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## Three Patients With Oculo-Auriculo-Vertebral Spectrum and Microdeletion 22q11.2

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### Abstract

We report on three unrelated patients with the 22q11.2 microdeletion syndrome (del22q11) who have phenotypic anomalies compatible with oculo-auriculo-vertebral spectrum (OAVS). Hemifacial microsomia, unilateral microtia, hearing loss, congenital heart/aortic arch arteries defects, and feeding difficulties were present in all three patients. Additional anomalies occasionally diagnosed included coloboma of the upper eyelid, microphthalmia, cerebral malformation, palatal anomalies, neonatal hypocalcemia, developmental delay, and laryngomalacia. Several clinical features characteristic of OAVS have been described in patients with del22q11 from the literature, including ear anomalies, hearing loss, cervical vertebral malformations, conotruncal cardiac defects, renal malformations, feeding and respiratory difficulties. Atretic ear with facial asymmetry has been previously described in one patient. Thus, clinical expression of hemifacial microsomia and microtia resembling OAVS should now be included within the wide phenotypic expression of del22q11. The occurrence of this manifestation in del22q11 is currently low. Nevertheless, patients with hemifacial microsomia and microtia associated with clinical features typically associated with del22q11 should now have for specific cytogenetic testing.

## Keywords

deletion 22q11.2; Goldenhar syndrome; hemifacial microsomia; oculo-auriculo-vertebral spectrum; velo-cardio-facial syndrome

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## Introduction

Deletion 22q11.2 syndrome (del22q11 OMIM #192430) (DiGeorge/velo-cardio-facial syndrome) is characterized by facial dysmorphisms, palatal anomalies, congenital heart defects (CHDs), hypoplastic thymus and immune deficit, neonatal hypocalcemia, speech and learning difficulties [Ryan et al., 1997; McDonald-McGinn et al., 1999]. Most of the structures primarily affected in del22q11 are derivatives of the branchial arch system, and a developmental relation to neural crest cell migrational anomalies has been noted [Van Mierop and Kutsche, 1986; Kirby and Waldo, 1990].

The oculo-auriculo-vertebral spectrum (OAVS, OMIM 164210) is a non-random association of unilateral microtia, hemifacial microsomia with mandibular hypoplasia, ocular epibulbar dermoid, and cervical vertebral malformations [Rollnick et al., 1987; Gorlin et al., 2001]. Cerebral, cardiac, and renal malformations can also be detected [Rollnick et al., 1987]. The condition is also known as Goldenhar syndrome, referring to its first description [Goldenhar, 1952]. Morphogenetic anomalies of the first and second branchial arches, usually of a unilateral nature, and neural crest cell migrational abnormalities have been suspected to be implicated in the etiopathogenesis of the condition [Lammer and Opitz, 1986], but chromosomal aneuploidies have been detected occasionally [Gorlin et al., 2001].

Here we report on three unrelated patients with del22q11 who have phenotypic anomalies compatible with OAVS.

## Clinical Reports

### Patient 1

This 5-month-old Caucasian male is the third child of healthy unrelated parents. Family history was unremarkable. At birth the mother was 31 years old, the father 39. The baby was born by vaginal delivery after an uneventful pregnancy. Birth weight was 3,470 g (50th–75th centile), length 50 cm (50th–75th centile), head circumference 34 cm (50th centile). Apgar scores were 8 at 1 min, and 9 at 5 min. Echocardiography performed shortly after birth revealed a double outlet right ventricle with valvular and infundibular pulmonary stenosis, subaortic ventricular septal defect, and normally related great arteries. Hypocalcemia secondary to hypoparathyroidism was diagnosed during the third day of life, and treated by calcium gluconate supplementation. Serum calcium concentration normalized after 10 days of therapy. Cerebral and abdominal ultrasound studies were normal. Audiologic screening was normal on the right, hearing loss was demonstrated on the left. A CT scan of the left ear demonstrated absence of the external auditory meatus and dysgenesis of the inner ear system. Ophthalmologic examination and vertebral column X-ray disclosed no abnormalities. T-lymphocyte count was low, serum immunoglobulin concentrations were normal for age. Clinical examination at 5 months of life revealed left hemifacial

microsomia, coloboma of the upper left eyelid, cleft palate, a small mouth, asymmetric mandibular hypoplasia, bilateral preauricular tags, microtia with aural atresia of the left ear (Fig. 1), and long fingers (Fig. 2). Standard chromosome analysis on peripheral blood lymphocytes revealed a normal 46,XY karyotype. Considering the association of conotruncal CHDs, cleft palate and facial anomalies, fluorescence in situ hybridization (FISH) with the N25 probe was performed, confirming the presence of a de novo 22q11.2 microdeletion.

## Patient 2

This 35-day-old Caucasian male is the first child of healthy nonconsanguineous parents. At birth the mother was 25 years old, the father 29. Family history was unremarkable. The baby was born by vaginal delivery at the 38th week of a normal pregnancy. Birth weight was 3,090 g (50th centile), length 47.5 cm (25th centile), head circumference 35 cm (75th–90th centile). At 2 weeks of age the patient was admitted to the hospital, with a history of feeding and respiratory difficulties. Phenotypic examination demonstrated a prominent forehead with a receding hairline, mild facial asymmetry (right cheek smaller than the left), asymmetric crying facies with a right facial droop, microtia of the right ear with a preauricular tag and atresia, low-set left ear with an overfolded, thick superior helix, asymmetric gynecomastia, a sacral dimple, and long fingers. Gastrointestinal radiological investigations performed for failure to thrive revealed severe gastro-esophageal reflux requiring a Nissan fundoplication and G-tube placement. Doppler two-dimensional echocardiography revealed an aberrant right subclavian artery, patent foramen ovalis, and trivial tricuspid regurgitation. Barium swallow confirmed a posterior indentation of the proximal thoracic esophagus and trachea due to aberrant subclavian artery. No vascular ring was evident by chest CT scan. Endoscopy of the upper airway showed normal vocal cord movement, and laryngomalacia. Full-night polysomnography disclosed several apneic events with oxygen desaturations. Brain MRI revealed an open fronto-temporal operculum with persistent cavum septum pellucidum, mild widening of the foramen of Magendie and the cisterna magna. Right external and internal ear anomalies were also detected by MRI images, including absence of the right pinna, non-visualization of the external auditory canal, and a prominent vestibule with no lateral semicircular canal. No MRI anomalies of the left internal and external ear were noted. Audiologic screening revealed right-sided hearing loss, and left-sided normal hearing. Ophthalmologic examination, vertebral column X-ray, EEG, and renal ultrasonography were all normal. Laboratory investigations, including T-lymphocyte counts, thyroid and parathyroid hormones, prolactin and estradiol dosages, were in the normal range. Chromosomal analysis from amniocytes and peripheral blood lymphocytes revealed a normal 46,XY karyotype. Microdeletion 22q11.2 was detected after birth using the N25 probe. Parental studies have not been obtained to date.

## Patient 3

This 23-month-old male is the fourth child of healthy non-consanguineous parents. At birth the mother was 34 years old, the father 39. The baby was born by vaginal delivery at term of an uneventful pregnancy. Birth weight was 3,500 g (75th centile). Developmental milestones were mildly delayed (sitting at 9 months, walking at 15 months, speech delay). Ophthalmologic examination revealed bilateral optic nerve hypoplasia. Audiologic

screening demonstrated hearing loss at the right ear. Echocardiography showed a small atrial septal defect ostium secundum type. Vertebral column X-ray revealed butterfly vertebra at the T8 and T10 levels. The baby had a history of dysphagia and feeding difficulties, resolved during the second year of life. Laryngomalacia required aryepiglottoplasty. Cerebral and renal ultrasonographies were normal. Serum calcium concentration and T- and B-cell subsets were normal. Clinical examination at 23 months of life showed left hemifacial microsomia, periorbital fullness, broad nasal root, bulbous nasal tip, hypoplastic nares, submucous cleft palate, small mouth, left microtia with aural atresia, small right ear with a simple protruding helix, tapered fingers, sacral dimple, and flat feet. Weight was 12,600 kg (25th–50th centile), length 86 cm (25th–50th centile), head circumference 49.6 cm (50th–75th centile). Standard chromosome analysis on peripheral blood lymphocytes showed a normal 46,XY karyotype. FISH with the N25 probe showed a de novo 22q11.2 microdeletion.

## Discussion

Several clinical features characteristic of OAVS have been described in patients with the clinical diagnosis of DiGeorge/velo-cardio-facial syndrome and/or cytogenetic detection of del22q11, including ear anomalies with preauricular pits or tags [Black et al., 1975; Ryan et al., 1997; McDonald-McGinn et al., 1999], hearing loss [Burn et al., 1993; Wilson et al., 1993; Britt Ravnán et al., 1996; Ryan et al., 1997; Digilio et al., 1999], cervical vertebral malformations [Ming et al., 1997], conotruncal cardiac defects [Marino et al., 2005], renal malformations [Devriendt et al., 1996; Stewart et al., 1999; Wu et al., 2002], feeding and respiratory difficulties [Ryan et al., 1997; Rommel et al., 1999; Eicher et al., 2000; Digilio et al., 2001] (Table I). Microtia with aural atresia [Derbent et al., 2003] or microphthalmia [Beemer et al., 1986] with facial asymmetry has also been described sporadically. Recently, a 1.12-Mb deletion partially overlapping with the distal end of the common 3 Mb deletion involved in the DiGeorge/velo-cardio-facial syndrome has been reported in a child with clinical features of OAVS [Xu et al., 2008].

Abnormal migration of neural crest cells is a developmental anomaly suggested to be implicated in the pathogenesis of both OAVS [Lammer et al., 1985] and DiGeorge/velo-cardio-facial syndrome [Lammer and Opitz, 1986; Van Mierop and Kutsche, 1986; Kirby and Waldo, 1990; Pizzuti et al., 1997], considering the phenotypically affected structures. With regard to del22q11, the differentiation of the branchial arches, including the precursor tissue of the ear, is controlled by neural crest cell development [Van Mierop and Kutsche, 1986; Kirby and Waldo, 1990]. Additionally, it must be pointed out that some of the genes located inside the 22q11.2 “critical region,” including *TBX1* and *UFDIL*, are specifically expressed during embryogenesis in the primordial ear [Pizzuti et al., 1997; Yamagishi et al., 1999; Vitelli et al., 2003; Raft et al., 2004]. In fact, *TBX1*<sup>-/-</sup> mice have a missing outer and middle ear, with a very malformed inner ear, lacking a cochlea or vestibular system [Vitelli et al., 2003; Raft et al., 2004]. Furthermore, malformation of the vertebral column could also be due to *TBX1* haploinsufficiency [Chapman et al., 1996; Ming et al., 1997].

An additional pathogenetic mechanism possibly linking OAVS and del22q11 is the occurrence of an early developmental anomaly in the embryonic vasculature. In fact,

vascular anomalies have been described in del22q11 and many clinical aspects of this condition are thought to be explained by vascular insufficiency or disruption [Shprintzen, 2005]. In OAVS, a mechanism interfering with vascular supply and focal hemorrhage in the developing first and second branchial arch region seems to be implicated in causing hemifacial microsomia [Poswillo, 1975; Soltan and Holmes, 1986].

A heterogeneous spectrum of CHDs is reported in 5–58% of patients with OAVS [Shokeir, 1977; Morrison et al., 1992; Kumar et al., 1993; Digilio et al., 2008], and conotruncal defects, particularly tetralogy of Fallot, have been described. Cardiac involvement in the present patients is characterized by double-outlet right ventricle, atrial septal defect ostium secundum type, and an isolated aortic arch anomaly (Table I). Double-outlet right ventricle has occasionally been described in patients with del22q11 [Ryan et al., 1997; Matsuoka et al., 1998; McDonald-McGinn et al., 1999; Marino et al., 2001], usually defined as associated with a subaortic ventricular septal defect and normally related great arteries [Marino et al., 2005]. Anomalies of branching of the aortic arch and brachiocephalic arteries have been reported in association with del22q11 [Momma et al., 1999; McElhinney et al., 2001; Toscano et al., 2002], and prenatal anomalous regression and/or persistence of the primitive branchial arches can explain embryologically the pathogenesis of these defects [Momma et al., 1999].

The association with neonatal hypocalcemia, immune deficit, and cleft palate in patient 1 was particularly suggestive of del22q11. Interestingly, the epibulbar dermoid characteristic of OAVS was absent in all three patients. A possible explanation is the fact that this anomaly is not derived from defects of neural crest cell migration.

The term OAVS is used to define patients with a combination of anomalies including microtia, ocular abnormalities, mandibular hypoplasia, and skeletal defects [Gorlin et al., 2001]. Goldenhar syndrome is generally used for variants of OAVS with epibulbar dermoids [Goldenhar, 1952]. Nevertheless, the condition is extremely complex and heterogeneous, so that hemifacial microsomia and isolated microtia with mandibular hypoplasia may also be variants of the same dysmorphic entity [Rollnick et al., 1987]. Additionally, family studies have identified isolated microtia or isolated mandibular hypoplasia in first-degree relatives of patients with OAVS [Rollnick and Kaye, 1983; Digilio et al., 2008]. For this reason, clinical features in patients in the present report are defined as OAVS or Goldenhar syndrome as manifestations of a spectrum, although ocular and cervical manifestations are lacking.

Facial appearance of the present patients combines characteristics of OAVS and del22q11. Facial anomalies of del22q11 are covered by hemifacial microsomia and mildly expressed, consisting in periorbital fullness in all cases, large nasal tip in two (with hypoplastic nares in one), and small mouth in two.

Fingers are long and tapering as usually observed in patients with del22q11. This is not a characteristic feature of OAVS, so that this sign could be useful to distinguish those patients with del22q11 from those without.

The occurrence of OAVS manifestations in patients with del22q11 is low. It must be considered that del22q11 and OAVS occur singularly very frequently (1/4,000 and 1/5,600, respectively), and coincidence cannot be excluded in the present patients. The possibility that both conditions occur together for chance in the same patient can be estimated as 1/22,400,000.

In conclusion, clinical expression of hemifacial microsomia and microtia resembling OAVS should be included within the wide phenotypic expression of del22q11. The occurrence of this manifestation in del22q11 is low. Nevertheless, patients with hemifacial microsomia and microtia associated with clinical features characteristic for del22q11 (conotruncal heart defects or anomalies of the aortic arch, neonatal hypocalcemia, immune deficit) should now be considered for cytogenetic testing FISH, MLPA, or array-based comparative genomic hybridization.

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**FIG. 1.**  
Facial appearance of Patient 1.



**FIG. 2.**  
Hands with long and tapering fingers in Patient 1.

**TABLE 1**  
 Clinical Findings in the Present Patients With Oculo-Auriculo-Vertebral Spectrum and Deletion 22q11 Syndrome

Clinical feature	Patient 1	Patient 2	Patient 3	OAVS	Del22q11
Hemifacial microsomia	+	+	+	+	-
Microphthalmia	+	-	-	+	+
Epibulbar dermoid	-	-	-	+	-
Unilateral microtia	+	+	+	+	-
Dysmorphic ear	+	+	+	+	+
Preauricular pit/tag	+	+	-	+	+
Hearing loss	+	+	+	+	+
Cerebral anomalies	-	+	-	+	+
Cervical malformations	-	-	-	+	+
Congenital heart defect	+	-	+	+	+
Aortic arch arteries anomalies	-	+	-	-	+
Renal malformations	-	-	-	+	+
Feeding difficulties	+	+	+	+	+
Laryngomalacia	-	+	+	+	+
Neonatal hypocalcemia	+	-	-	-	+
T-cell deficiency	+	-	-	-	+

Del22q11, deletion 22q11 syndrome; OAVS, oculo-auriculo-vertebral spectrum.