

# Diprosopus: A Unique Case and Review of the Literature

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## ABSTRACT

**Background:** We present a case of partial facial duplication in a male infant.

**Methods:** The clinical, radiological, and laboratory findings for this patient are described, followed by a review of the literature.

**Results:** Craniofacial duplication is a rare form of conjoined twinning and presents in a wide spectrum, from dicephalus to diprosopus to partial facial duplication. Many of these cases can be diagnosed prenatally. Prenatal assessment of our patient revealed only agenesis of the corpus callosum.

**Conclusions:** The pathogenesis is believed to involve duplication of the notochord. Where there are more severe associated anomalies, the prognosis is poor. Partial facial duplication, as in our case, is associated with fewer anomalies, and the prognosis is better. Symmetry and an excess of tissue, rather than deficiency, favor a positive result.

*Teratology* 66:282-287, 2002. © 2002 Wiley-Liss, Inc.

mandible, or oral cavity) have a normal central nervous system. In these children, excision of the duplicated parts to give a normal appearance have been variably successful (McLaughlin, '48; Beatty, '56; Ghosh et al., '71; Davies et al., '73; Borcbakan, '78; Price and Zarem, '79; Maisels, '81; Fearon and Mulliken, '87; Verdi et al., '91). These are rare cases that differ enough from one another to make each case unique (Gorlin et al., '90).

## CASE REPORT

B.S. was a full-term infant boy born to a 32-year-old G2P1T1LC1 mother. The pregnancy was unremarkable. Routine prenatal ultrasonography at 21 weeks revealed agenesis of the corpus callosum.

The infant was delivered by caesarian section because of fetal bradycardia. The birth weight was 2,845 g and the head circumference was 34.5 cm. Neonatal examination revealed low-set ears, orbital hypertelorism, a widow's peak, and downward obliquity of the palpebral fissures. The central portion of the forehead had prominent transverse wrinkles. Cupid's bow was wide and the nasal tip was bifid. The maxilla and mandible were duplicated, and there were two tongues with a common base. There was also a duplicated upper labial frenulum and a complete cleft of the secondary palate. There were four infraorbital foramina. He had alternating exotropia. He also had a microphallus and generalized hypotonia. The patient desaturated at birth and required continuous positive airway pressure (CPAP) for oxygenation. He was transferred to our center at 1 month of age for further evaluation and management (Fig. 1).

The parents were nonconsanguineous Ashkenazi Jews. Their appearance, as well as their craniofacial plain films, was normal. An older child was a normal

## INTRODUCTION

Craniofacial duplication, or diprosopus, is considered an unusual variant of conjoined twinning. The phenotype comprises a wide spectrum and ranges from partial duplication of a few facial structures to complete dicephalus (Ivy, '68; Okazaki et al., '87; Pavone et al., '87; Rai et al., '98). The incidence of diprosopus is unknown. Sharony et al. ('93) estimated that 85 cases have been reported; since their report, an additional 3 cases of diprosopus have been described (Carles et al., '95; Rai et al., '98). To the best of our knowledge, 26 cases of incomplete craniofacial duplication have been reported in the medical literature (Table 1).

The earliest known report of diprosopus is credited to Ambroise Paré (*Of Monsters and Prodigies*) in the 16th century. Most diprosopic infants with complete duplication and single body, normal limbs have severe defects in the central nervous system (Turpin et al., '81; Machin, '93; Carles et al., '95). In contrast, most infants with incomplete diprosopus (duplication of the maxilla,

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Received 17 January 2002; Accepted 16 July 2002

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/tera.10102

**TABLE 1. Cases of incomplete craniofacial duplication reported in the literature**

Year	Authors	Remark
1876	Smith	
1948	McLaughlin	
1950	Fontaine	
1951	Robertson	
1956	Beatty	
1957	Morton	
1964	Bacsich et al.	
1964	Goulian and Conway	
1969	Avery and Hayward	
1971	Bell	
1971	Ghosh et al.	
1973	Davies et al.	
1975	Gupta	
1976	Fish	
1976	Mazzola	Four cases
1978	Borcbakan	
1978	Chandra	
1978	Obwegeser et al.	
1979	Price and Zarem	
1981	Maisels	
1984	Wittkamp and van Limborgh	
1987	Fearon and Mulliken	
1991	Verdi et al.	

and healthy girl. A head MRI of the mother taken in 1994 for a syncopal episode was negative.

Upon admission to our neonatal intensive care unit, neurological examination of the infant revealed intact sucking and gag reflexes, normal cranial nerve and motor examination. He did not fixate or track visually but the fundoscopic examination was normal. His visual acuity was estimated to be 20/200 for the right eye, 20/400 for the left eye, and the optic nerves were normal by fundoscopy.

Abdominal ultrasonography and two-dimensional echocardiography were normal. Endocrine evaluation revealed normal cortisol and prolactin levels and thyroid function tests. A normal male karyotype was recorded, and FISH for KAL 1 showed no deletion [ish Xp22.3(KALx1)].

Repeated laryngoscopy confirmed normal vocal cords. The epiglottis was deviated to the left and did not contact the posterior pharyngeal walls. There was reflux esophagitis, confirmed by a pH probe.

An EEG at 1 month of age was normal. However, another EEG at 2 months of age, done because of apnea and desaturation, showed excessive transient activities in the right occipital and left central areas, with rhythmic/semirhythmic delta activity posteriorly.

A skeletal survey documented brachycephaly, a split mandible, and bifurcation of the upper cervical spine. The craniofacial findings were demonstrated by an MRI, which showed absence of the corpus callosum and abnormal olfactory gyri, a midline cleft, hypertelorism, and a malformed anterior mandible. The midbrain was dysmorphic. The medulla had a triangularly shaped, partially split appearance. The clivus had a sagittal split. The pituitary gland and stalk were duplicated as well. A midline hamartoma was noted to originate in

the basi sphenoid. There was a dermoid noted within the foramen cecum with a possible tract extending into the anterior nasal septum.

These findings were confirmed by a head CT with three-dimensional reconstruction, which also revealed an abnormal tectum with no distinct separation of the colliculi, a midline cleft involving the tongue and mandible, and a cleft of the hard palate. There were two partially formed, separate mandibular bodies and two separate menta, and a duplication of the intermaxillary (premaxilla) segment. The medial mandibular bodies were demonstrated as a sclerotic, soft tissue mass within the oral cavity (Fig. 2). A separate interparietal bone was observed (Fig. 3). A CT scan of the spine revealed duplicated vertebral bodies from C2 to C5 and partial duplication of the vertebral bodies from C6 to T3. An MRI of the spine revealed no split cord, with the conus ending at the L1-L2 level.

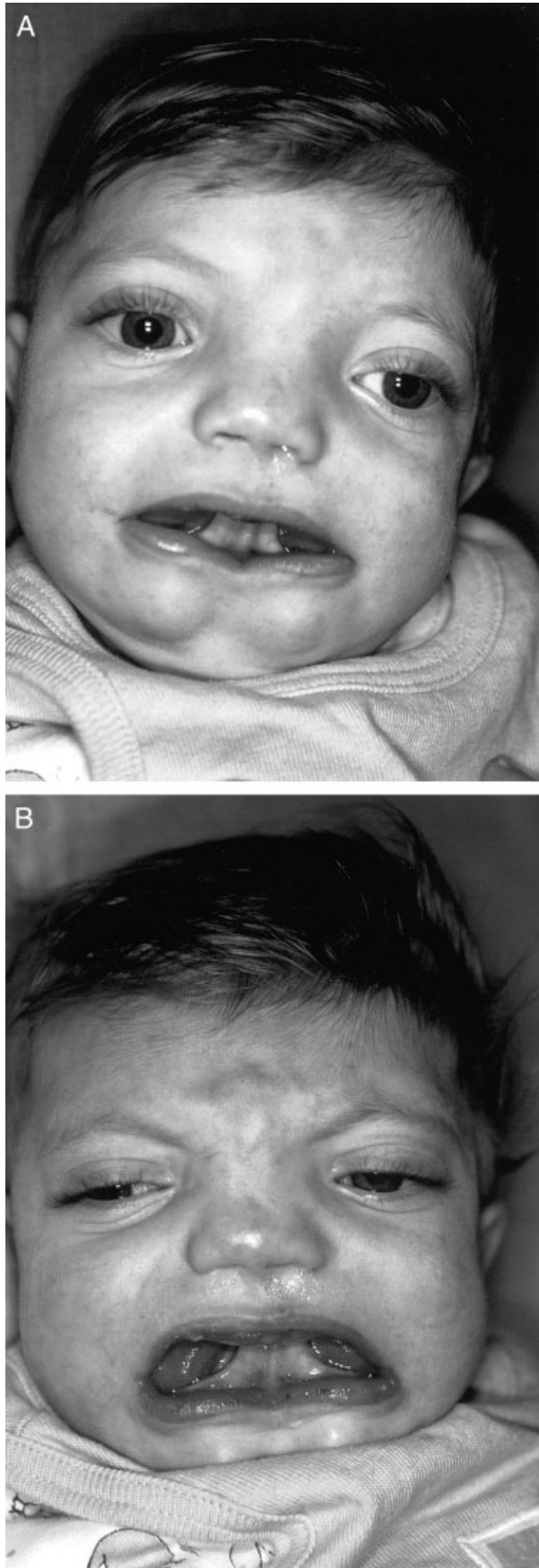
His postnatal course was punctuated by repeated episodes of respiratory decompensation—probably from secretions—and aspiration pneumonia requiring CPAP and laryngeal mask ventilation. The infant was able to tolerate oral-gastric tube feedings and a gastrostomy tube was inserted at age 3 months. After stabilization, he was transferred to a residential home pending surgical intervention.

## DISCUSSION

Diprosopus denotes a complete duplication of facial structures. There is also a high incidence of anomalies in the central nervous system, cardiac (Changaris and McGavern, '76; Turpin et al., '81; Moermann et al., '83; Okazaki et al., '87; Pavone et al., '87; Sharony et al., '93), gastrointestinal (Turpin et al., '81; Moermann et al., '83; Fontanarosa et al., '92), and respiratory (Moermann et al., '83) systems, as well as cleft lip and palate (Maizels, '38; Changaris and McGavern, '76; Ornoy et al., '80; Turpin et al., '81; Barr, '82; Carles et al., '95). There is also a preponderance of female infants (Strauss et al., '87; Rai et al., '98). Chromosomal analyses have been normal (Moermann et al., '83; Sharony et al., '93; Rai et al., '98).

Interestingly, there are two cases of twin pregnancies discordant for diprosopus. In one report of dizygotic twins, the unaffected twin was completely normal and of a different sex than the affected twin (Rai et al., '98). In the other report, the unaffected twin developed hydrocephalus requiring a ventriculoperitoneal shunt. The placenta was diamniotic monochorionic (Changaris and McGavern, '76).

In infants with partial diprosopus, the mandible and mouth are the most commonly duplicated craniofacial structures (McLaughlin, '48; Beatty, '56; Davies et al., '73; Borcbakan, '78; Price and Zarem, '79; Maisels, '81). The case reported by Borcbakan ('78) represents a craniopagus parasite. It is the only one in the literature in which the supernumerary mouth was in the temporal area and in which the blood supply passed directly through the cranium. At least one case of isolated nasal



duplication has been reported (Ghosh et al., '71). Chromosomal analysis has shown normal karyotype (Fearon and Mulliken, '87). There are usually no major central nervous system (CNS) deficits or abnormalities (Maisels, '81; Verdi et al., '91). As in complete diprosopus, there appears to be a female preponderance in partial duplication.

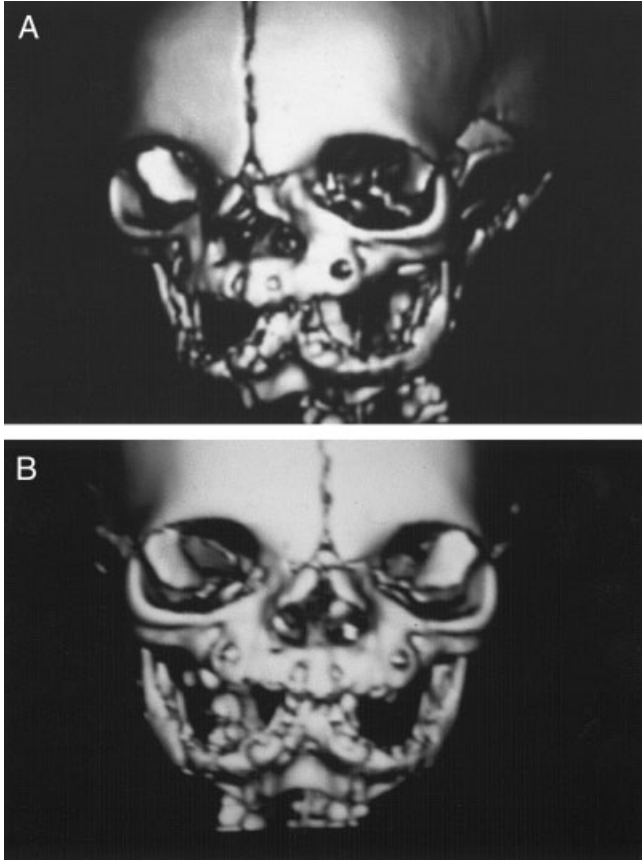
Prenatal diagnosis of anencephaly or partially duplicated CNS, severe neural tube defects, diprosopus, and dicephalus has been noted as early as the first trimester (Fontanarosa et al., '92). Maternal  $\alpha$ -fetoprotein was increased in these cases (Rydner et al., '85; Strauss et al., '87; Sharony et al., '93; Carles et al., '95). However, one case in which a woman carrying diprosopus twins with craniorachischisis had below-normal levels of  $\alpha$ -fetoprotein (Fontanarosa et al., '92), and another with normal  $\alpha$ -fetoprotein levels (Okazaki et al., '87).

Polyhydramnios is a common ultrasonographic finding in conjoined twinning (Riccardi and Bergmann, '77; Ornoy et al., '80; Turpin et al., '81; Moermann et al., '83; Okazaki et al., '87). It occurs more often in conjoined twins when compared to normal twins or normal singletons (Strauss et al., '87). It is interesting to note that the report of diprosopus by Onuf (1895) commented on an "enormous quantity" of amniotic fluid by clinical examination, in 1895, before sonography. Other reported prenatal sonographic findings include mishaped cranium, widened vertebral column (as in our case) (Strauss et al., '87), heart-shaped appearance (Rai et al., '98) or bifid shape (Fontanarosa et al., '92) of the cranial vault. On occasion, facial duplication can be clearly depicted on sonography (Okazaki et al., '87; Sharony et al., '93). All of the reported prenatal diagnoses involved diprosopus with severe CNS anomalies. In our patient, prenatal ultrasonography at 21 weeks of gestation showed only the absence of the corpus callosum and, remarkably, did not demonstrate gross facial duplication.

Diprosopus is believed to be the result of an error related to neurulation of the embryo. The notochord defines the axis of the embryo and induces neurulation. The surrounding neural crest cells give rise to the connective tissue mesenchyme of the facial and oral regions and pharyngeal arches (Carles et al., '95). Any disturbances in neurulation can result in the failure of neural tube closure (Moore, '88). There are several examples of the association of diprosopus with anencephaly (Gorlin et al., '90).

The pathogenesis of craniofacial duplication is believed to involve bifurcation or forking of the notochord rostrally, leading to two side-by-side-oriented vertebral axes (Machin, '93) and the formation of two neural plates and their neural crest derivatives. The experiments of Stockard ('20, '21) on fish and chicken embryos produced incomplete division. The author was able to produce dicephalic fish by lowering of the tem-

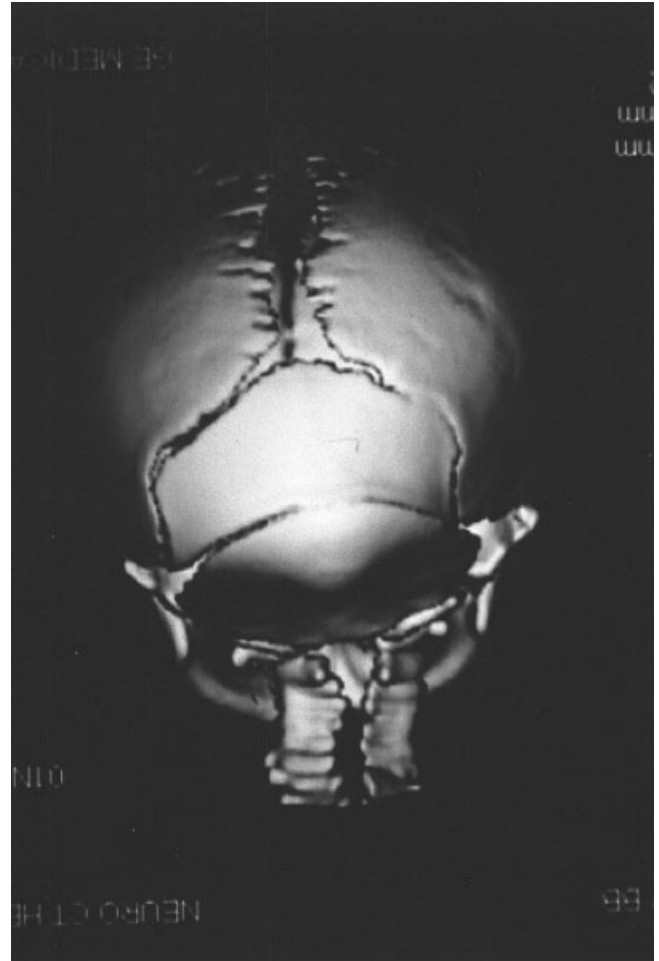
Fig. 1. A and B: Two views of the patient.



**Fig. 2. A and B:** Three-dimensional reconstruction head CT scan of the patient. Note the duplicated mandible and maxilla, with four infraorbital foramen.

perature and deprivation of oxygen, although only 1% to 2.3% of total embryos had this anomaly.

At about 16 days of embryonic life, the notochordal process grows between ectoderm and endoderm until it reaches the prochordal plate, a small circular area of columnar epithelial cells. The notochord can extend no further because the prochordal plate is firmly attached to the overlying ectoderm forming the oropharyngeal membrane. The notochordal process elongates and the neural plate broadens and eventually extends cranially as far as the oropharyngeal membrane by about 20 days. The branchial arches begin to develop early in the 4th week. The first arches, the mandibular, fuse in the midline at about 26 days. The oropharyngeal membrane separates the stomadeum from the foregut until it ruptures at about 24 days. At about the end of the 4th week, a median triangular elevation, the tuberculum impar, appears in the floor of the primitive pharynx and eventually fuses with two oval lateral lingual swellings. All three elevations arise from proliferation of mesenchyme from the first pair of branchial arches. The thyroid gland begins to develop at about 24 days from a median endodermal thickening caudal to the tuberculum impar. Thus, it is easy to appreciate that these temporal-spatial relationships predict the com-



**Fig. 3.** Three-dimensional reconstruction head CT showing interparietal bone.

mon involvement of the forebrain, mouth, mandible, maxillae, tongue, and thyroid. It is difficult to explain the chain of events in cases of diprosopus with oral and facial anomalies and normal brain development.

Some clinicians have maintained that frontonasal dysplasia also represents an incomplete form of twinning. However, there has never been any convincing evidence of structural duplications in this disorder. Furthermore, experimental animal models suggest that the etiology of frontonasal dysplasia is cell death in the frontonasal process midline mesenchyme and in the neural epithelium.

Carles et al. ('95) expanded on the hypothesis of notochordal division and duplication. During neurulation of duplicated notochords, each neural tube and crest migrate inwardly and separate from the surface ectoderm. If the distance between the two neural grooves over each notochord is wide, there will be enough tissue to allow for complete coverage of the neural tubes from the inner folds. Hence, complete neurulation investing each notochord could occur. However, if this distance were narrow, there would not

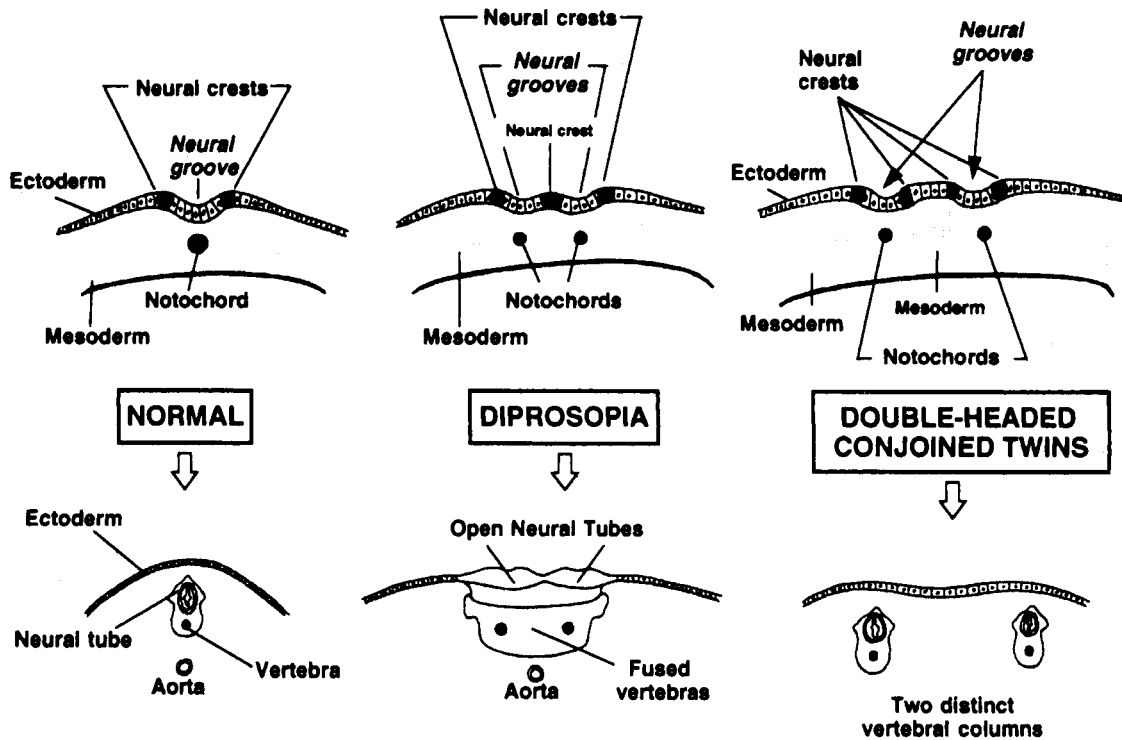


Fig. 4. How the distance between the two notochords induces malformation (diprosopus or dicephalus). From Carles et al. ('95). Reproduced with permission from Munksgaard International Publishers.

be enough ectoderm to cover the inner folds properly as inward migration occurred. This could result in failure of the neural tubes to close (Fig. 4).

The hypothesis of Carles et al. ('95) is supported by clinical findings in infants with dicephalus and diprosopus. Itoh et al. ('93) described two infants with dicephalus and anencephaly, and in both infants there were two complete vertebral columns. One of the two infants had normal skin covering the vertebral columns, while the other had a myelomeningocele. On the other hand, frequently there is bifurcation of vertebral column in diprosopus, as in our patient (Onuf, 1895; Maizels, '38; Riccardi and Bergmann, '77; Ornoy et al., '80; Turpin et al., '81; Moermann et al., '83; Pavone et al., '87). In addition, duplication of the prosencephalon often accompanies forking of the notochord (Turpin et al., '81; Strauss et al., '87; Sharony et al., '93; Rai et al., '98).

Beatty ('56) proposed an alternate hypothesis for partial craniofacial duplication based on his case of an accessory mouth, complete with well-formed lips and vermilion, an alveolar process, and tongue. He quoted the embryologist Knouff who theorized that such an oral duplication results from "developmental excess." According to this theory, an accessory growth center appears in the normal right mandibular process and develops into an accessory mandible and mouth.

Experimental and embryologic evidence suggests the importance of notochord formation in the development

of facial duplication. It is hoped that this case and future cases as well as discoveries in notochordal signaling pathways will eventually result in a clearer understanding of the pathogenesis of this defect.

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