C-300

Prenatal Detection of a Cryptic Derivative Chromosome: Association of Ultrasound Findings with an Imprinted Region

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I. Introduction

SNP Microarray analysis has become part of the routine diagnostic process in cases of prenatal ultrasound anomalies. Unfortunately in the majority of these cases, a cause for the ultrasound findings is not identified, limiting the information available to aid in counseling these families regarding the possible severity of the findings and recurrence risk. These statistics might make us question if SNP microarray is worth the expense for these families. We would like to highlight two cases where SNP microarray provided some unexpected but critical findings, making the case for just how valuable these results can be when an anomaly is identified. In these cases, SNP microarray was not only able to provide an explanation for the ultrasound observations, but was also able to deliver a diagnosis that had important reproductive counseling implications.

II. Methods

SNP MICROARRAY METHODOLOGY: All studies were done utilizing the Affymetrix® Cytoscan® HD array [Affymetrix® and CytoScan® are Registered Trademarks of Affymetrix, Inc.]. This array contains approximately 2.695 million markers across the entire human genome. There are approximately 743,000 SNPs (single nucleotide polymorphism probes) and 1,953,000 structural non-polymorphic probes (NPCNs). On the average there is approximately 0.88 kb between each marker. DNA was extracted utilizing standard methods and 250 ng of total genomic DNA was digested with NspI, ligated to adaptors, and amplified using Titanium Taq with a GeneAmp PCR System 9700. PCR products were purified using AMPure beads and quantified using NanoDrop 8000. Purified DNA was fragmented and biotin labeled and hybridized to the Affymetrix Cytoscan® HD GeneChip. Data was analyzed using Chromosome Analysis Suite. The analysis is based on the GRCh37/hg19 assembly.

III. Case Presentations

Case 1:

An ultrasound at **36 weeks gestation** identified a fetus with **unilateral right side ventriculomegaly** and a **small omphalocele**. Amniocentesis was performed and **karyotype results were normal**. The ordering physician ordered SNP microarray analysis which revealed a **1.6 Mb terminal deletion of 6q27->6qter** (reported in patients with brain anomalies) **and a 5.26 Mb terminal duplication of 11pter->11p15.4**. The 11p duplication contained an imprinted region that would be associated with either Beckwith-Wiedemann syndrome (BWS) or Russell-Silver syndrome (RS).

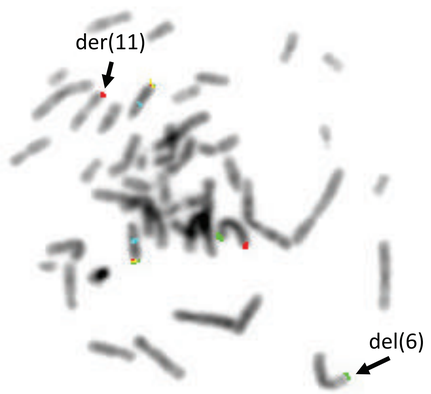
These findings suggested that the **fetus had a cryptic derivative chromosome** possibly arising from a parental balanced rearrangement. Based on the potential reproductive implications for future pregnancies, the parents elected to pursue parental follow up testing by fluorescent in situ hybridization (FISH). **This analysis revealed a paternal 6;11 balanced translocation**. Whereas isolated BWS is not expected to recur in future pregnancies (in the absence of an affected parent), a balanced translocation does carry with it the risk for recurrence of an unbalanced derivative in future conceptions.

Case 2:

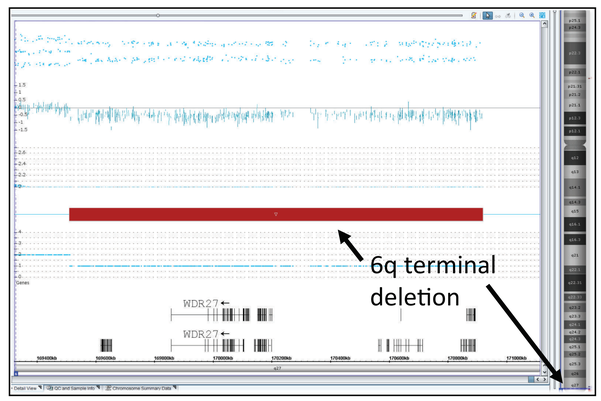
A chorionic villus sampling (CVS) was submitted from a **13.4 weeks gestation** fetus with a **cystic hygroma** and **hydrops** by ultrasound. Routine karyotype was not ordered for this patient, however aneuploidy FISH resulted normal male. SNP microarray analysis revealed a **1.38 Mb terminal deletion of 5q35->5qter and a 4.51 Mb terminal duplication of 11pter->11p15.4**. Again, the 11p duplication contained an imprinted region that would be associated with either BWS or RS.

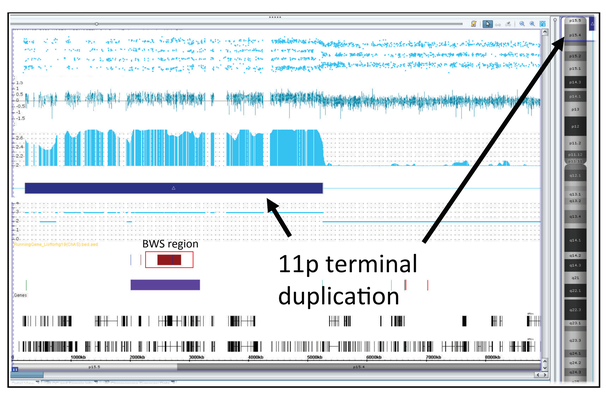
The findings for this fetus were also suggestive of a **cryptic derivative chromosome**. Concerned about the risk for future pregnancies, these parents also elected to pursue parental FISH analysis. It was found that the **father of the pregnancy carried a 5;11 translocation**.

6;11 unbalanced translocation

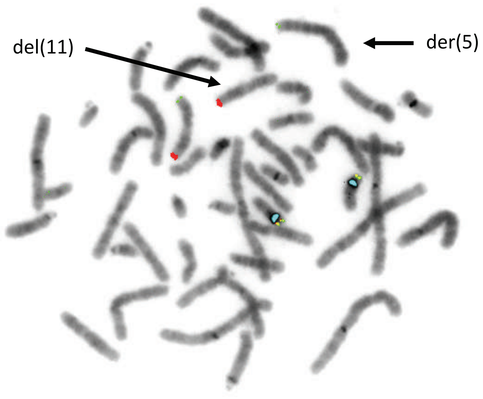


FISH image of 6;11 translocation

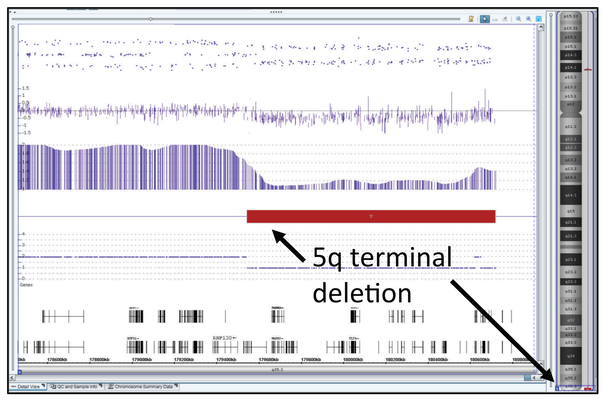


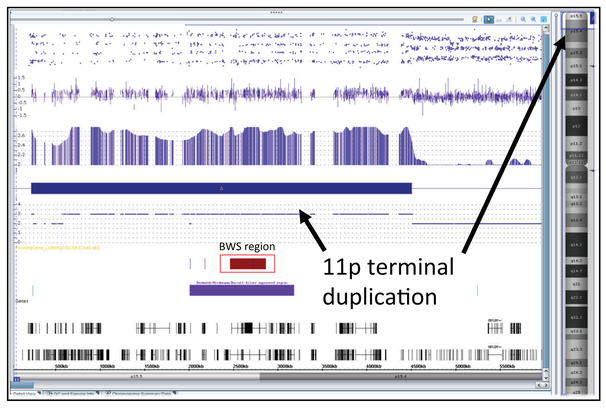


5;11 unbalanced translocation



FISH image of 5;11 translocation





IV. Discussion

Typical ultrasound presentation in cases of Beckwith-Wiedemann syndrome may include a fetus that is large for gestational age, omphalocele, cleft palate, heart abnormalities, kidney abnormalities, macroglossia, and organomegaly.[1] The fetus in the first example *did* present with an omphalocele. The fetus in the second example, while much earlier in gestation, *did not* present with any findings that would indicate a diagnosis of Beckwith-Wiedemann syndrome. Cases like the second example show us that ultrasound on its own may not be able to provide enough information to make a definitive diagnosis, nor provide families with the information they need to make decisions about the pregnancy or future family planning.

Routine karyotype and aneuploidy FISH are excellent tools for validating ultrasound findings that fit a known pattern for an established aneuploidy. However, they usually don't identify an abnormality when the ultrasound findings are rarer in nature or less specific to a known condition. In these cases you need a higher resolution "magnifying glass" able to interrogate at the submicroscopic level and identify the defect causing the ultrasound findings. SNP microarray can accomplish that task. In both case examples presented here, the SNP microarray results provided a prenatal diagnosis and enhanced pregnancy management and delivery options. This alone has great value for the families affected by this diagnostic odyssey, because they have been provided with much needed answers for the ultrasound anomalies in the pregnancy. Where SNP microarray really proves its superiority to other diagnostic tools for this situation is in the area of risk for future pregnancies. In both cases a parental translocation was discovered which has with it a risk for an adverse outcome in future pregnancies. Armed with this knowledge, these families now have more power over their fate because they can use this risk information to decide if and how to expand their family.

V. References

1. Shuman C, Beckwith JB, Weksberg R. Beckwith-Wiedemann Syndrome. 2000 Mar 3 [Updated 2016 Aug 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.Available from: https://www.ncbi.nlm.nih.gov/books/NBK1394/ Accessed on September 17,2018.

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