Genetics Corner: Translocation Down syndrome

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Case Summary:

A 15-week-old female was referred to Pediatric Genetics upon discharge from the NICU for translocation Down syndrome (DS). The prenatal history was uncomplicated. There were normal fetal movements. The infant was born at 36 weeks 5 days gestation by vaginal delivery to a 32 year old G2P1 mother. Birth weight was 2631 grams (2nd percentile) and head circumference was 31.5 cm (10th percentile). She was in the NICU for 2 weeks due to poor feeding and respiratory distress. She passed her newborn hearing screen. Chromosome analysis and chromosome microarray were ordered during her admission because of a clinical suspicion of DS.

Reportedly, all prenatal maternal screening tests and ultrasounds were normal and there was no indication of aneuploidy throughout the pregnancy. Parents discussed that retrospective review of the patient's detailed fetal ultrasound revealed a minor cardiac abnormality that the family was not alerted to.

Genetics Evaluation:

On physical exam, the infant had minor dysmorphic facial features suggestive of Down syndrome. She was being followed by Pediatric Cardiology for a small atrial septal defect with left to right shunting and by Hematology/Oncology for thrombocytopenia. She was s/p surgical removal of bilateral pre-auricular skin tags and a cutaneous skin tag on her right cheek.

Developmentally, the patient was doing well: she lifted her head at 2 months, rolled over at 2 months, and bore weight well, milestones that are advanced for an infant with Down syndrome. She cooed and interacted well socially. She received developmental therapy once a week that focused on motor, muscular, and speech development.

The family history was not significant. There was no family history of birth defects, developmental delay, intellectual disability, early infant deaths or multiple miscarriages. Parents are of Icelandic and Native American ancestry. Parental consanguinity was denied.

Chromosome analysis detected an 46 chromosomes, one of which was a derivative chromosome 21, that involved two copies of chromosome 21: 46,XX,+21,der(21;21)(q10;?q21). This resulted in partial duplication of the distal long arm of chromosome 21. The chromosome microarray identified a 21.2 Mb terminal duplication of chromosome 21 from 21q21.3 to 21qter, indicating partial trisomy for this region.

Conclusion and Counseling:

The patient has an atypical form of translocation DS due to a derivative 21;21 chromosome causing partial duplication of the distal long arm of chromosome 21. In approximately 3-5% of patients

Figure 1: At 12 months, the patient is crawling and starting to pull to a stand. Note the mild facial features of Down syndrome: epicanthal folds, round face with flat profile. Her muscle tone is remarkably good, which is atypical for DS.

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with DS, the chromosome number is normal and the extra chromosomal material is translocated to another chromosome (2). This type of rearrangement is known as a Robertsonian translocation. Robertsonian translocations result from the fusion of two acrocentric chromosomes (chromosomes 13, 14, 15, 21 and 22), with chromosome 14 being the most common partner chromosome involved in Robertsonian translocations (2).

Our patient has a rare type of translocation because the breakpoint is in the long arm of one copy of chr 21, not in the centromere as expected. She has a partial duplication of the distal long arm of chromosome 21. This has been called "Partial Trisomy 21" in the medical literature and the phenotype may be somewhat

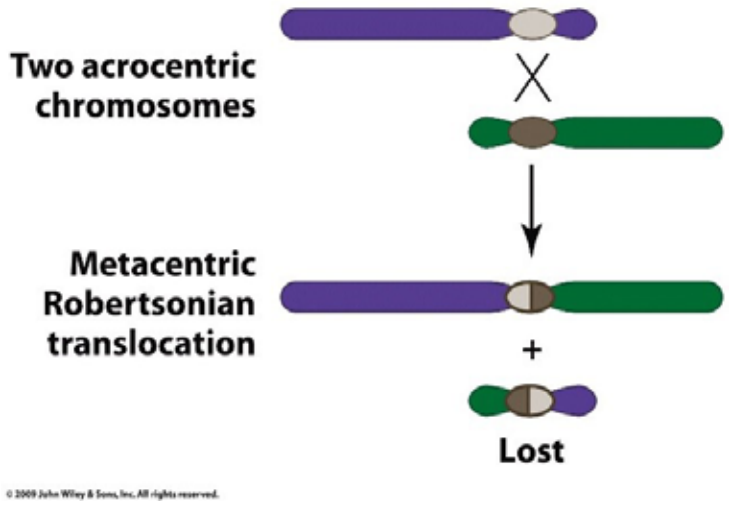

Figure 2: In a typical Robertsonian translocation, the breakpoints are in the centromeres and there are two copies of the long arms of the acrocentric chromosomes in the derivative chromosome

milder than the more typical types of DS that include a complete extra copy of chromosome 21. However, since she has three copies of the DS critical region at 21q22.13, on the distal long arm of chromosome 21, we expect her to demonstrate most of the features typically associated with DS.

This case highlights the critical importance of obtaining chromosome analysis to confirm the clinical suspicion of Down syndrome. As stated in the previously described Down syndrome toolkit (please see the September issue of Neonatology Today for a detailed description of this toolkit) chromosome analysis is usually a confirmatory test, but it also distinguishes the more common trisomy 21 from the less common translocation and mosaic types of Down syndrome. , which differ in their recurrence risks. Chromosome analysis is therefore necessary for providing appropriate genetic counseling.

Additionally, (as previously described in the August issue of Neonatology Today) chromosome analysis is a better first-line test when an aneuploidy is suspected or when there is a family history of multiple miscarriages or infertility when a balanced translocation is suspected. Chromosome microarray analyzes DNA rather than whole chromosomes, and does not identify translocations, inversions or other structural chromosome rearrangements. Whereas, conventional cytogenetic analysis uses microscopic analysis of banded chromosomes and examines explicitly the shape and morphology of chromosomes.

Parental chromosome analysis was recommended to identify mosaicism for this derivative chromosome in one of the parents or any structural changes (e.g. Inversion) in chromosome 21 that may predispose to an unbalanced rearrangement in their future offspring and to clarify the recurrence risk for DS in future pregnancies. Approximately 25% of Robertsonian translocation DS is familial and 75% is de novo. (1) Both parents had a normal chromosome result.

The difference between prenatal diagnostic and screening test options for the detection of chromosome abnormalities was discussed with the family. Prenatal screening options, such as maternal serum screening, ultrasound and non-invasive prenatal screening (NIPS), will not identify all cases of DS. Maternal serum screening has an 80-90% detection rate for DS depending on the type of screening that is performed. (4) NIPS has a detection rate of 99% (which varies somewhat with the laboratory and the technique) for Down syndrome. (3) Additionally, approximately 30% of fetuses with Down syndrome have a major structural anomaly present on ultrasound and about 50-60% may have one or more findings on an 18-20-week ultrasound (3). Prenatal diagnostic tests, such as amniocentesis and chorionic villus sampling, have the highest detection rate for DS at > 99.5%. Prenatal genetic counseling was recommended in all future pregnancies as parental germline mosaicism cannot be ruled out. The recurrence risk

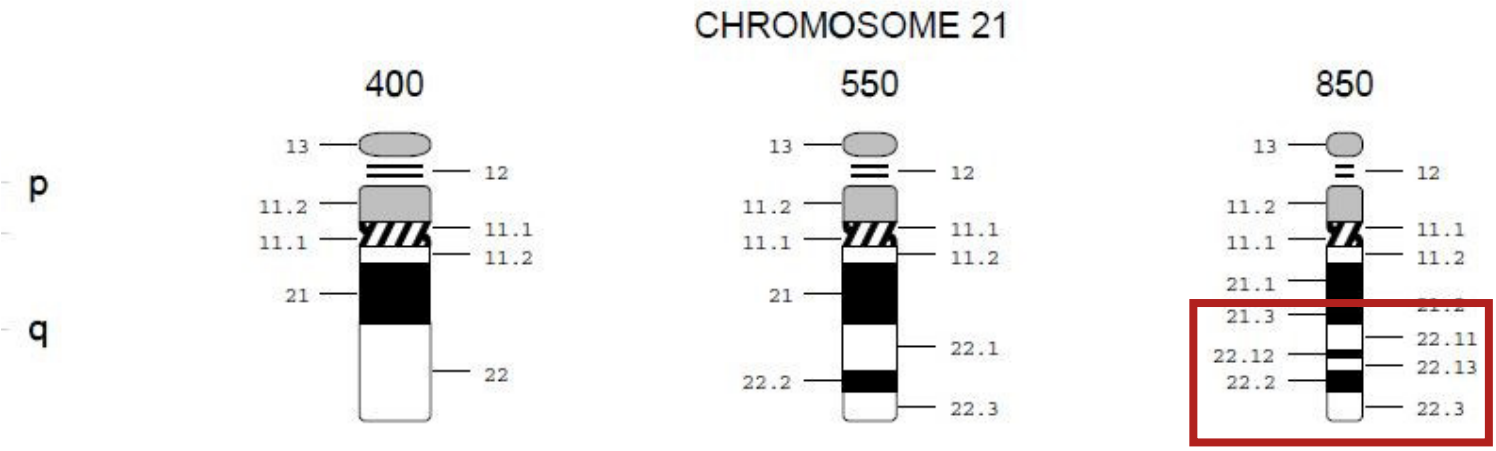

Figure 3: http://www.pathology.washington.edu/research/cytopages/idiograms/human/hum_21.pdf

The duplicated region in our patient is boxed in red.

for another child with Down syndrome is 1% above the maternal age-related risk for this family.

"Prenatal genetic counseling was recommended in all future pregnancies as parental germline mosaicism cannot be ruled out. The recurrence risk for another child with Down syndrome is 1% above the maternal age-related risk for this family."

Practical Applications:

1. Features of Down syndrome can be subtle. Be aware that the phenotype can between patients and in rare cases it can indicate partial trisomy 21.
2. Use chromosome analysis as your first line test when Down syndrome is suspected. Chromosome analysis is critical for confirming a diagnosis of DS as atypical cases of DS may not be identified with chromosome microarray or fluorescence in situ hybridization (FISH).
3. Parental follow up testing is necessary to clarify the recurrence risk for DS ONLY when a translocation is involved.
4. Prenatal screening options for aneuploidy such as maternal serum screening, ultrasound or NIPS may not identify all cases of DS.

References:

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4. *California Department of Public Health. (2017). The California Prenatal Screening Program. Richmond, CA.*

Permission was obtained from the patient's parents to distribute her picture for education purposes.

The authors have no relevant disclosures.

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