			+			+	+	+
Rib or chest anomaly													+	
Hand/foot anomalies	+	+	+		+	+			+				+	
Small nails		+												

Table 1 (continued)

Features	Wentzel et al., 2010		Van Esch et al., 2010				Becker et al., 2012		Duarte et al., 2016	Our patient	Toriello-Carey syndrome
	patient 1	patient 2	patient 1	patient 2	patient 3	patient 4	patient 1	patient 2			
Cytogenetic or cytogenomic abnormality	arr[hg19] 6q14.1q15 (79,324,861–88,043,414) × 1	arr[hg19] 6q14.1q15 (83,833,396–88,334,350) × 1	arr[hg19] 6q13q14.1 (68,156,441–76,262,098) × 1	arr[hg19] 6q13q14.1 (72,597,333–76,869,202) × 1	arr[hg19] 6q13q16.1 (72,100,590–97,078,142) × 1	arr[hg19] 6q13q14.1 (72,100,590–80,896,703) × 1	arr[hg19] 6q14.1q14.3 (76,343,159–85,247,699) × 1	arr[hg19] 6q12.1q14.1 (68,491,706–79,746,176) × 1	arr[hg19] 6q14.1q16.1 (81,728,627–94,438,332) × 1	arr[hg19] 6q12q14.3 (68,809,340–86,346,698) × 1	NA
Respiratory distress										+	+
Feeding abnormalities								+		+	+
Postnatal growth failure					+	+	+	+		+	+
Global delay	+	+	+	+	+	+	+	+	+	+	+
Intellectual disability			+	+		+		+		+	+
Large anterior fontanelle									+	–	+
Microcephaly							–	–		–	+
Abnormal eyebrows				+			+	+		+	–
Telecanthus, hypertelorism								–		+	+
Short ascendent palpebral fissures			–	–	–	–	+	+	+	+	+
Short nose/anteverted nares	+	+	–	–	–	–	+	+	+	+	+
Full cheeks	+	+							+	+	+
Cleft or highly arched palate	+		+	–	+	–	–	+			+
Long/smooth philtrum			+	+	+	+			+	+	–
Thin upper lips	+		+	+	+	+	+	+		+	–
Micrognathia, retrognathia					+				+	+	+
Ear anomalies	+	+	+	+	+	+	+	+	+	+	+
Short neck/nuchal fold								+		+	+
Abnormal corpus callosum	+		–	–	–				–	–	+
Other brain anomaly	+		–	–	–				–	–	+
Spinal/vertebral anomaly		+	+	–	–			+	–	–	–
Hypotonia			+	+	+	+		+	+	+	+
Joint laxity			+	+	+	+		+		+	–
Hearing loss	+				+			+	+	–	+
Laryngeal/tracheal anomaly									+	+	+
Cardiac defect		+		–			+		–	+	+
Urogenital anomaly	+		+		+	+		+	–	+	+
Hernia	+	+		+	+				+	–	–
Rib or chest anomaly		+		+					–	+	+
Hand/foot anomalies	+		+	+	+		+	+		+	+
Small nails							+			–	+

NA, not applicable; +, present; –, absent.

ly-onset hypotonia and marked developmental delay were also clinical findings in our patient. Both the joint hypermobility and the lack of adequate stimulation could be factors that contributed to the severe global developmental and cognitive delay observed at 9 years of age.

The size of the deletion identified in our patient is >17 Mb, spanning 46 OMIM genes. Some of them encode proteins that may explain part of the observed phenotype, such as *COL12A1*, *TBX18*, *MYO6*, *HTR1B*, *RIPPLY2*, and *PHIP*. Other genes encode proteins involved in autosomal recessive phenotypes such as inborn errors of metabolism (*LMBRD1*, *SLC17A5*, and *ELOVL4*), immunodeficiency (*PGM3*), and arterial calcification (*NT5E*).

It is noteworthy to mention the haploinsufficiency of 3 genes involved in fibril-associated collagen (*COL12A1*, *COL9A1*, *and COL19A1*) may be related to the various musculoskeletal problems in our case. Mutations in *COL12A1* (6q14.1) could cause variable muscle and connective tissue anomalies, such as myopathy, muscle weakness, distal joint hyperlaxity, pectus anomalies, scoliosis, and micrognathia [Zou et al., 2014; Punetha et al., 2017]. *COL12A1* is also expressed in the aorta [Oh et al., 1993] and inner ear [Ficker et al., 2004]. Heterozygous mutations in *COL9A1* (6q13), not a gene deletion, are associated with mild chondrodysplasia [Czarny-Ratajczak et al., 2001], while in mutations in *COL19A1* (6q13), no phenotypic association is recognized, even though the protein is ubiquitously expressed in embryo tissues but restricted to the brain in adults [Sumiyoshi et al., 1997; Su et al., 2010].

Another relevant gene to consider is *MYO6* (6q14.1) which encodes myosin-VI, an essential protein in the maintenance of the structural integrity of the inner ear hair cells [Self et al., 1999] and found to be the cause of both autosomal dominant and recessive nonsyndromic hearing loss [Melchionda et al., 2001; Ahmed et al., 2003].

The *PHIP* gene (6q14.1), also found in this region, modulates insulin signaling and has been reported as a candidate for developmental delay, intellectual disability, obesity, and facial dysmorphisms [de Ligt et al., 2012; Webster et al., 2016].

The *HTR1B* gene (6q14.1) encodes a serotoninergic receptor that has been associated with behavior and psychiatric disorders [Drago et al., 2010], but the association with neurodevelopmental delay remains elusive.

In relation to scoliosis and short neck, the *RIPPLY2* gene (6q14.2) could be a candidate gene that participates in these phenotypes because of its role in the *NOTCH* signaling pathway by regulating *TBX6* [Zhao et al., 2015]. *TBX6* is a key element in the process of somitogenesis and is also involved in congenital scoliosis [Wu et al., 2015]. In addition, recessive mutations in *RIPPLY2* cause vertebral segmentation defects as Klippel-Feil syndrome [Karaca et al., 2015].

The *TBX18* gene (6q14.3) is a good candidate for genitourinary abnormalities because it is crucial in ureteral development and renal vasculature [Xu et al., 2014]. Our patient had right cryptorchidism with a left duplex collecting system and bilateral vesicoureteral reflux.

Other genes associated with human phenotypes include the *RIMS1* gene (6q13) related to autosomal dominant cone-rod dystrophy; therefore, a formal ophthalmological evaluation is pending.

Conclusion

We present a patient with a large proximal 6q deletion resembling TCS. Deletion 6q13q14 leads to a distinctive phenotype that should be considered as part of the differential diagnosis of TCS, especially because the facial phenotype including a short nose, short palpebral fissures, smooth philtrum, large ears, and short neck was constant in these patients. Joint laxity, scoliosis, cardiac and renal anomalies are also frequent findings. All patients had developmental delay without structural brain anomalies in contrast to the patients reported by Toriello et al. [2016] who presented with corpus callosum anomalies. Musculoskeletal abnormalities were found to be common findings related to the deletion, probably due to the deletion of collagen genes, especially *COL12A1*.

Acknowledgments

The authors thank María Luisa Guzmán, clinical nurse, for her logistical support, and Sonia Margarit, genetic counselor, for the critical review of the manuscript.

Statement of Ethics

The study protocol was approved by the local Ethics Committee. Written informed consent was obtained from the patient's guardian for publication of this case report and photographic images.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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