Autosomal Dominant Oculoauriculovertebral Spectrum and 14q23.1 Microduplication

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Oculoauriculovertebral spectrum (OAVS; OMIM 164210) is characterized by anomalies derived from an abnormal development of the first and second branchial arches, with marked inter and intra-familial phenotypic variability. Main clinical features are defects on auricular, oral, mandibular, and vertebral development. Cardiac, pulmonary, renal, skeletal, and central nervous system anomalies have also been described. Most affected individuals are isolated cases in otherwise normal families. Autosomal dominant inheritance has been observed in about 2–10% of cases and linkage analysis as well as array-CGH analysis have detected candidate loci for OAVS offering new insights into the understanding of pathogenesis of this entity. We describe a family with clinical diagnosis of OAVS, autosomal dominant inheritance pattern, and detection of a 14q23.1 duplication of 1.34 Mb in size which segregates with the phenotype. This region contains OTX2, which is involved in the development of the forebrain, eyes, and ears, and appears to be a good candidate gene for OAVS. © 2013 Wiley Periodicals, Inc.

Key words: oculoauriculovertebral spectrum; hemifacial microsomia; Goldenhar syndrome; 14q23.1 duplication; OTX2

INTRODUCTION

OAVS represents a very heterogeneous and complex group of disorders involving structures derived from the first and second branchial arches, and includes those conditions previously known as hemifacial microsomia and Goldenhar syndrome. Findings include facial asymmetry resulting from maxillary and/or mandibular hypoplasia; preauricular or facial tags; ear malformations such as microtia, anotia, or aural atresia; and hearing loss [Gorlin et al., 1963; Hennekam et al., 2010]. Severity is highly variable and wide inter and intrafamiliar variability has been described.

OAVS primarily involves ocular and aural anomalies but may also have vertebral malformations, renal and limb defects [Vendramini et al., 2007]. Cardiac, pulmonary, and central nervous system anomalies, although rarely, have also been reported [Schrander-Stumpel et al., 1992; Castori et al., 2006; Digilio et al., 2008]; as well as cleft lip and/or palate as less frequent craniofacial malformations [Witters et al., 2001]. Most patients have hemifacial microsomia, but bilateral involvement may also occur [Tasse et al., 2007]. Some authors have suggested that patients with autosomal dominant inheritance of OAVS are more often bilaterally affected than patients with sporadic occurrence [Tasse et al., 2007; Vendramini-Pittoli and Kokitsu-Nakata, 2009], and rarely present extracranial abnormalities [Vendramini-Pittoli and Kokitsu-Nakata, 2009].

Most cases are sporadic and non-genetic factors such as maternal diabetes [Wang et al., 2002], retinoic acid, pirimidone and thalidomide [Jacobsson, 1997; Heike and Hing, 2009], or vascular disruption [Hartsfield, 2007] have been suggested as possible environmental influences. Familial instances compatible with autosomal dominant inheritance have been observed [Tasse et al., 2007; Vendramini-Pittoli and Kokitsu-Nakata, 2009] in about 2–10% of cases. Linkage analysis in families with autosomal dominant inheritance and array-CGH analysis have detected candidate loci for OAVS offering new insights into the understanding of pathogenesis of this entity. We describe a family with clinical diagnosis of OAVS, autosomal dominant inheritance pattern, and detection of a 14q23.1 duplication of 1.34 Mb in size which segregates with the phenotype. This region contains OTX2, which is involved in the development of the forebrain, eyes, and ears, and appears to be a good candidate gene for OAVS. © 2013 Wiley Periodicals, Inc.

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of pathogenesis of this entity [Kelberman et al., 2001; Callier et al., 2008; Ou et al., 2008; Rooryck et al., 2009; Huang et al., 2010; Northup et al., 2010; Rooryck et al., 2010].

Identification of the OAVS gene/s will be important to better understand the molecular pathways underlying the development of the first and second pharyngeal arches.

We describe a family with autosomal dominant OAVS and a duplication at 14q23.1 identified by array-based CGH (aCGH) which clearly segregates with the phenotype. This finding will help to narrow down the region in order to identify a candidate gene for OAVS.

CLINICAL REPORT

We report on a 31-year-old female patient (III-4, Fig. 1) who had previously been clinically diagnosed with Treacher Collins syndrome, who came to consultation for molecular analysis and genetic counseling. She was the second child of a nonconsanguineous couple. Her father was born with preauricular tags and right macrostomia. He had no hearing defect and normal intelligence. Her mother, sister, and brother were healthy. Her uncle had preauricular tags as well as her cousin and her two children, suggestive of autosomal dominant inheritance.

She was the product of a spontaneous, normal pregnancy. There was no gestational diabetes, uterine malformations, or toxic environment during pregnancy. Delivery was at full-term (39 weeks gestation) with normal growth parameters. At birth she was admitted to the hospital due to congenital anomalies. On physical examination down slanting palpebral fissures, micrognathia, macrostomia, bilateral preauricular pits and tags, left auricular agenesis with external auditory canal atresia, and a large abnormal right ear with no tragus, were all detected. Brain and abdominal ultrasound, ophthalmological evaluation, and echocardiogram were performed at that moment showing normal results. The skeletal survey was also normal, except for mandibular hypoplasia. She was diagnosed as Treacher Collins syndrome (TCS). Her psychomotor development and growth parameters were within normal limits.

She underwent plastic surgery (mandibular osteotomy) at 17 years of age due to mandibular hypoplasia. Her right lower canine was also removed because of horizontal displacement. She carried a left auricular prosthesis. Audiological examination revealed left ear conductive deafness (due to inner, middle, and external ear atresia) and 11% right ear hearing loss. She was fitted with a bone conducting hearing aid.

Physical examination at 31 years of age revealed bitemporal narrowing, a long narrow face, bilateral preauricular pits and right macrostomia. He had no hearing defect and normal intelligence. Her mother, sister, and brother were healthy. Her uncle had preauricular tags as well as her cousin and her two children, suggestive of autosomal dominant inheritance.

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(56,278,628-57,623,179)x3) was identified which segregates with the phenotype within the family (Fig. 3). This region contains 7 RefSeq genes, including OTX2, involved in the development of the forebrain, eyes, and antenna (Fig. 3). qChip Post is a 60K-oligonucleotide microarray with variable coverage along the human genome. Subtelomeric and pericentromeric regions and over 150 regions of recurrent rearrangement associated with genomic disorders are covered with one probe every 30 kb on average, which provides a practical resolution of approximately 100–125 kb, using standard analysis parameters. The rest of the genome is covered with one probe every 100 kb on average, which would allow for the detection of alterations in the range of 350 kb and over. We have checked for similar rearrangements in public databases. We could not find any similar rearrangement annotated in the Database of Genomic Variants (http://projects.tcag.ca/variation), which collects copy number and structural variation published in the

![Clinical pictures of our index patient](a), her father (b) and her cousin’s children (c and d), showing intrafamilial clinical variability.

**TABLE I. Clinical Features of Our Index Patient and Relatives With OAVS**

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Index patient (Fig. 1 III-4/Fig. 2a)</th>
<th>Father (Fig. 1 II-3/Fig. 2b)</th>
<th>Uncle (Fig. 1 II-1)</th>
<th>Cousin (Fig. 1 III-1)</th>
<th>Cousin’s son (Fig. 1 IV-1/Fig. 2c)</th>
<th>Cousin’s daughter (Fig. 1 IV-2/Fig. 2d)</th>
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<tbody>
<tr>
<td>Facial asymmetry</td>
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<td>Facial cleft</td>
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<td>Temporomandibular joint/condyle abnormality</td>
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<td>Ear constriction/cleft</td>
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<tr>
<td>Auricular pits</td>
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<td>Pre- or post-auricular tags</td>
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<td>Stenotic/narrow ear canals</td>
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<td>Abnormal palate</td>
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<tr>
<td>Micrognathia</td>
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<td>Renal anomalies</td>
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<td>Vertebral anomalies</td>
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<tr>
<td>Hearing loss</td>
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<td>nr</td>
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<tr>
<td>Hypotonia/mild developmental delay</td>
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nr, not referred.
literature and identified in the general population using different types of genomic tools (microarrays and NGS). Much smaller copy number alterations, both gains and losses, were identified within this region in the general population. In the DECIPHER database, a total of seven affected individuals (DECIPHER IDs 2177, 253268, 255207, 255939, 257236, 265080, and 268144) were found to carry partially overlapping alterations; in all cases, rearrangements were deletions and we could not find any duplication. Craniofacial

FIG. 3. Array-CGH results in our patient and relatives. From top to bottom: father versus mother, healthy brother, healthy sister, and index patient. Note the segregation of the duplication within the affected family members (father and index patient).
abnormalities were common among these patients, but not characteristic of OAVS (microcephaly in three of them), just one of them (2177) had absent auditory canal as well as other malformations (anophthalmia, polydactyly, and transposition of the great arteries) but not described as OAVS. In addition, no similar alteration has been found in our internal database, composed of >1,000 cases of Iberian origin (data not shown).

In the mean time two of her affected relatives (IV-1 and IV-2, Fig. 1) were initially diagnosed as ACS in another hospital [McGowan et al., 2011]. One of them (IV-1) was a 6-year-old boy referred for consultation with mandibular hypoplasia, facial asymmetry, lateral facial cleft, and auricular deformities (auricular clefting, preauricular skin tags and pits). The CT scan showed aural atresia in one ear canal but hearing was normal. No vertebral or renal defects were detected and growth parameters and general development were normal (Fig. 2c; Table I). IV-2 was evaluated at 3 years of age and also had auricular cleft, preauricular skin tags and pits, a narrow ear canal and an abnormal pinna. She had slight hypoplasia of the right jaw. Growth parameters and development were normal at that time and ocular and vertebral anomalies were also ruled out (Fig. 2d; Table I). The mother of these children (III-1, Fig. 1) only had preauricular skin tags. Her ear canals were normal and she lacked auricular deformity and facial asymmetry. II-1 was also referred to the hospital because of preauricular tags (Table I). They were both contacted and array-CGH was also performed identifying the same chromosomal duplication (data not shown).

In the family we identified a total of seven informative meiosis in living individuals, and we inferred two additional ones corresponding to the oldest members in the family. Based on this information, an a priori probability of 1/512 (1/29) that the two events (phenotype + genotype) occurred by chance has been estimated among these family members. In contrast, the observed frequency of all affected individuals carrying the genetic variant, points to an association between the two events. Estimated LOD score for this CNV segregating in this family is 2.71.

**DISCUSSION**

Our patient’s phenotype is consistent with OAVS as it has previously been described. Macrostomia detected in her father was a useful sign for clinical differential diagnosis, as a characteristic feature for OAVS. Highly intra-familial variability is observed in our family (Fig. 1; Table I). Affected individuals are bilaterally affected and no extracranial abnormalities have been detected, as has previously been described in inherited OAVS [Tasse et al., 2007; Vendramini-Pittoli and Kokitsu-Nakata, 2009].

TCS and ACS were considered as part of differential diagnosis. The broad phenotypic variability in TCS sometimes makes its clinical diagnosis difficult, especially in patients with minimal expressivity. Mutations in TCOF1 are responsible for most of the cases [Huston and Wan, 2011]. Treacher Collins syndrome was excluded in our patient due to the absence of eyelid colobomas and the presence of normal lower eyelashes and a normal zygomatic arch, as well as a normal molecular analysis of TCOF1.

ACS is another autosomal dominant disorder of the first and second pharyngeal arches in which the clinical phenotype may overlap with OAVS and TCS. Penetrance seems to be complete, but there is wide intra and inter-familiar phenotypic variability including the lack of obvious external anomalies in some individuals to a severe clinical phenotype in others [Storm et al., 2005]. Minimal signs may be detected on examination of the external ears or through radiographic analysis of the mandible or temporomandibular joint (TMJ). Our patient did not present typical question mark ear. Morover macrostomia was present in her father (II-3), which is not a feature of ACS but characteristic of OAVS. We reviewed clinical information and CT scans from other family members with clinical diagnosis of ACS [McGowan et al., 2011]. Condyle hypoplasia or TMJ anomalies were not detected. Lastly linkage to PLCB4 and GNAI3 was excluded through microsatellite segregation.

Genetic heterogeneity in OAVS has been widely described [Kelberman et al., 2001; Callier et al., 2008; Ou et al., 2008; Rooyck et al., 2009, 2010; Huang et al., 2010; Northup et al., 2010]. Genome-wide search in a family with autosomal dominant OAVS suggested linkage to chromosome 14q32 which included a good candidate gene (goosecoid gene), but analysis of the gene in familiar and sporadic cases of OAVS detected no mutations or rearrangements [Kelberman et al., 2001]. Northup et al. [2010], described a patient with features of Goldenhar syndrome and a pericentric inversion on chromosome 14 with breakpoint distal to 14q21.1, suggesting the possibility that a candidate gene for OAVS could have been disrupted in that region. Array-CGH analysis was performed on a cohort of 86 patients with OAVS [Rooyck et al., 2010] and a patient with a deletion of 2.7 kb on 14q32.2 was described. This patient also had bilateral involvement and was dominantly inherited. These are other families that point to candidate regions for OAVS on 14q, which might suggest that the long arm of chromosome 14 could contain candidate genes involved in development of first and second branchial arches.

The finding of a duplication at 14q23.1 segregating with the phenotype within our family also points out to a new locus, and supports the notion of genetic heterogeneity for OAVS. This region contains seven RefSeq genes (Fig. 3). Five of these seven genes have a corresponding mouse ortholog. Out of these five, only the OTX2 ortholog (Otx2) is expressed during mouse embryonic development, and shows a restricted expression pattern in the forebrain, eye, and ear. It is a homeobox family gene encoding a DNA binding protein that acts as a transcription factor and may play a role in brain and sensory organ development. It is tempting to speculate that a dosage alteration can lead to abnormal gene expression that might interfere with the normal expression pattern and jeopardize development of the above-mentioned biological structures, often compromised in OAVS individuals. Thus, OTX2, which is involved in the development of the forebrain, eyes, and ears, appears to be a good candidate for OAVS.

Ou et al. [2008] described a father and son with clinical features of OAVS and branchiootorenal (BOR) syndrome and the detection of an 11.79 Mb duplication of chromosome 14q22.3–q23.3 and a loss of approximately 4.38 Mb sequence in 13q21.31–q21.32 due to a complex chromosomal rearrangement. He proposed that the increased dosage of genes included in the duplication (SIX1, SIX6, or OTX2) might be responsible for the BOR and OAVS-like features in his family. The duplication found in our patients (1.34 Mb duplication on 14q23.1) is included in the duplicated region...
described in Ou’s family, which contains OTX2. This finding supports the important role of 14q in OAVS phenotype and narrows down the candidate region to 14q23.1.

In summary, we are presenting a new family with autosomal dominantly inherited OAVS and a 14q23.1 duplication segregating with the phenotype, which may point to a new locus for OAVS and supports clinical heterogeneity of this entity. In this region, OTX2, which is involved in the development of the forebrain, eyes, and ears, appears to be a good candidate for OAVS. Molecular analysis of OTX2 in additional OAVS cases, familial or simplex, and functional study of the detected mutations would be very important in order to clarify the role of this gene in the development of the first and second pharyngeal arch structures and in the pathogenesis of the OAVS.

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REFERENCES


