



Case Report

Prenatal Evaluation of a Fetal Cystic Hygroma: An Unexpected Finding of a De Novo Fetal *BRCA1* Deletion Case Report

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Abstract: This case presents a novel occurrence of a de novo *BRCA1* gene deletion in a fetus with a cystic hygroma. Chorionic villus sampling (CVS) was performed for chromosome G-banding analysis, demonstrating a normal karyotype: 46, XX. Chromosome microarray analysis performed as a reflex test revealed an 80 kb deletion on 17q21.31, encompassing the *BRCA1* gene. Follow-up FISH analysis performed on parental blood samples yielded negative results, confirming that the deletion was de novo in the fetus. Subsequent anatomic ultrasound evaluation showed no identifiable structural defects, and it was concluded that the microdeletion was unlikely to be the cause of the cystic hygroma. Regardless, it will be imperative that the patient's daughter be appropriately counseled regarding the implications of carrying a *BRCA1* deletion and the need for heightened surveillance in adulthood. As *BRCA1* genetic testing is traditionally performed on adult patients with informed consent, this case report highlights the need for ongoing conversations and research in the management of incidental fetal diagnosis discovered during routine prenatal testing, as well as the care and counseling of these patients and their families.



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1. Background

A cystic hygroma is an abnormal collection of lymphatic fluid most often found in the fetal neck region, though it may extend the entire length of the fetus. In the first trimester, the prevalence of cystic hygroma is approximately 1/285. Affected fetuses are at higher risk for chromosome abnormalities, structural defects, or genetic syndromes of non-chromosomal etiology [1,2]. Due to these risks, measurement of nuchal translucency has become a common part of first-trimester prenatal care. When a cystic hygroma is present, neither first-trimester maternal serum analyte screening nor cell-free DNA aneuploidy screening is the best testing option as the risk for aneuploidy is significant, approximately 50%. Instead, prenatal diagnostic testing via chorionic villus sampling or amniocentesis should be offered. Chromosome analysis via G-banding and/or chromosome microarray analysis should be the first line of testing to assess for aneuploidy [1–4]. If fetal karyotyping is first performed and is normal, chromosome microarray analysis should be offered as a reflex test. Clinically significant copy number gains or losses are detected in approximately 5% of fetuses with cystic hygroma and normal G-banding analysis [1–3].

BRCA1 is a tumor suppressor gene; loss-of-function mutations in this gene confer a significantly increased lifetime risk for hereditary breast and/or ovarian cancer [5]. Most pathogenic variants within *BRCA1* are detected via Next-generation Sequencing. However, this technology will not detect large rearrangements or whole gene deletions [6–8]. With a haploinsufficiency score of 3 [9], there is sufficient evidence that large rearrangements or whole gene deletions of *BRCA1* are associated with an increased risk for hereditary

breast and/or ovarian cancer [6–9]). In this report, we present a case of incidental prenatal diagnosis of a BRCA mutation during the evaluation of a fetal cystic hygroma.

2. Case Summary

The patient, a 33-year-old G3P0020 at 13 0/7 weeks of pregnancy, was referred for consultation after a first-trimester nuchal translucency ultrasound evaluation showed a 6 mm septated cystic hygroma. Following genetic counseling, the patient elected to pursue diagnostic testing via chorionic villus sampling. The results were significant for the unexpected finding of a de novo microdeletion encompassing the *BRCA1* gene. These results were disclosed to the patient and her significant other in person during a follow-up prenatal visit.

The patient had a normal second-trimester anatomic ultrasound exam and normal fetal echocardiographic evaluation. She developed gestational diabetes which was controlled with Glyburide and her pregnancy was otherwise uncomplicated. The patient had a normal spontaneous vaginal delivery at 38 4/7 weeks. Neonatal evaluation was unremarkable.

3. Methods

First-trimester chorionic villi were obtained at 13 0/7 weeks gestation via transabdominal chorionic villus sampling. Fetal karyotype was produced using standard G-banding techniques. DNA was subsequently extracted from cultured cells using the QIAamp DNA Blood Mini Kit (Cat #51106). DNA concentration was measured using the Nanodrop ND-2000 spectrometer (Thermo Scientific, Wilmington, DE, USA). Reflex microarray comparative genomic hybridization (aCGH) experiments were performed on SurePrint G3 ISCA CGH + SNP Microarray Kit, 4 × 180 k v2.0 platform (Agilent Technologies, Santa Clara, CA, USA), featuring approximately 110,715 custom oligonucleotides + 59,647 SNPs (60 mers) and covering 1282 ISCA regions, resulting in 25.3 kb resolution. Patient data was scanned (Agilent Model #G2505C) at 3-micrometer resolution and visualized (Agilent CytoGenomics v5.3) with log2 threshold ratios of −0.25 for losses and 0.25 for gains. Confirmatory FISH was then performed using SureFISH (Agilent Technology, Santa Clara, CA, USA) and TelVysion (Abbott Molecular Inc., Des Plaines, IL, USA).

4. Results

Chromosome G-banding analysis demonstrated a normal fetal karyotype: 46,XX. Reflex chromosome microarray analysis was significant for the unexpected finding of an 80-kb deletion on 17q21.31 (41,186,542–41,266,359), encompassing the *BRCA1* gene (Figure 1). No other clinically significant copy number variants were detected, and the SNP array was negative for regions of homozygosity. The deletion was confirmed via FISH (Figure 2). Parental blood samples were then sent for FISH analysis to determine the origin of the microdeletion. These results were negative, confirming that the deletion was de novo in the fetus (Figure 3).

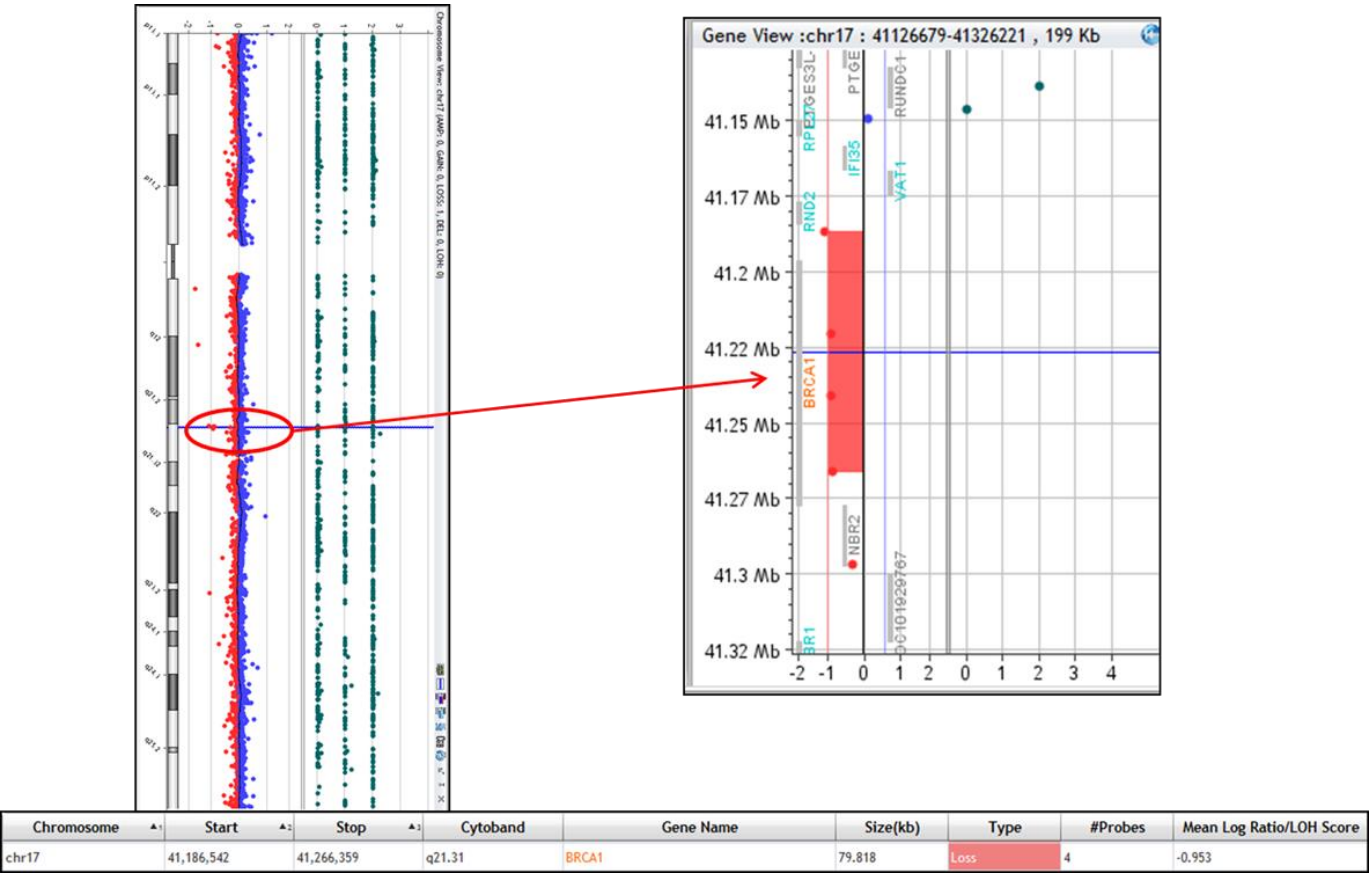


Figure 1. Identification of deletion in 17q21.31 region by aCGH. Chromosome view of chromosome 17 showing the deletion in the 17q21.31 region (red circle indicates the deleted oligo probes and the red arrow points to the Gene View showing the *BRCA1* gene deletion). The log₂ ratio is shown in the table (bottom of image).

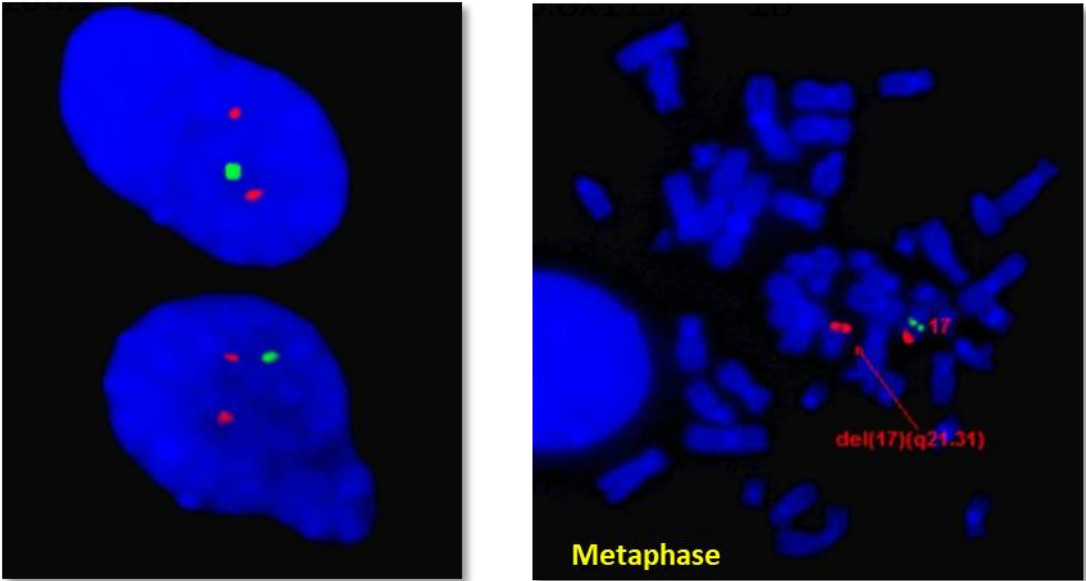


Figure 2. FISH confirmation of ArrayCGH finding in the fetus. aCGH finding was confirmed by *BRCA1* (41,162,433–41,265,378) SureFISH probe (green signal); the control Vysis DNA FISH probe TelVysion 17q (red signals) was used.

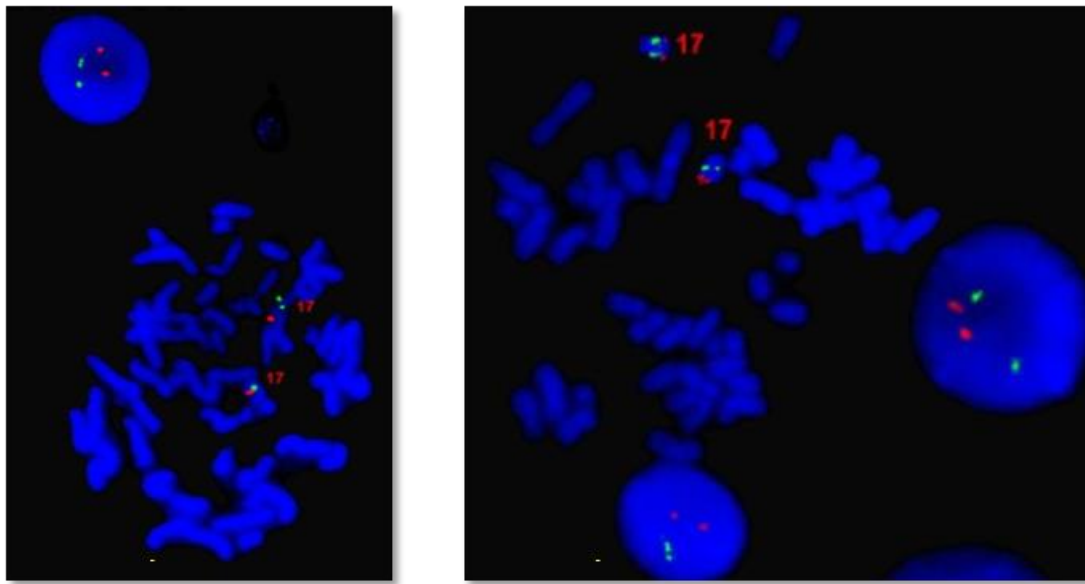


Figure 3. Parental follow-up for the inheritance of *BRCA1* deletion in the fetus. FISH analysis of parental blood samples with *BRCA1* probe showed no evidence of deletion 17q21.31, confirming the deletion is de novo in this fetus.

5. Discussion

We performed a literature review and, to our knowledge, there are no other cases of prenatal diagnosis of a *BRCA* mutation. Our search excluded the literature on preimplantation genetic diagnosis for known carriers of *BRCA* 1/2 pathogenic variants, as those are cases where testing was intentional. While we do not believe the *BRCA1* deletion was associated with cystic hygroma, this incidental finding has important implications. Genetic testing of minors or fetuses for adult-onset conditions is generally not endorsed by any of the major professional societies [10–13]. The rationale is that testing for an adult-onset condition for which there is no treatment in childhood that can reduce disease morbidity and/or mortality offers no clinical benefit to the minor, and in fact, poses a risk for undue psychosocial burden. Additional arguments against predictive/susceptibility testing of minors include the ethical duty to respect the future autonomy of the child, regarding their “right to not know” as well as concern for potential discrimination related to life, disability, and long-term care insurance [10–15].

While targeted genetic testing of fetuses and minors for specific adult-onset conditions is discouraged, it is also acknowledged that the advent of more expansive tests, such as Whole Exome Sequencing, can result in the discovery of incidental findings. The American College of Medical Genetics has published recommendations on the reporting of such findings in which they specifically support disclosure of known or expected pathogenic mutations associated with certain “medically actionable,” primarily adult-onset conditions. Their statement includes acknowledgment of the need for thoughtful pre-test counseling regarding incidental findings as part of the informed consent discussion for prenatal WES/WGS [16].

This case presented unique challenges in that the incidental finding was detected via chromosome microarray analysis, rather than WES/WGS. While guidelines are clearly in place for managing medically actionable incidental findings via the latter methodologies (both prenatally and post-natally) to allow for patient education and informed consent [4,16]), these guidelines are not necessarily incorporated into routine counseling about chromosome microarray analysis. At present, both *BRCA1* and *BRCA2* are classified as genes that should be reported as incidental findings, regardless of the age of the individual being tested. Likewise, the ACMG (American College of Medical Genetics) standards and guidelines for interpretation and reporting of postnatal constitutional copy number

variants recommend that incidental CNVs known to increase the risk for neoplasia (and which could be medically actionable), should be reported, regardless of the indication for the which testing was performed [16].

The patient and her significant other were counseled that the chromosome microarray result was unlikely to be the direct cause of the cystic hygroma, and it did not necessitate any alteration in prenatal or pediatric care. However, it was shared with the patient and her significant other that there would be implications for their daughter as she reached adulthood regarding cancer risk. This case was particularly unique in disclosing hereditary cancer risk to offspring, as the deletion was de novo. The current literature examining parental opinions about offering predictive/susceptibility testing in minors as well as disclosure of genetic risk is derived from a population of “high-risk” adults whose offspring is at a 50% risk to inherit a pathogenic mutation [17–19]. The lived experience of this population is likely quite different than this case of a “low-risk” family, making it imperative that sensitive and knowledgeable clinician support be provided for the couple when discussing the results with their daughter. The case highlights the continuing complexity of routine genetic testing where a standard prenatal diagnostic assay inadvertently resulted in predictive/susceptibility testing being performed on the patient’s fetus.

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