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# A novel mutation of orthodenticle homeobox 2 contributing to a case of otocephaly initially diagnosed by prenatal ultrasound in the first trimester

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## List of key features

Otocephaly
Micrognathia/agnathia
Microstomia
Synotia
Prenatal ultrasound
Dysmorphic features
OTX2
Mutation

## Introduction

Otocephaly is a rare and severe, typically lethal, malformation of the first and second brachial arches with a prevalence of 1–60/70 000 pregnancies (Kamnasaran *et al.*, 2010; Chassaing *et al.*, 2013). It can be characterized by a very small or completely absent mandible (agnathia), synotia, microstomia, and micro/aglossia. Some cases previously reported in the literature have also had brain anomalies (holoprosencephaly), situs abnormalities, skeletal, and visceral abnormalities. To date, 11 cases of otocephaly in association with situs abnormalities have been reported, five have had holoprosencephaly, and three have had skeletal and/or visceral abnormalities; therefore, these are not considered to be constant features. Otocephaly does not appear to have a sex nor ethnic selection (Faye-Petersen *et al.*, 2006).

Approximately 13% of cases have been suspected or diagnosed before delivery, most of which were diagnosed at 19 weeks' gestation. In addition to the previously described malformations, polyhydramnios can be found on prenatal ultrasound in about 20% of cases (Faye-Petersen *et al.*, 2006). Historically, the otocephaly–agnathia complex was believed to be a sporadic condition without a specific genetic etiology. More recently, two genes have been found to be associated with the phenotype: orthodenticle homeobox 2 (*OTX2*) and paired-related homeobox 1 (*PRRX1*). Although these genes have been associated with some cases of otocephaly, no genotype–phenotype correlation has been established.

Here, we report a prenatal case of an unspecified facial defect identified in the first trimester of pregnancy, later found to be a case of otocephaly caused by a mutation in *OTX2*.

## Case report

A female fetus of a healthy, nonconsanguineous couple of Mexican ancestry was stillborn following spontaneous labor at 38.5 weeks' gestation. The mother was a 37-year-old G3 now P1020 woman and the father was a 34-year-old man. The mother presented at 24 6/7 weeks' gestation as a transfer of care from an outside institution because of a suspected severe fetal facial anomaly that was initially identified on routine first-trimester ultrasound. Fetal karyotype analysis indicated a normal female karyotype (46, XX) and subsequent microarray analysis was also that of a normal female [arr(1-22, X) x2].

The mother had a history of infertility with unsuccessful artificial reproductive technology attempts (intrauterine insemination and in-vitro fertilization) with a previous partner. Our case is the second pregnancy for this couple by natural conception. Their first pregnancy was found to have trisomy 21 and was terminated. Family history was noncontributory. The mother denied exposure to medications, recreational substances, and had no signs of infection.

Ultrasound indicated agnathia, synotia (otocephaly), and microstomia; a Dandy–Walker variant was also initially suspected. In addition, the pregnancy was complicated by symptomatic polyhydramnios, which required three amnioreductions during the course of the pregnancy. Fetal MRI was performed, showing normal brain anatomy that was not suspicious for a Dandy–Walker variant. A multidisciplinary meeting concluded that the fetus was unlikely to benefit from an *ex utero* intrapartum treatment procedure and/or other intervention after birth, and the decision was made to proceed with nonintervention for fetal indications at the time of delivery. Following the birth of the stillborn infant, otocephaly was confirmed on physical examination by the geneticist. Autopsy was consistent with a 38-week female fetus with moderate maceration and features of otocephaly: microstoma (teardrop-shaped mouth measuring $1 \times 0.4$ cm), synotia (low-set ears located at the anterior neck with lower helices fused at the midline), and


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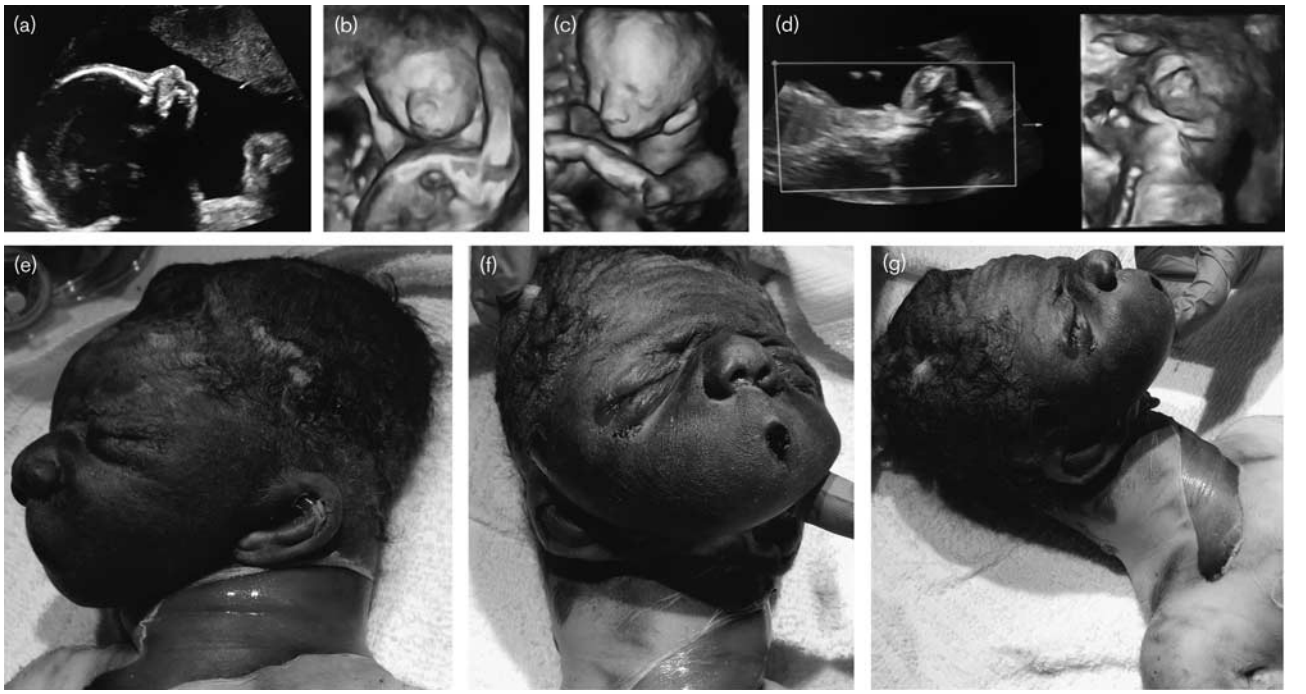
**Fig. 1**




(a) Profile view of agnathia. (b) 3D view of microstomia. (c) 3D view of synotia. (d) 2D and 3D view of the elongated neck and synothia. (e) Postmortem photograph showing agnathia. (f) Postmortem photograph showing microstomia and synotia. (g) Postmortem photograph of synotia, microstomia, and agnathia. 2D, two dimensional; 3D, three dimensional.

hypoplastic airway. Agnathia was confirmed by skeletal survey (Fig. 1). A skin biopsy was tested for mutations of *PRRX1* and *OTX2*.

## Mutations analysis

DNA analysis using Next Generation Sequencing and confirmed by Sanger sequencing through Fulgent Diagnostics (Temple City, California, USA) showed a heterozygous mutation in *OTX2*, which has not been reported in the literature, but is believed to be pathogenic. Specifically, the mutation found was c.534C > A p. CYS178* (C178X) in exon 3 of the *OTX2* gene. This is a heterozygous nonsense mutation that results in a premature stop codon at amino acid position 178, which leads to a truncated protein. Deletion/duplication analysis of *OTX2* was negative. DNA analysis of *PRRX1* was negative for sequence alterations and deletions/duplications within the gene. Subsequent parental testing was negative for the *OTX2* variant found in the infant.

## Discussion

*OTX2* maps to chromosome 14q22.3 and consists of five exons, only three of which are translated (Hever *et al.*, 2006). It encodes a transcription factor with essential functions in the early development of the anterior neuroectoderm during gastrulation and in later developmental stages of the eye and brain (Hever *et al.*, 2006; Sergouniotis *et al.*, 2015). Expression of *OTX2* decreases after birth; however, it maintains an important role in the retina (Sergouniotis *et al.*, 2015).

Mutations in OTX2 are well known to be associated with septo–optic dysplasia, microphthalmia, and pituitary dysfunction. However, otocephalic cases presumed to be caused by mutations in *OTX2* do not always have ocular involvement (Patat *et al.*, 2013). This could be hypothesized to be because of the inability to assess retinal development and function secondary to the lethality of the condition. In our case, fetal MRI and physical examination by the geneticist did not indicate any eye involvement. The autopsy report did not comment on the presence of eye anomalies. Personal discussion with the pathologist confirmed no apparent ophthalmological abnormalities.

A review of the literature including several case reports suggests that mutations in *OTX2* contribute toward the overall agnathia–otocephaly phenotype; however, the exact contribution remains unclear. There have been reports of recurrence in families with apparently phenotypically normal parents and variable presentations of otocephaly in offspring (Chassaing *et al.*, 2013). There has also been a report of mother to daughter transmission, with variable findings. Genetic testing was not performed in this case; however, the authors speculate that there

could be a familial mutation in *OTX2* on the basis of the phenotype of the two individuals (Erlich *et al.*, 2000). It is believed that *OTX2* mutations may be the main contributing factor; however, the presence of as yet unidentified modifier genes and other genetic factors cannot be excluded and may be necessary for the severe agnathia–otocephaly phenotype (Chassaing *et al.*, 2013; Patat *et al.*, 2013). More research is needed to further elucidate the role of *OTX2* in the abnormal development associated with this phenotype.

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### Conflicts of interest

There are no conflicts of interest.

## References

Chassaing N, Sorrentino S, Davis EE, Martin-Coignard D, Iacovelli A, Paznekas W, *et al.* (2012). OTX2 mutations contribute to the otocephaly-dysgnathia complex. *J Med Genet* **49**:373–379.

Erlich MS, Cunningham ML, Hudgins L (2000). Transmission of the dysgnathia complex from mother to daughter. *Am J Med Genet* **95**:269–274.

Faye-Petersen O, David E, Rangwala N, Seaman JP, Hua Z, Heller DS (2006). Otocephaly: report of five new cases and a literature review. *Fetal Pediatr Pathol* **25**:277–296.

Hever AM, Williamson KA, van Heyningen V (2006). Developmental malformations of the eye: the role of PAX6, SOX2 and OTX2. *Clin Genet* **69**:459–470.

Kamnasaran D, Morin F, Gekas J (2010). Prenatal diagnosis and molecular genetic studies on a new case of agnathia–otocephaly. *Fetal Pediatr Pathol* **29**:207–211.

Patat O, van Ravenswaaij-Arts CM, Tantau J, Corsten-Janssen N, van Tintelen JP, Dijkhuizen T, *et al.* (2013). Otocephaly–dysgnathia complex: description of four cases and confirmation of the role of OTX2. *Mol Syndromol* **4**:302–305.

Sergouniotis PI, Urquhart JE, Williams SG, Bhaskar SS, Black GC, Lovell SC, *et al.* (2015). Agnathia-otocephaly complex and asymmetric velopharyngeal insufficiency due to an in-frame duplication in OTX2. *J Hum Genet* **60**:199–202.