Congenital Diaphragmatic Hernia in a Fetus with a De novo Terminal Deletion of Chromosome 15q26.1

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Abstract

De novo terminal deletions of chromosome 15q26.1 are rare occurrences. Deletions of this region have been previously linked to congenital diaphragmatic hernia (CDH) as well as congenital malformations and developmental delay. This article presents a prenatal case of this *de novo* terminal deletion, detected by cytogenetic analysis and confirmed by fluorescence in situ hybridization (FISH), in a fetus with CDH and intrauterine growth restriction (IUGR). Genetic evaluation of pre- and postnatal cases of CDH should include at least a close examination of the terminal region of chromosome 15q26. As with any de novo substantial loss of genetic material, the prognosis is likely to include additional neurologic impairment and other congenital malformations in comparison to CDH patients without genomic alterations.

Introduction

De novo terminal deletions of chromosome 15q26.1 are rare events and/or seldom diagnosed. Likewise, few are reported in the literature. We present a prenatal case of a *de novo* terminal deletion of one copy of chromosome 15 in a fetus with CDH. This case report describes the defined deleted region and discusses its association with CDH, while presenting further support for the role of molecular genetic testing in fetuses and infants with CDH.

Case Report

A 20-year-old gravida 2, para 1 mother and her 30-year-old husband were referred to our fetal diagnostic center at 11 weeks 4 days gestation for first trimester nuchal translucency (NT) screening. The initial ultrasound was significant for a NT measurement of 4 mm. Given the increased NT thickness, the couple was counseled about the option of chorionic *villus* sampling (CVS) to detect a possible fetal chromosomal abnormality. They consented to the CVS procedure, and cytogenetic analysis revealed an abnormal male karyotype with a terminal deletion of the long arm of one copy of chromosome 15 (Figure 1). Fluorescence in situ hybridization studies using a whole chromosome paint probe for chromosome 15 and a subtelomere probe for the long arm of chromosome 15 (Vysis, Inc.) confirmed the terminal deletion (Figure 2). Parental chromosome analyses were normal for the nonconsanguineous couple. Therefore, the deletion in the fetus was *de novo* in origin: 46,XY,del(15)(q26.1)dn.ish del(15)(wcp+, D15S396-).

The couple returned to our fetal diagnostic center at 17 weeks 0 days gestation for a fetal anatomy survey by ultrasound, which showed intrauterine growth restriction (IUGR) and a left-sided CDH (Figure 3). Fetal head circumference was 131.6 mm (18th percentile), abdominal circumference was 91.9 mm (<3rd percentile) and femur length was 20.6 mm (<3rd percentile). The stomach appeared in the chest, and the heart was displaced to the right. The lung to head ratio was 2.1. There was no liver herniation into the chest.

The family was counseled on the combined abnormal findings of the fetal karyotype, CDH, and early IUGR. Termination of the pregnancy was elected at 18 weeks 2 days gestation. Fetopsy was declined by the family.

Discussion

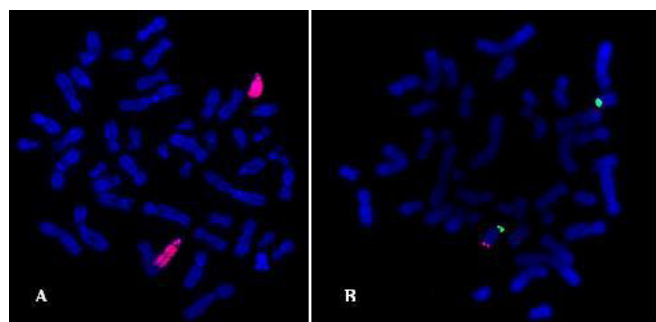Congenital diaphragmatic hernia, a severe birth defect involving
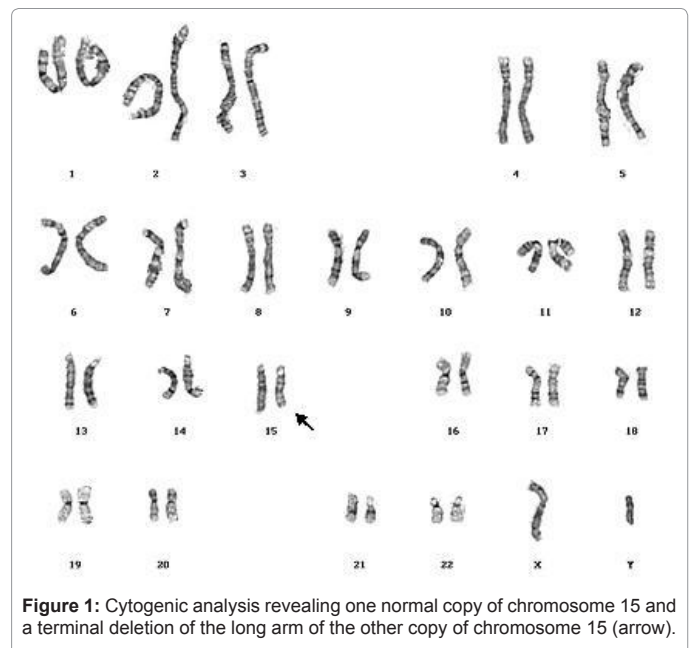
Figure 1: Cytogenic analysis revealing one normal copy of chromosome 15 and a terminal deletion of the long arm of the other copy of chromosome 15 (arrow).

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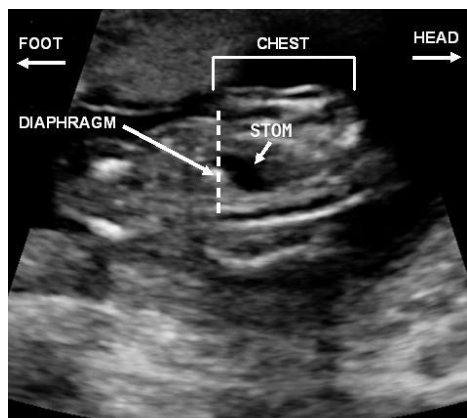
Figure 2: Fluorescence in situ hybridization studies using a whole chromosome paint probe for chromosome 15 (A) and a subtelomere probe for the long arm of chromosome 15 (B) (Vysis, Inc). There is one subtelomeric signal on the long arm of one copy of chromosome 15, indicating a terminal deletion on the other copy of chromosome 15.

Figure 3: Sagittal ultrasound image of the fetal chest and abdomen revealing congenital diaphragmatic hernia at 17 weeks gestation. The stomach (STOM) appears in the chest consistent with CDH.

incomplete or abnormal diaphragmatic closure, is frequently associated with life-threatening pulmonary hypoplasia and postnatal pulmonary hypertension. Half of the cases present with other non-pulmonary congenital anomalies and at least 5-10% of cases have a specific underlying chromosomal etiology [1].

Biggio et al. [2] presented a patient with a 46,XX,del(15)(q26.1) karyotype who was born with a CDH, coarctation of the aorta, and dysmorphic features. They hypothesized that *MEF2A*, a myocyte-specific enhancer factor, which maps to 15q26, may play a crucial role in the control of muscle differentiation and development of the diaphragm [2].

Slavotinek et al. [3] screened patients with CDH and additional phenotypic characteristics of Fryns syndrome. They used array comparative genomic hybridization (CGH) to identify more occult chromosomal aberrations. Results showed submicroscopic chromosome deletions in three probands who had normal karyotypes and were previously diagnosed with Fryns syndrome. Two of the three probands were found to have microdeletions in 15q26.6 while the other had a deletion in 8p23.1 [3]. Furthermore, You et al. [4] observed dorsolateral Bochdalek-type congenital diaphragmatic hernias in mice with *NR2F2* gene deletions, and therefore, suggested that *NR2F2* is a likely contributor to the formation of CDH in patients with 15q deletions.

Klaassens et al. [5] reported a patient with CDH with an approximately 5-Mb deletion at 15q26.1-26.2. This region contained four known genes of which two, *NR2F2* and *CHD2*, were particularly interesting candidates for CDH. Likewise, Lopez et al. [6] reported two cases of CDH and congenital heart disease, with one patient having a 15q26.1 deletion confirmed by FISH and array CGH [6].

Klaassens et al. [1] described two patients with a deletion of 15q26 with a common phenotype of IUGR, CDH, cardiac anomalies, and characteristic facial features similar to those seen in Fryns syndrome. They believed that this constellation of birth defects warranted further investigation to evaluate for 15q26 deletions. Also, Jaillard et al.[7] presented a female patient with multiple congenital malformations, including CDH and a heart defect, who was detected to have a terminal 6.9-Mb deletion of chromosome 15q associated with a structurally abnormal chromosome X.

Clugston et al. [8] used rodent diaphragms to study the expression of CDH candidate genes from 15q26, as well as *FOG2* and *GATA4*, two genes in other CDH critical regions at 8q22-q23 and 8p23.1, respectively [8]. They concluded that the 15q26 critical region contains a cluster of genes, such as *MEF2A*, *NR2F2*, and *CHD2*, that are expressed in rodent diaphragm development, thus supporting other reports that deletions in this region are associated with CDH [8].

In contrast, there are many other patients described in the literature with 15q26.1 deletions who do not have CDH but have variable phenotype presentations, including facial dysmorphisms, short neck, complex heart defects, developmental delay, failure to thrive/growth restriction, cholestatic liver disease, severe feeding issues, and kidney and spinal cord abnormalities [9-11]. Therefore, haploinsufficiency of this region does not show complete penetrance for CDH.

The chromosomal region 15q26.1 has many genes and presumed genetic regulatory regions. As such, the list of candidates that may be involved with CDH is large. In this particular case, the deleted region consisted of up to 59 genes and/or known gene regulatory loci, including all of the genes previously mentioned in this article: *MEF2A*, *NR2F2*, and *CHD2*. Unfortunately, array CGH was not available in our case to define the deleted region further. The terminal deletion in this case was visible by chromosome analysis, so it may be much larger than deletions in other reported patients.

While the fetus in this case showed CDH and IUGR, other malformations could not be observed given the early ultrasound examination and termination of pregnancy without autopsy. Therefore, we cannot compare and contrast the phenotypic findings with those previously reported in other patients with 15q26.1 deletions. However, this case supports this chromosomal region's association with CDH. Furthermore, as seen in some of the above case reports, molecular methods and FISH studies helped narrow down the genes and/or regulatory regions that are likely involved with CDH from 15q26 deletions.

Based on this case, as well as a review of the literature, we recommend paying close attention to the 15q26 region in prenatal cases with clinical findings of CDH. Deletions of this region contain many genes and/or regulatory elements that, in addition to CDH, would be expected to involve other congenital malformations and neurologic impairment. Such deletions may lead to an overall poorer prognosis than that of isolated cases of CDH without genomic alterations.

Therefore, as some small deletions or rearrangements of this region can sometimes be missed by karyotype, molecular methods such as chromosomal microarray, could be considered first tier genetic testing for CDH as their results may change pre- and postnatal counseling as well as overall prognosis.

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