Oculo-auriculo-vertebral spectrum: a review of the literature and genetic update

Ana Beleza-Meireles,[1,2,3] Jill Clayton-Smith,[3,4] Jorge M Saraiva,[1] May Tassabehji[3,4]

[1]Serviço de Genética, Departamento Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[2]Center for Human Genetics, Cliniques Universitaires St Luc, Université Catholique de Louvain, Brussels, Belgium
[3]Faculty of Medical and Human Sciences, Manchester Centre for Genomic Medicine, Institute of Human Development, University of Manchester, Manchester, UK
[4]Central Manchester University Hospitals NHS Foundation Trust as part of Manchester Academic Health Science Centre (MAHSC), Manchester, UK

Correspondence to
Dr May Tassabehji, Faculty of Medical and Human Sciences, Manchester Centre for Genomic Medicine, Institute of Human Development, University of Manchester, Manchester M13 0JH, UK; m.tassabehji@manchester.ac.uk

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ABSTRACT

Oculo-auriculo-vertebral spectrum (OAVS, OMIM 164 210) is a developmental disorder primarily involving structures derived from the first and second pharyngeal arches during embryogenesis. The phenotype is clinically heterogeneous and is typically characterised by abnormal development of the ear, mandible anomalies and defects of the vertebral column. OAVS may occur as a multiple congenital abnormality, and associated findings include anomalies of the eye, brain, heart, kidneys and other organs and systems. Both genetic and environmental factors are thought to contribute to this craniofacial condition, however, the mechanisms are still poorly understood. Here, we present a review of the literature on OAVS, discussing what is known about the aetiology, candidate loci, possible mechanisms and the range of clinical features that characterise this condition. We also comment on some important aspects of recurrence risk counselling to aid clinical management.

OVERVIEW OF OCULO-AURICULO-VERTEBRAL SPECTRUM

Oculo-auriculo-vertebral spectrum (OAVS) is a disorder of craniofacial morphogenesis,[1 2] with a reported prevalence of up to 1/3500 births.[3–6] It includes a group of malformations primarily involving structures derived from the first and second pharyngeal arches, in particular the ear, mouth and mandible.[7–28] OAVS is aetiologically and pathogenetically heterogeneous. As a result of this, many terms have been used to designate this complex spectrum of anomalies, such as hemifacial microsomia, first and second pharyngeal arch anomalies, facio-auriculo-vertebral syndrome and Goldenhar syndrome. The term OAVS has its origin from the designation 'oculoauriculovertebral dysplasia', suggested by Cohen *et al* (1989),[2] who noted that there was a significant overlap between the different entities described above and suggested that they represent a phenotypic continuum.

Generally, the OAVS phenotype can range from mild to severe. Craniofacial abnormalities include asymmetric ear anomalies (preauricular tags and pits, ear dysplasia, anotia, microtia) with or without hearing loss (conductive and/or sensorineural); hemifacial microsomia resulting in facial asymmetry; orofacial clefts; ocular defects (epibulbar dermoids, microphthalmia, coloboma of upper eyelid); and vertebral abnormalities. Facial abnormalities are limited to one side in many, but not all cases. The majority of patients have some degree of facial asymmetry.[13] When bilateral involvement is present, most of them demonstrate asymmetric involvement[4 18] with more severe expression on one side.[1] The right side appears to be more frequently involved.[18] Other features such as cardiac, genitourinary and cerebral malformations have also been reported.[7] Since not all patients with OAVS present with all the common features, microtia is accepted as the minimum criterion for diagnosis, but microtia, facial asymmetry and epibulbar dermoids/lipodermoids are considered 'typical' phenotypes.

OAVS usually occurs sporadically. However, segregation analysis has suggested genetic transmission in some cases.[29] Reports of familial cases following autosomal dominant[30–33] or autosomal recessive inheritance,[4 34 35] as well as evidence for genetic linkage in two families,[36 37] and the presence of OAVS features in patients with various chromosomal aberrations and genomic imbalances,[35–67] all suggest that OAVS has a genetic basis in some cases. Environmental causes have also been suggested, such as maternal diabetes during pregnancy, gestational or pre-existing vasoactive drugs, smoking and twinning, indicating that a multifactorial aetiology (environmental and genetic) also contributes to some cases of OAVS.[68–85]

The OAVS clinical phenotype

The spectrum of phenotypic features in OAVS is variable, ranging from subtle facial asymmetry with a small skin tag in front of an otherwise normal-appearing ear, to a complex phenotype comprising multiple congenital abnormalities (see figure 1 and table 1 for summary of phenotypes and their prevalence in 158 published cases[7–10]). Due to the variable expressivity, there is no consensus regarding the minimum diagnostic criteria for OAVS. Tasse *et al*[7] suggested either isolated microtia or hemifacial microsomia together with mild ear malformations, such as preauricular tags and hillocks, (suggested to be variants of microtia) as minimal diagnostic criteria. From our clinical experience of the condition and evidence from the literature, we suggest that the presence of isolated hemifacial microsomia associated with a family history of OAVS should also be considered to be diagnostic.

Nearly all patients with OAVS have some degree of hemifacial microsomia, resulting from maxillary and/or mandibular hypoplasia (see summary of phenotypes in table 1). External ear abnormalities are also very common and include microtia, anotia, aural atresia, preauricular tags or hillocks and preauricular pits. Most affected individuals have some degree of hearing loss, therefore, all patients with OAVS need to have an audiological evaluation. Facial clefts, or cleft lip and/or palate may be observed, but these are not common features; but macrostomia is frequently seen. The craniofacial involvement is most commonly unilateral; but it

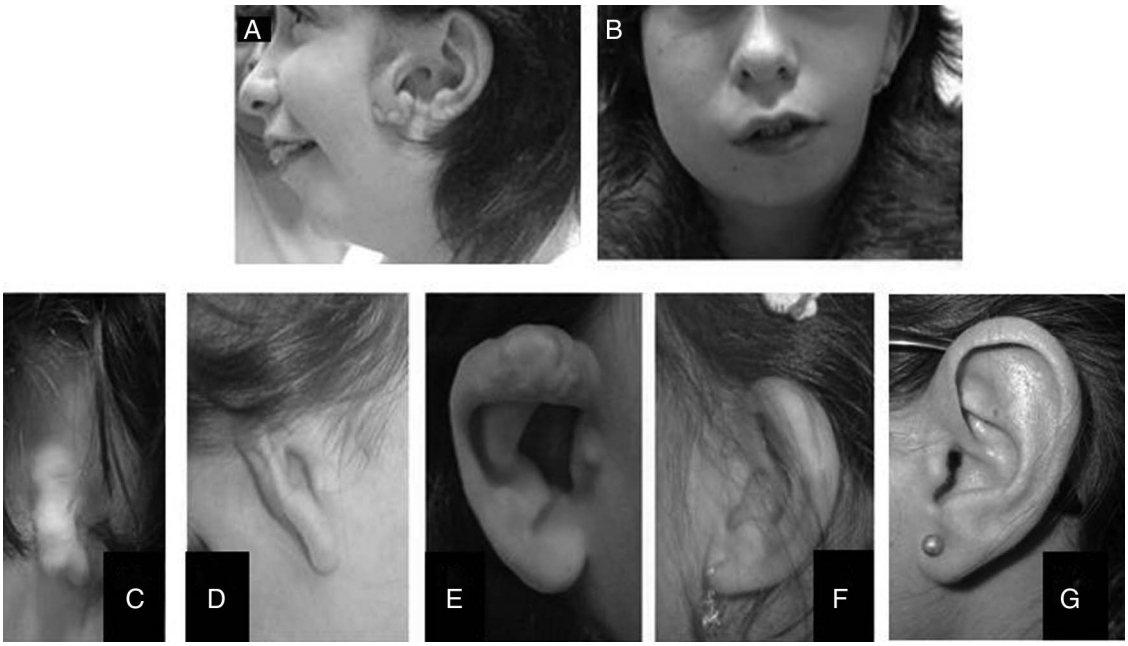

Figure 1 Characteristic craniofacial features of oculo-auriculo-vertebral spectrum (OAVS). (A–B) Two girls with OAVS, showing hemifacial microsomia and external ear defects. The first girl presents right hemifacial microsomia and right microtia, with agenesis of the external auditory meatus; she has no facial palsy, and her visual acuity is normal. The second girl has a left hemifacial microsomia and a displastic right ear with preauricular tags and displaced tragus; she has no facial palsy, and her visual acuity is normal. Neither had any additional malformations. (C–F) Different severities of microtia. The auricle is formed by a series of auricular hillocks that surround the 1st pharyngeal groove during the 6th week of gestation. At the initial stages, the auricle is formed at the base of the neck, but as the mandible develops, the auricles migrate to their normal anatomical position. Microtia occurs when the structures that form the auricle fail to develop normally. Several authors define four types of microtia according to the level of severity (type I, when the external ear is small, the auricle retains most of its normal structure, including the external auditory; type II, when the external ear is moderately anomalous, including hook-shaped, S-shaped or question mark-shaped auricle; type III, when the external is a rudimentary soft tissue structure with no cartilage and the auricle does not have a normal appearance; and type IV, characterised by anotia and absence of all external ear structures). Most cases of microtia may be difficult to define as the different forms of microtia-anotia follow a spectrum as opposed to tight groups as depicted in these photos. (G) normal ear.

can also be bilateral, usually asymmetrical. Facial palsy, asymmetric palatal elevation, impairment of extraocular movements and trigeminal anaesthesia have been described in OAVS.

A variety of ocular abnormalities may also be observed, although less frequently than the name of the condition would suggest. Epibulbar dermoids is the most common ocular findings. Microphthalmia or other severe eye malformations may also be present but are rare. Spine deformities, impaired mobility of the spine, restricted neck movements and torticollis should raise the suspicion of vertebral anomalies in patients with OAVS. Moreover, congenital heart defects (tetralogy of Fallot, septal defects, transposition of the great vessels, aortic arch anomalies, situs inversus, dextrocardia) are not uncommon in patients with OAVS,[7–10] and screening for structural cardiac anomalies should be part of the clinical evaluation of these patients.

Limb (particularly radial anomalies), renal (unilateral kidney agenesis, double ureter, renal ectopia, hydronephrosis, hydroureter) and central nervous system (developmental delay, microcephaly, encephalocele, hydrocephaly, hypoplasia of the corpus callosum, Arnold–Chiari malformation, holoprosencephaly) anomalies have also been observed in patients with OAVS.[1 2 7–25]

The aetiology of OAVS

Although knowledge of the genetic basis of human disease and its effect on embryonic development has greatly expanded in recent years, the causes of OAVS are still largely unknown, and the involvement of both genetic and environmental factors have been suggested.[1 9] OAVS involves primarily the derivatives of the first and second pharyngeal arches, so it has been proposed that the aetiology and mechanisms of OAVS are related to the development of these structures. The pharyngeal arches, which start to develop in the 4th week of embryonic development, are composed of mesenchymal cells and give rise to various facial structures, including skeletal, muscular and neural elements, through a complex but poorly characterised signalling network.[26–28] The morphogenesis of the pharyngeal arch derivatives depends on continuous and reciprocal tissue–tissue interactions. One of the key features of craniofacial development is the formation of cranial neural crest cells, which migrate ventrolaterally as they populate the craniofacial regions. Disturbances in the specification, migration, proliferation, survival and ultimate fate determination of the cranial neural crest cells have been proposed as a possible mechanism for OAVS.[26–28] The phenotypic characteristics of OAVS and severity of the defects probably depend on how the expression and activation of certain developmental genes and proteins have been disrupted during facial development.

Microtia is a common phenotype in OAVS, which may arise as a consequence of neural crest cell defects and/or vascular disruption. This clinical feature can occur as an isolated defect or in association with other anomalies, such as Treacher Collins (*TCOF1–3* mutations) and Branchio-oto-renal (*EYA1*, *SIX1*, *SIX5*) syndromes.[86 87] Although the role of these genes in external ear development is not clearly defined, it does show that single gene defects can cause this phenotype by interfering in

Table 1 Comparison of the prevalence of phenotypes from 158 published cases (7–10). (A) Summary of phenotype prevalence rates from 19 reports published between 1983 and 1996 as described by Cousley & Calvert, 1997,[8] and adapted by Heike & Hing, 2009.[9] (B) Clinical evaluation of 53 patients[7]; (C) Analysis of a cohort of 86 patients[10]

Principal anomalies	Study A (%)[8 9]	Study B (%)[7]	Study C (%)[10]
*Head and face**			
Hemifacial microsomia†	–	83	84
Macrocephaly	–	–	5
Microcephaly	–	8	–
Cleft lip/palate	15–22		18
Macrostomia/facial cleft	1762		13
Facial nerve palsy	10–45		–
Ear			
Anotia or microtia†	66–99	100‡	70
Preauricular tags†	34–61		67
Preauricular sinus/pit	6–9		7
Hearing loss	50–66§	85	68
Ocular			
Epibulbar dermoids	4–35	22	31
Coloboma of the upper eyelid	12–25	8	11
Microphthalmia	–	10	12
Orbital dystopia	15–43	–	–
Lacrimal duct atresia/stenosis	11–14	–	–
Velopharyngeal insufficiency	35–55	–	–
Vertebral anomalies	16–60¶	53	35
Congenital heart defects	4–33	15	27
Anomalies of extremities	3–21	12	–
Developmental delay	–	9**	14
Central nervous system anomalies	5–18	17††	2††
Urogenital anomalies	4–15	18	7‡‡
Pulmonary anomalies	1–15	–	–
Gastrointestinal anomalies	2–12	–	–

*Mandibular, malar, maxillary, or facial muscular hypoplasia.
†Minimal diagnostic criteria for OAVS.
‡Described as microtia/preauricular tag.
§Conductive hearing loss.
¶Vertebral/rib.
**Delay of speech development.
††Brain anomalies.
‡‡Renal anomalies.
OAVS, Oculo-auriculo-vertebral spectrum.

Table 2 Published chromosomal anomalies in patients with phenotypic characteristics of OAVS

Chromosomal abnormality	Reference
Deletion in 1p22.2–p31.1	35
Deletion 5q13.2	37
Deletion 5p15 (5p15.33–pter)	39 40 41 42
Duplication 10p14–p15	43
Deletion in 12p13.33	44 45
Duplication 14q23.1	46 47
Deletion 14q31.1q31.3	48
Deletion 15q24.1	49
Trisomy 18	50
Deletion 22qter	51
Deletions 22q11.2	52 53 54
Trisomy 22	55
Duplication 22q11.1–q11.21	56 57
Partial 22 trisomy of the 22q11 region	58
X chromosome aneuploidies	59 60 61
Translocation t(9;18)(p23;q12.2)	62
Inversion inv9(p11;q13)	63
Inversion inv14(p11.2;q22.3)	64
Mosaicism of trisomy 7	65
Mosaicism of trisomy 9	66 67
Mosaicism of trisomy 22	66

the genetic pathways necessary for normal development of mesenchymal tissues during fetal development.

Most OAVS cases are sporadic with no relevant family history. However, a genetic predisposition has been proposed based on growing evidence from the literature.[29–34] Segregation analysis performed in 311 members of the families of 74 probands with OAVS provided evidence for an autosomal dominant mode of inheritance with reduced penetrance.[29] Interestingly, a positive family history has been documented in only 2% of patients with OAVS,[30–34] however, from our clinical experience of the condition, we believe that this number is an underestimate, and it is noteworthy that a recent report by Rooryck *et al*[10] identified 12% of familial cases in a cohort of 95 patients. An additional clinical study by Rollnick *et al*[19] has presented pedigree data on 97 cases, 44 of whom had a family history of the same or similar anomaly, even if it was only minor OAVS manifestations (minor external ear anomalies or preauricular tag, which might have been removed, being the most common). The authors have reported that first-degree relatives were most often affected (35/433, 8%). Of 176 sibs cited, 11 (6%) were considered affected. In view of the family segregation of these anomalies, the authors suggest a multifactorial determination. Furthermore, the authors observe a broad phenotypic spectrum within families, an aspect that has also been reported by others,[17 18] and have proposed that familial inheritance is more frequent than originally reported.[19] The evidence, so far, does not suggest that the familial OAVS phenotype is different from the sporadic OAVS cases.

Additional evidence for a genetic basis for OAVS comes from the identification of chromosomal anomalies in patients with phenotypic characteristics of this spectrum (summarised in table 2). Some of these abnormalities are recurrent. The 5p15 deletion has been observed in several patients with OAVS features;[39–41] the region was further narrowed down to 5p15.33-pter by Ala-Mello, *et al*.[42] Deletions of the 12p13.33 region, involving the *WNT5B* gene, were observed in some but not all patients with OAVS features.[44 45] Partially overlapping microduplications on 14q23.1 were identified in two families with autosomal dominant OAVS;[46 47] one of these families included two first-degree relatives with clinical features of OAVS and Branchio-oto-renal syndrome; hence, the region 14q23.1 might harbour candidate genes for OAVS and additional first and second pharyngeal arch developmental disorders. Anomalies in 22q have been frequently documented in patients with OAVS, particularly the 22qter deletion,[51] 22q11.2 deletions,[52–54] the 22q11.1-q11.21 (Cat-eye) region,[56 57] and a partial 22 trisomy (47,XX,+der(22)t(11;22)(q23;q11)), which duplicates the 22q11 region.[66] Chromosomal mosaicism for trisomy 22[66] has also been described, making this region a good candidate for some cases of OAVS.

Other candidate single gene loci for OAVS have also been suggested. Kelberman *et al*,[36] reported linkage to a region of approximately 10.7 cM on chromosome 14q32 (D14S987 and

Table 3 aCGH CNV loci reported in patients with OAVS

Dosage anomaly (reference)	Sequence coordinates	Phenotype	Genes in interval	Minimum size (kb)	Inheritance	Array CGH platform
Del 1p22.2–p31.1[35]	Distance from pter Mb band 74–89.5	Craniofacial dysmorphism: facial asymmetry, R epibulbar dermoid cyst, downslanting palpebral fissures, long nose, small mouth, high arched palate, and teeth abnormalities; narrow ears. Additional anomalies: Psychomotor delay; short stature; hypermetropia; conductive hearing loss; short neck, scoliosis; cryptorchidism.	*FPGT*, *CRYZ*, *ACADM*, *RABGGTB*, *MSH4*, *ST6GALNAC3*, *ST6GALNAC6*, *PIGK*, *AK5*, *FUBP1*, *PTGFR*, *IFI44*, *LPHN2*, *PRKACB*, *DNASE2B*, *GNG5*, *CTBS*, *SSX2IP*, *EDG7*, *MCOLN2*, *MCOLN3*, *BCL10*, *DDAHI*, *CYR61*, *COL24A1*, *CLCA1/ CLCA2/ CLCA3*, *SH3GLB1*, *SEP15*, *HS2ST1*, *LMO4*, *PKN2*, *GTF2B*,*KAT3*, *GBP1/ GBP2*, *GBP3*	15 600	n/a	High-resolution karyotype and FISH + Genosensor Array 300 aCGH
Del 2p11.2[10]	87 552 703–89 275 144	Craniofacial dysmorphism: L mandibular hypoplasia, cleft palate, micrognathia; L microtia, R preauricular tags, L pits. Additional anomalies: not described	*RGPD2*, PLGLB1, PLGLB2, KRCC1, SMYD1, FABP1, THNSL2, C2orf51, EIF2AK3, RPIA	1722	F (P)	105 K Agilent Technologies
Del 2q11[10]	99 119 770–99 167 676	Craniofacial dysmorphism: maxillary and facial musculature hypoplasia, mandibular hypoplasia, L preauricular tags, L epibulbar dermoids. Additional anomalies: not described	*TSGA10*, C2orf15, LIPT1, MITD1, MRPL30	48	F (M)	44 K Agilent Technologies
Dup 4q35.113q13.1[10]	186 295 254–86 317 114 79 675 676–81 318 868	Craniofacial dysmorphism: L mandibular hypoplasia, B preauricular tags, R pit, R epibulbar dermoids. Additional anomalies: IUGR; agenesis of the 12th rib pair.	*SLC25A4*, KIAA1 430, SPRY2	221 643	n/a	105 K Agilent Technologies
Del 5 (pter→p15.33)[42]	(45, XX, inv(2) (q32q37)mat, dic(5;21) (p15.3;q22.3)dn)	Craniofacial dysmorphism: upslanting palpebral fissures, hypertelorism, epicanthi, epibulbar dermoids, broad nose; 'asymmetric macrostomia' with L hemifacial microsomia and cleft-like extension of the L corner of mouth; L cleft of upper lip, submucous cleft palate and two preauricular tags on L; normal ears. Additional anomalies: language delay; IUGR, short stature; recurrent middle ear infections; hypernasal voice; severe myelodysplasia; history of neonatal trombocytopenia.	*PLEKHG4B*, *CCDC127*, *SDHA*, *PDCD6*, *AHRR*, *C5orf55*, *EXOC3*, *SLC9A3*, *CTD-2228K2.7*, *CEP72*, *TPPP*, *ZDHHC11*, *BRD9*, *TRIP13*, ***NKD2***, *SLC12A7*, *SLC6A19*, *SLC6A18*, *TERT*, *CLPTM1 L*, *SLC6A3*, *LPCAT1*, *MRPL36*, *NDUFS6*, ***IRX4***, ***IRX2*** (the smallest 5p deletion associated to OAVS features)	2000	S	44 K and 244 K Agilent Technologies
Dup 8q11.23[10]	53 635 269–53 719 594	Craniofacial dysmorphism: B preauricular tags, L epibulbar dermoids. Additional anomalies: not described	*FAM150A*, RB1CC1	84	F (M)	105 K Agilent Technologies
Dup 9q34.11[10]	130 591 031–130 822 006	Craniofacial dysmorphism: high arched palate, B hearing loss, B mandibular hypoplasia. Additional anomalies: block vertebrae C3C4	*TBC1D13*, ENDOG, C9orf114, LRRC8A, PHYHD1, CCBL1, DOLK, NUP188, SH3GLB2	230	F (P)	105 K Agilent Technologies
Dup 11q21[10]	95 725 560–95 766 136	Craniofacial dysmorphism: R epibulbar dermoids, L mandibular hypoplasia, L microtia with preauricular tags. Additional anomalies: not described	*CCD82*, JRKL	41	F (P)	44 K Agilent Technologies
Del 12p13.33[10]	0–2 309 191	Craniofacial dysmorphism: L mandibular hypoplasia, wide L corner of the mouth, L microtia, preauricular tags and pits. Additional anomalies: learning difficulties, IUGR, patent foramen ovale, short QT	*IQSEC3*, SLC6A12, SLC6A13, JARID1A, CCDC77, B4GALNT3, NINJ2, WNK1, HSN2, RAD52, ERC1, FBXL14, WNT5B, ADIPOR2, CACNA2D4, LRTM2, DCP1B, CACNA1C	2309	De novo	44 K Agilent Technologies

Continued

Table 3 Continued

Dosage anomaly (reference)	Sequence coordinates	Phenotype	Genes in interval	Minimum size (kb)	Inheritance	Array CGH platform
Del 12 (pter→p13.33)[44]	between BAC RP11–275A6 (73.9 Mb, 1p31.1) and RP5–908D6 (89.5 Mb, 1p22.2)	Craniofacial dysmorphism: mild hypertelorism, broad nasal tip, thin upper lip, wide L corner of the mouth, and L hemifacial microsomia with L mandibular and condylar hypoplasia; wide-spaced teeth; gingival hypertrophy; bilateral dysplastic low-set ears with over-folded helix, L microtia, L preauricular tag and pit. Additional anomalies: delayed psychomotor development; axial hypotonia and peripheral hypertonia; lumbar kyphosis; patent foramen ovale; moderate L conductive hearing loss. MRI showed L temporal arachnoid cyst with widened subarachnoid spaces. History of IUGR and polyhydramnios.	*IQSEC3*, *SLC6A12*, *SLC6A13*, *JARID1A*, *CCDC77*, *B4GALNT3*, *NINJ2*, *WNK1*, *HSN2*, *RAD52*, *ERC1*, *FBXL14*, **WNT5B***, ADIPOR2, CACNA2D4, LRTM2, DCP1B, CACNA1C (*highlighted by the authors as candidate gene.)	2300	S	44 K Agilent Technologies
Dup 14q23.1[46]	56 278 628–57 623 179	Craniofacial dysmorphism: defects on aural, oral, mandibular and vertebral development. Additional anomalies: cardiac, pulmonary, renal, skeletal and CNS anomalies.	*AK024921*, *BC041486*,*C14orf105*, *C14orf37*, *LOC145407*, *EX9OC5*, *SEC10*, *MUDENG*, *NAT12* , **OTX2***, SLC35F4 (*In common with[47])	1034	AD	qChip-Post; qGenomics SL)
Dup 14q22.3–q23.3[47]	14q22.3 at ~55.774 Mb to 14q23.3 at ~67.571 Mb	Craniofacial dysmorphism: short palpebral fissures an lacrimal duct stenosis, bilateral facial clefts; short nose with broad nasal bridge; micrognathia with severe hypoplasia of mandible, high arched palate; multiple skin tags and pits in preauricular and cheek regions; low-set ears with abnormal antihelix and ear lobe L ear; Eustachian tube dysfunction; adhesive otitis media. Additional anomalies: IUGR; failure to thrive; short neck with fusion of the pedicles and laminae on the L at C2–4; hearing loss; torticollis; anterior ventricular septal defect; 5 cm meningocele and thin corpus callosum on MRI; deep sacral dimple associated with conus tip at L3 with mild thickening and fatty infiltration of the filum terminale; small kidneys; hypoplastic genitalia.	**OTX2***, PSMA3, DAAM1, RTN1, **SIX6***, **SIX1***, SIX4, MNAT1, PRKCH, HIF1A, KCNH5, PPP2R5E, SYNE2, ESR2, ZNF46, HSPA2, SPTB, GPX2, FNTB, MAX, FUT8, MPP5, PIGH, ARG2, RDH11, RDH12 (* *SIX1* gene is disease causing BOR and located at 14q23.1)	11790	F (P) AD	244 K and 44 K Agilent Technologies
Del 14q31.1–q31.3)[48]	79 617 936–87 566 775	Unilateral right-sided microtia, mild facial asymmetry; (CT) scan unilateral aplasia of the middle cranial fossa floor on the right, with a narrow external auditory duct; growth retardation; no vertebral anomalies. Mother showed a preauricular tag on R and hypothyroidism.	*DIO2*, *TSHR*, *GTF2AI*, *STON2*, *SELIL*, *FLRT2*, *GALC* *(*adjacent to GSC locus*)*	7948	F (M)	Karyotype and BAC FISH CTD-2540C19 (AC010849) and CTD-2357B9 (AQ062473)
Del 14q32.2[10]	98 250 689—98 253 385	Craniofacial dysmorphism: retrognathism; high arched palate; B anotia, B mandibular hypoplasia (R>L). Additional anomalies: not described	*C14orf177*	2.7	F (M)	105 K Agilent Technologies
Del 15q24.1q24.2[49]	**74 419 546–75 931 476	Craniofacial dysmorphism: cleft of the soft palate, hemifacial microsomia due to malar and mandibular hypoplasia, R grade IV microtia. Additional anomalies: moderate psychomotor delay and learning difficulties, growth retardation; myopia and strabismus; bilateral conductive hearing loss hypotonia; acute dyspnoea episodes and recurrent respiratory infections; gastrointestinal reflux; history of IUGR.	*STRA6*, *CCDC5*, *CYP11A1*, *UBL7*, *ARID3B*, *CLK3*, *CPLX3*, *GOLGA6C*, *GOLGA6D*, *SIN3A*, *PTPN9*, *MAN2C*, *CSK* (according to the figure 2)		S	60 K Agilent Technologies

Continued

Table 3 Continued

Dosage anomaly (reference)	Sequence coordinates	Phenotype	Genes in interval	Minimum size (kb)	Inheritance	Array CGH platform
Del 15q24[49]	**70.708–73.856 Mb to **74 419 546–75 931 476	Craniofacial dysmorphism: round, asymmetric face, smooth philtrum cup-shaped protruding ears. Additional anomalies: cognitive impairment, hypotonia; recurrent ear infections, microphallus.	*STRA6*, *CYP11A1*, *SEMA7A*, *CSK*, *CPLX3*, *MPI*, and *SIN3A* (defined as the minimum critical region for the 15q24 deletion syndrome)	3148	S	Chromosomal Microarray Analysis (CMA Versions 6 and 7 OLIGO)
Dup 18p11.23–p11.31[10]	6 932 021–8 074 805	Craniofacial dysmorphism: mandibular hypoplasia; R grade III microtia with preauricular tag. Additional anomalies: not described	*PTPRM*, LRRC30, LAMA1	1142	F (P)	244 K Agilent Technologies
Dup 20p12.2[10]	9 971 936–10 124 896	Craniofacial dysmorphism: R microphtalmia, R hemifacial microsomia, R microtia with preauricular tag. Additional anomalies: learning disabilities, hemivertebrae T1, abnormal ribs, R renal agenesis.	*ANKRD5*	153	F (M)	105 K Agilent Technologies
Del 22q11.21–q11.22[52]	20 128 705–21 246 612 20 453 484–20 551 970	Craniofacial dysmorphism: microcephaly, bilateral cleft lip and palate, L macrostomia, multiple bilateral preauricular tags, and small external auditory canals; Additional anomalies: IUGR, developmental delay, multiple ventricular septal defects.	*HIC2*, *LOC220686*, *UBE2L3*, *LOC150223*, *CCDC116*, *SDF2L1*, *PPIL2*, *YPEL1*, *MAPK1*, *PPM1F*, *TOP3B*, *VPREB1*, *LOC96610*, *SUHW2*, *SUHW1*, *PRAME*	1118	S	High-resolution G-banding (~850 band level) and aCGH44 K array
Del 22q11.2[53]	See N25 FISH probe coordinates at the 22q11 D22S75 locus (Vysis)	Craniofacial dysmorphism: coloboma of upper L eyelid, cleft palate, small mouth, asymmetric mandibular hypoplasia, L hemifacial microsomia, bilateral preauricular tags, microtia with aural atresia of L ear; absence of external auditory meatus and dysgenesis of inner ear system on L; hearing loss in L ear. Additional anomalies: CHD (double outlet R ventricle with valvular and infundibular pulmonary stenosis, subaortic ventricular septal defect, and normally related great arteries); hypocalcaemia secondary to hypoparathyroidism; low T-lymphocyte count, normal serum immunoglobulins.	Genes located inside the 22q11.2 critical region including *TBX1* and *UFD1L*	22q11.2	S	FISH with N25 probe
Del 22q11.2[53]	See N25 FISH probe coordinates at the 22q11 D22S75 locus (Vysis)	Craniofacial dysmorphism: prominent forehead with a receding hairline, mild facial asymmetry (smaller R cheek), asymmetric crying facies, R facial droop; R ear microtia with preauricular tag and atresia, low-set L ear with overfolded, thick superior helix, R internal ear anomalies (prominent vestibule, no lateral semicircular canal). Additional anomalies: brain MRI showed open fronto-temporal operculum with persistent cavum septum pellucidum, mild widening of foramen of Magendie and cisterna magna; feeding and respiratory difficulties, severe gastro-oesophageal reflux; R-sided hearing loss; sacral dimple, long fingers; CHD (aberrant R subclavian artery, patent foramen ovalis, trivial tricuspid regurgitation).	Genes located inside the 22q11.2 critical region including TBX1 and UFD1L	22q11.2	S	FISH with N25 probe
Del 22q11.2[53]	See N25 FISH probe coordinates at the 22q11 D22S75 locus (Vysis)	Craniofacial dysmorphism: hemifacial microsomia, periorbital fullness, broad nasal root, bulbous nasal tip, hypoplastic nares, submucous cleft palate, small mouth, L microtia with aural atresia, small R ear with simple protruding helix.	Genes located inside the 22q11.2 critical region including TBX1 and UFD1L	22q11.2	De novo	FISH with N25 probe

Continued

Table 3 Continued

Dosage anomaly (reference)	Sequence coordinates	Phenotype	Genes in interval	Minimum size (kb)	Inheritance	Array CGH platform
		Additional anomalies: developmental delay; bilateral optic nerve hypoplasia; R ear hearing loss; tapered fingers; butterfly vertebra at T8 and T10 and sacral dimple; CHD (small atrial septal defect ostium secundum type). Dysphagia, feeding difficulties and laryngomalcia.				
Del 22q11.2[54]	19 782 237–22 969 069	Craniofacial dysmorphism: epibulbar dermoid, hemifacial microsomia, bilateral ear tags Additional anomalies: postnatal growth restriction (note, maternal diabetes).	Not listed	3200	S	Illumina HumanCytoSNP-12 v1.0 BeadChip
Dup 22q11.1–q11.21[56]	**17 381 569–18 618 107	Craniofacial dysmorphism: frontal bossing, facial asymmetry, flat nasal bridge, bilateral mandibular hypoplasia with asymmetric retrognathia; asymetric ears with simplified helices, preauricular ear tag on L and larger ear tag associated with the tragal cartilage on the R, atretic R ear canal and associated sensorineural hearing loss. Additional anomalies: hypotonia; branchial cleft sinus, R-sided muscular torticollis, esotropia, bilateral clinodactyly, tapered fingers, L lower extremity shorter than R, sacral dimple; sparse hair,	CECR1, CECR2, CECR3, CECR5, CECR6, CECR7, GAB4, AS1, IL17RA, ATP6V1E1, BCL2L13, BID, MIR3198–1, MIR648, FLJ41941, PEX26, TUBA8, MICAL3, USP18, G6T3P	1500	S	Combimatrix CMDX BAC array+FISH (VYSIS probes D22Z1, and TUPLE1)
Dup 22q11.1q11.21 Del 22q11.21q11.22[57]	20 000 000–21/22 000 000	Craniofacial dysmorphism: short stature and icrocephaly. R-sided facial cleft; R-sided external auditory canal atresia and bilateral conductive hearing loss; flattening of zygoma; mandibular asymmetry; bilateral epicanthal folds; myopia. Additional anomalies: IQ of 77; mild lumbar lordosis.	22q11.1q11.21 dup: IL17RA, CECR1, CECR2, SLC25A18, ATP6V1E1, BID, MICAL3, PEX26, TUBA8, and USP18. 22q11.21q11.22 del: HIC2, RIMBP3B, RIMBP3C, UBE2L3, SDF2L1, MIR130B, PPIL2, YPEL1, MAPK1, TOP3B, VPREB1, PRAME, GGTLC2, and RTDR1.	1100	n/a	Nimblegen oligo12-plex array +FISH (RP11–829C4)
Dup Yp–q11.221, Del Yq11.222–q12[10]	2 715 688–18 073 734 19 492 239–57 432 638	Craniofacial dysmorphism: L epibulbar dermoids, micrognathia, R mandibular and maxillary hypoplasia, macrostomia, cleft palate, B anotia. Additional anomalies: IUGR; block cervical vertebrae.	Y chromosome (not all genes listed)	15000 38000	S	105 K Agilent Technologies
Amplification Xp22.33[10]	3 588 423–3 645 922	Craniofacial dysmorphism: R epibulbar dermoids, R mandibular hypoplasia, R preauricular tags. Additional anomalies: not described	*PRKX*	57	F (P)	105 K Agilent Technologies
Trisomy X[10]		Craniofacial dysmorphism: R hemifacial microsomia, micrognathia, R microtia with preauricular tags and pits, Additional anomalies: asymmetric legs and R breast hypoplasia.	X chromosome (not all genes listed)	X	S	105 K Agilent Technologies

Genes in bold are possible candidates for the OAVS phenotype.
Genome builds: **GRcH37/hg19, all other genome loci are in NCBI36/hg18.
OAVS, Oculo-auriculo-vertebral spectrum; AD, autosomal dominant; CHD, congenital heart disease; Del, deletion; dup, duplication; F, familial; IUGR, intrauterine growth restriction; L, left; M, maternal; n/a, not available; None, no pathogenic changes; P, paternal; R, right; S, sporadic/de novo.

D14S65) containing the *GSC (GOOSECOID)* gene in an OAVS family with apparent autosomal dominant inheritance. Additionally, Gimelli *et al*,[48] reported an interstitial 14q31.1q31.3 deletion, a region adjacent to *GSC*, transmitted from a mother to her daughter, both with features of hemifacial microsomia. Although *GSC* could be regarded as a candidate gene, no mutation has been found in OAVS cases with normal karyotypes. However, *GSC* is now known to be mutated in a syndrome of short stature, auditory-canal atresia, mandibular hypoplasia and skeletal abnormalities (SAMS syndrome).[88] This is a rare autosomal-recessive developmental disorder with a unique skeletal phenotype which, in our view, represents a different entity, clinically distinct from OAVS.

In another family with five OAVS patients, *potential linkage* was suggested at 15q26.2-q26.3.[37] Moreover, 12 genomic rearrangements (4 deletions and 8 duplications) ranging from 2.7 kb to 2.3 Mb, were found by Rooryck *et al*,[10] by high-density oligonucleotide array comparative genomic hybridization (aCGH) analysis (see table 3). These included a de novo 12q13.33 deletion, which has previously been associated with OAVS[44 45]; a 2q11 deletion, which was present in a proband and his affected maternal aunt; and trisomy X in a girl OAVS. Table 2 summarises the putative chromosomal loci for OAVS based on the abnormalities described in this review. In spite of growing evidence for high heritability, the molecular basis of OAVS is still elusive and, although Mendelian inheritance is more likely in familial cases of OAVS, sporadic cases may have polygenic or multifactorial causes.

There is no doubt that environmental factors, such as maternal diabetes during pregnancy, thalidomide, vasoactive drugs, smoking and multiple pregnancy may also play a part in causation of this condition. One of the most favoured hypotheses is that of vascular disruption of insufficiency in utero.[68–71] In fact, disruption of embryonic blood flow during development, maternal vasoactive medication use, diabetes and twinning are predisposing factors to a number of structural congenital anomalies.[72 73] Moreover, a great number of case reports on concordant and discordant twins with OAVS suggest that there might be an association between reproductive abnormalities, twinning and OAVS.[74–76] An excess of affected infants born after assisted reproductive techniques and frequent twinning among naturally conceived patients with OAVS has been reported.[75 76] Furthermore, the high frequency of sporadic cases and the notable occurrence of discordant monozygotic twins defy simple Mendelian inheritance.[77–83] It is worthwhile pointing out that some of these reports, in which an environmental exposure was considered causative, do not all mention whether or not the relatives were carefully evaluated in order to exclude the effect of genetic background.

Epigenetic mechanisms may be one of the ways to explain how genes and the environment interact to impair cranial neural crest cell development and cause this spectrum of craniofacial disorders. Both assisted reproduction and monozygotic twinning may predispose to epigenetic modification. Studies with model organisms reveal how the identity and patterning of vertebrate-specific portions of the skull are epigenetically regulated and how epigenetic dysregulation in cranial neural crest cells induces severe skull vault defects.[84] Epigenetic factors have been suggested as a possible pathogenic mechanism leading to histone acetylation-dependent imbalance of allelic expression of the *BAPX1* gene, a member of the NKX family of homeobox-containing proteins, which play a role in skeletal development and patterning of the middle ear, in five patients with OAVS.[85]

Heterogeneity encompassing genetic, epigenetic and non-genetic factors appears to be the most likely explanation for OAVS. A multifactorial and complex aetiology is a possible model to explain the occurrence of this birth defect. In support of this hypothesis, an increased recurrence risk was observed in families with an affected OAVS relative.[17–20] The recurrence risk in first-degree relatives of affected individuals is estimated to be 2%–3% (as we have discussed, this is probably an underestimate). It has been proposed that the presence of rare and common genetic variation, of variable penetrance and effect, combined with environmental factors, may affect specific tissue interactions that occur between the cranial neural crest cells and the endoderm, mesoderm and ectoderm, and the way they connect during their migration in establishing the foundations of craniofacial morphogenesis, hence affecting the risk to OAVS.

Differential diagnoses of OAVS

Some patients with OAVS have clinical findings that overlap with other syndromes involving structures derived from the first and second pharyngeal arches. We highlight five syndromes with known causative genes in table 4: Treacher Collins syndrome,[86] Townes–Brocks syndrome,[89] CHARGE syndrome,[90] Branchio-oto-renal spectrum disorders,[91] and the phenotypic spectrum associated with mutations in *EFTUD2*.[92 93] Our view is that these conditions are distinctive and recognisable phenotypic entities. The presence of anal anomalies, for instance, points strongly towards Townes–Brock syndrome; the shape of the ear and semicircular canal abnormality in CHARGE syndrome are very characteristic, and individuals with *EFTUD2* mutations have microcephaly and may also have associated oesophageal atresia. However, if features are sufficiently suggestive, molecular testing of the genes that cause these syndromes might be considered in some OAVS cases.

RECOMMENDATIONS FOR GENETIC COUNSELLING

The diagnosis of OAVS is frequently based only on clinical phenotyping, since no specific genetic tests are available and chromosome abnormalities have been identified in only a few cases. The lack of consensus regarding the minimum clinical diagnostic criteria for OAVS and the uncertainties regarding its aetiology cause difficulties in genetic counselling. An empiric sibling recurrence risk of 2%–3% is given in the case of a proband with OAVS, with normal chromosomes and no family history. However, one must be aware of occasional autosomal dominant or autosomal recessive inheritance observed in some cases. Before counselling these families, parents and siblings must be observed and the family history ascertainment must be thorough. The identification of subtle clinical manifestations of OAVS in relatives is important for recurrence risk counselling. A three-generation family history profile specifically enquiring about other relatives with facial asymmetry, ear tags, ear pits, hearing loss, vertebral malformations, eye abnormalities, cardiac or urogenital malformations and/or abnormalities of the extremities is essential.

If an individual with OAVS is found to have an inherited or de novo chromosome abnormality, genetic counselling for that condition is advised, although because of phenotypic heterogeneity, one cannot accurately predict the severity of OAVS should it occur in another child with the same chromosomal disorder. To illustrate this, we can take into account the phenotypic variability in genomic disorders such as those on 22q11 (Cat-eye syndrome, der(22) syndrome and velocardiofacial syndrome/DiGeorge syndrome), where chromosomal rearrangements lead to abnormal gene dosage, resulting in phenotypes including intellectual disability and congenital malformations.[94–99]

Table 4 Differential diagnoses of OAVS

Diagnosis	Main clinical features	Gene	Ref.
Treacher Collins syndrome OMIM 154500, 613717, 248390	▶ Hypoplasia of the zygomatic bones and mandible ▶ External ear abnormalities frequently associated with hearing impairment ▶ Coloboma of the lower eyelid ▶ Absence of the lower eyelashes ▶ Preauricular hair displacement onto the cheeks ▶ Craniofacial involvement is generally symmetrical	*TCOF1*	86
Townes–Brocks syndrome OMIM 107480	▶ Imperforate anus ▶ Dysplastic ears (overfolded superior helices and preauricular tags) frequently associated with sensorineural and/or conductive hearing impairment ▶ Thumb malformations (triphalangeal thumbs, duplication of the thumb, preaxial polydactyly or hypoplasia of the thumbs) ▶ Renal impairment with or without structural abnormalities	*SALL1*	89
CHARGE syndrome OMIM 214800	▶ Coloboma of the iris, retina-choroid, and/or disc ▶ Unilateral or bilateral choanal atresia or stenosis ▶ Ear abnormalities (external ear malformation, ossicular malformations, Mondini defect of the cochlea and/or absent/hypoplastic semicircular canals) ▶ Cryptorchidism in males and hypogonadotrophic hypogonadism in both males and females ▶ Cardiovascular malformations ▶ Orofacial clefts ▶ Tracheoesophageal fistula ▶ Cranial nerve dysfunction	*CHD7*	90
Branchio-oto-renal spectrum disorders (branchio-oto-renal and branchio-otic syndromes) OMIM 113650, 610896, 602588	▶ Malformations of the outer, middle and inner ear ▶ Conductive, sensorineural, or mixed hearing impairment ▶ Branchial fistulae and cysts, ▶ Renal malformations ranging from mild renal hypoplasia to bilateral renal agenesis. ▶ Branchio-otic syndrome has the same features as branchio-oto-renal syndrome but without renal involvement.	EYA1, SIX5 and SIX1	91
Mandibulofacial dysostosis, Guion–Almeida—type OMIM 610536	▶ Oto-facial abnormalities (acrofacial dysostosis) ▶ Oesophageal atresia ▶ Thumb anomalies ▶ Intellectual disability ▶ Zygomatic anomalies ▶ Microcephaly	*EFTUD2*	92 93

OAVS, oculo-auriculo-vertebral spectrum.

Therefore, although no specific genetic test is currently available, aCGH screening should be considered in patients with OAVS when recurrence risk counselling is sought, particularly in those with multiple anomalies and/or developmental delay.

Prenatal diagnosis of sporadic cases has been seldom reported and when achieved, has typically been in those with severe malformations, but with the advent of more detailed 3D scans, milder cases may be detectable (reviewed in Ref 9). Fetal ultrasound examination to detect microtia, preauricular tags and/or asymmetric mandibular hypoplasia is possible. However, since the genetic causes of OAVS have not been identified, prenatal diagnosis using genetic testing is not yet possible.

Understanding the molecular basis of these malformations will contribute to the identification of critical genes for craniofacial development and the identification of causative gene(s) will provide tools for diagnosis and genetic counselling of this complex disorder.

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