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Genetics Corner: An Infant with a Right Congenital Diaphragmatic Hernia and a Small 1h5q26.3 Deletion with Loss of IGF1R

Robin Clark, MD, Subhadra (Subha) Ramanathan, M.Sc., M.S.

Clinical Summary:

A preterm SGA female with unrepaired right-sided diaphragmatic hernia (CDH) was found to have a pathogenic 68 Kilobase deletion of 15q26.3 on chromosome microarray: arr[hg19] 15q26.3 (99,173,480-99,241,724) x1. A genetic consultation was requested. Other problems included severe pulmonary HTN, mild Ebstein's anomaly, MSSA bacteremia, history of lower extremity deep vein thrombosis, intermittent hypertensive episodes and seizures, well controlled with phenobarbital.

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This infant was born preterm at 34w 2 d by C-section in the vertex presentation to a 37-year-old G10P4-5SAb5 mother who presented with polyhydramnios and premature rupture of membranes. Intrauterine growth retardation and diaphragmatic hernia had been diagnosed prenatally by fetal ultrasound. The delivery was complicated by nuchal cord x1, fetal decelerations, and bleeding from placental abruption and previa. Apgar scores were 5^{1} and 7^{5}. Birth weight was 1650 grams (8^{th} %ile), birth length 42 cm (18^{th} %ile), and birth head circumference 30 cm (27^{th} %ile). Her growth remains poor at 52 days (corrected 41w 5d gestational age). Her most recent weight is 2.635 kg ($<1^{st}$ %ile); her length and head circumference are also $<1^{st}$ %ile.

Physical exam was limited by oral intubation and dependent edema. Pertinent features were a square forehead, anteverted nares, long fingers, and toes; the little finger overlapped the ring finger on the left.

Relevant labs include: normal chromosome analysis (46, XX) and IGF1

Component *Latest Ref Rng & Units*	6/29/2022	7/3/2022
IGF-1 Z-score *-2.0 - 2.0*	-1.65	-1.04
Insulin-Like Growth Factor I *ng/mL*	27	37

The family history was pertinent for five spontaneous abortions in the patient's mother. She had four miscarriages with her first partner and one with her current partner; all were in the first trimester and unexplained. Both parents are of average stature: Mother is 5'2", and the father, age 43, is 5'8". The couple has one other son together, a healthy 18-month-old.

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Discussion:

A genetic diagnosis can be established in about 37% (1) of patients who present with a congenital diaphragmatic hernia (CDH), with a greater share of diagnoses in the "complex" or "non-isolated" group in whom additional anomalies are present in other organ systems (2). Our patient presented with a small size for gestational age and a cardiac defect, Ebstein's anomaly. This puts her in the group of "non-isolated" or "complex" CDH, in whom a genetic diagnosis is more likely.

Chromosome microarray is a first-line test that identifies copy number variants, deletions, and duplications in infants with unex-

plained CDH(3). Yu *et al.* (2014) identified *de novo* copy number variants (CNVs) in 11/256 parent-child trios with CDH, which is more than double the expected rate. *De novo* CNVs occur in 0.5-3% of the general population. The most common recurrent CNVs reported in association with CDH are duplications of 11q23 and deletions of 1q41-42, 8q23.1, and 15q26.

Patients with CDH and 15q26 deletion were first reported almost 20 years ago (4,5,) and since then, the association has been well established. The deletions on distal 15q26 associated with CDH have variable breakpoints, ranging from 15q26.1 to 15q26.3, but all are generally much larger than the deletion in our patient. However, not all patients with 15q26 deletions have CDH. The various reports of 15q26.1-q26.3 deletions associated with CDH share a critical region comprising four genes: *IGF1R, NR2F2, CHD2*, and *MEF2A (*myocyte-specific enhancer factor 2). *NR2F2* has been identified as the most promising candidate gene for CDH. A heterozygous *de novo* frameshift mutation in *NR2F2* has been reported in a patient with CDH and an atrial septal defect(6). Trio exome sequencing of 22 fetuses with CDH identified likely damaging variants in 6 genes, including *NR2F2* (7). Such evidence supports a role for *NR2F2* in the pathogenesis of CDH and makes it all the more remarkable that *NR2F2* was not deleted in our patient, whose small 15q26.3 deletion includes only one of the four genes in the critical region for CDH.

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Deletion of *IGF1R* alone causes small size for gestational age (SGA) at birth and subsequent poor growth (OMIM #612626), but deletion of I*GF1R* alone has not previously been reported with SGA and diaphragmatic hernia. The smallest reported 15q26.2 deletion involving *IGF1R* that we could find is in a patient with 95 kb deletion in a family with moderate to severe short stature. The proband presented with mild developmental delay and short stature. The endocrine evaluation revealed variable but normal serum IGF1 levels in all family members without consistent peripheral IGF1 resistance(8). Patients with *IGF1R* deletion have been treated with growth hormone with good growth response.

Our patient may have the smallest 15q26 deletion reported in association with CDH. Notably, it includes only *IGF1R* and a long non-coding RNA, *IRAIN*, which is transcribed in an antisense direction from an intronic promoter within *IGF1R*. *IGF1R* encodes the Insulin-like Growth Factor 1 Receptor, and its loss explains our patient's small size at birth and subsequent poor growth. Although this is likely to be a *de novo* variant because the parents and siblings of our patient are of normal size, parental testing must be done to establish whether this is a *de novo* or a familial deletion. Given the family history of multiple maternal miscarriages, a subtle familial chromosome rearrangement, such as an inversion involving distal 15q26 in one parent, must be excluded.

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Practical Applications:

1. Order chromosome microarray in infants with an unexplained congenital diaphragmatic hernia, isolated or complex CDH. Recall that recurrent copy number variants are associated with CDH, including deletion 15q26.2.
2. Search for other birth defects in infants with CDH to identify the "non-isolated" or "complex" CDH group in whom an underlying genetic disorder is more likely.
3. Consider ordering chromosome microarray analysis in infants with unexplained small size at birth. SGA infants are also more likely to have a copy number variant on chromosome microarray. Recall that deletion or genetic variant within *IGF1R* can cause small size at birth with subsequent poor growth.

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Corresponding Author

Robin Clark, MD
Professor, Pediatrics
Loma Linda University School of Medicine
Division of Genetics
Department of Pediatrics
Email: rclark@llu.edu

Corresponding Author

Subhadra (Subha) Ramanathan, M.Sc., M.S.
Licensed and Certified Genetic Counselor
Assistant Professor, Pediatrics
Loma Linda University Health
2195 Club Center Drive, Ste A
San Bernardino, CA 92408
SRamanathan@llu.edu