Peer Reviewed

Genetic Corner: Two Different Unbalanced Translocations of 15q and 21q in Dizygotic Twins Presenting with Differing Phenotypes

Andrew Mueller, Skylar Muchmore, June-Anne Gold MD FACMG

"A genetic consult was requested for two 16-week-old dizygotic twins, one female and one male, born to G3P4 mother with advanced maternal age. At the time of the visit, the mother reported that she was concerned that both twins could have Prader-Willi Syndrome. Her doctor had told her this. "

Case history:

A genetic consult was requested for two 16-week-old dizygotic twins, one female and one male, born to G3P4 mother with advanced maternal age. At the time of the visit, the mother reported that she was concerned that both twins could have Prader-Willi Syndrome. Her doctor had told her this.

Baby Girl (BG) was born with respiratory distress at 31 3/7 weeks gestation. BW: 1435g BHC: 29cm BL: 35cm APGARS 1, 5: 4, 9. She was noted to have low tone and difficulty feeding following birth and was found to be plagiocephalic and brachiocephalic. Chromosome analysis studies found a translocation of chromosomes 15q and 21q. The chromosome microarray studies found 6.6 MB proximal deletion of 15q11.2q13.1 and 6.9 MB Proximal Duplication of 21q11.2q21.1, consistent with an unbalanced translocation of 15q and 21q. The 21q micro duplication observed in BG does not overlap the Down syndrome critical region and is not currently associated with a clinical disorder. The 15q deletion includes the region associated with the Type I deletion of either Prader-Willi syndrome (PWS) or Angelman syndrome (AS), and the PWS / Angelman Methylation testing confirmed the absence of the paternal SNRPN gene expression confirming Prader-Willi Syndrome (PWS).

On physical exam, BG had features typical for PWS bi-temporal narrowing, almond-shaped eyes with upslanting palpebral fissures, downturned corners to the mouth, and severe hypotonia with decreased reflexes (Picture 1). She had hypoplastic labia and was reportedly very still in pregnancy with decreased fetal movements. Growth percentiles were as follows: Length <1% (z=-3.59), weight <1% (-2.83), and head circumference <1% (z=-3.5). She had a nasogastric tube(NG) to help with nutrition, given feeding difficulties due to failure to thrive, severe hypotonia, and difficulty sucking.

Her twin brother, Baby Boy (BB), was born at 31 3/7 weeks gestation with PTL and respiratory distress. BW: 1770g BHC: 30cm BL: 38cm APGARS 1, 5: 8, 9. His chromosomal microarray study found a 6.6MB terminal duplication of 15q11.2q13.1 and a 6.95MB terminal deletion of 21q11.2q21.1, consistent with an unbalanced translocation.

Compared to his twin, he was active during pregnancy, very fussy on examination, and had normal pigmentation. Growth percentiles at the time of the exam were: Length <1% (z=-3.13), weight 16% (z=-1.01), and head circumference 3% (z=-1.94) larger than his sister. He had different dysmorphic facial features with a broad nasal bridge, large low, set ears, deep nasolabial folds, wide open fontanelles, broad first toes, minimal 2-3 toe syndactyly, slightly increased tone, and deep palmar creases with short fingers and thumbs (Picture 2-3). During the examination, he was not fixing or following. His appearance and physical features are quite different from his sister's.

"The maternal family history was largely non-contributory. Mother had two healthy children from a previous relationship, and father has no other children. Parental consanguinity was denied. Maternal ancestry is from Guatemala, and paternal ancestry is from Honduras. One significant finding on the paternal side is that the paternal grandmother had three children who passed early in life. It is unclear why."

The maternal family history was largely non-contributory. Mother had two healthy children from a previous relationship, and father has no other children. Parental consanguinity was denied. Maternal ancestry is from Guatemala, and paternal ancestry is from

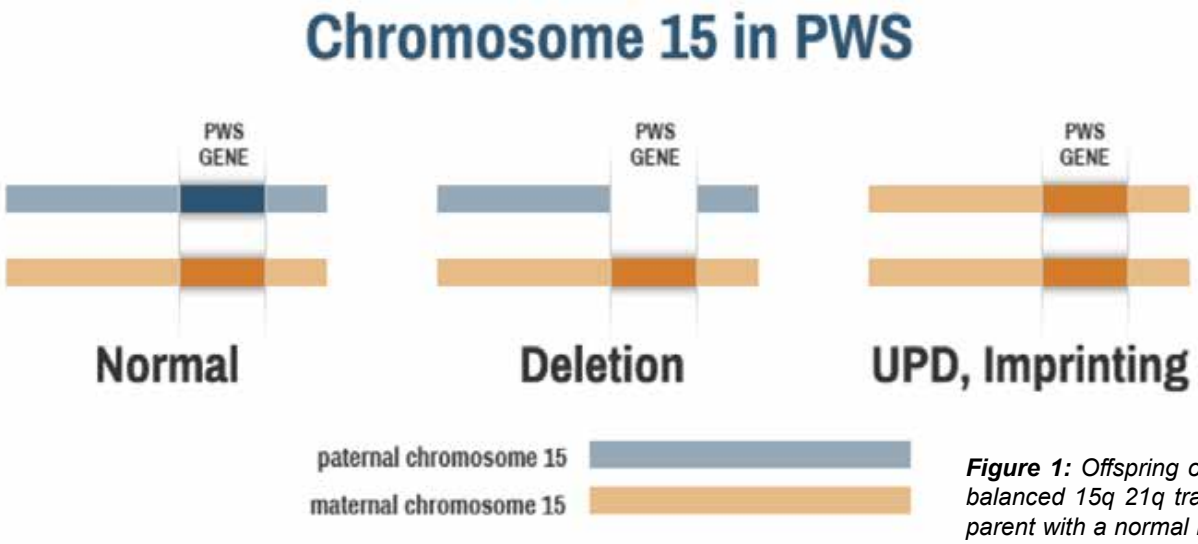

Figure 1: *Offspring of a parent with a balanced 15q 21q translocation and a parent with a normal karyotype. (Made with http://cydas.org/OnlineAnalysis/WebExample4.aspx (Hiller et al.))*

Picture 1: *Baby Girl (BG)*

Picture 2: *Baby Boy (BB)*

Honduras. One significant finding on the paternal side is that the paternal grandmother had three children who passed early in life. It is unclear why.

Assessment:

The 15q 21q unbalanced chromosome translocations observed in the twins are most likely the result of a balanced translocation in one of the parents. Presumably, the father is Prader Willi due to 15q deletion being associated with paternal inheritance of a 15q deletion (Driscoll et al.).

"The 15q 21q unbalanced chromosome translocations observed in the twins are most likely the result of a balanced translocation in one of the parents. "

The 15q 21q balanced translocation in the parent would result in 4 different chromosome arrangements in the children (Fig. 1),

Picture 2: *Baby Boy (BB) Right Hand*

including the 15q duplication 21q deletion observed in BB and the 21q duplication 15q deletion observed in BG.

21q11.2q21.1 Duplication: Duplications of 21q have been associated with multiple phenotypic characteristics of Down syndrome when the Down Syndrome Critical Regions (DSCR) are duplicated (Olson et al.). In its most precise description, this region extends around 5.4 MB from between the *D21S17* and *D21S55* markers to *MX1* and *BCEI* markers (Olson et al.). The 21q11.2q21.1 duplication found in BG notably does not include the DSCR. Duplications in these regions that do not include DSCR have been reported in individuals without a Down Syndrome phenotype or other mental and physical anomalies (Su et al.).

15q11.2q13.1 Deletion - Prader Willi Syndrome: Prader-Willi Syndrome (PWS) is a complex neurodevelopmental disorder attributed to a lack of paternal gene expression within the chromosome 15q11-13 region. Three primary mechanisms lead to the lack of paternal gene expression in the 15q11-13 region, including deletions, maternal uniparental disomy, and imprinting center defects. In this case, BG had a 15q deletion due to an unbalanced chromosome translocation, most likely resulting from a paternal balanced translocation of 15q and 21q. Since the Prader-Willi Syndrome is likely due to a paternal balanced translocation, the recurrence risk is expected to be 1 in 4 (Fig. 1).

PWS can be confirmed with methylation studies, which test for the absence of paternal SNRPN gene expression. While PWS is generally the result of the *de novo* gene alterations mentioned above, here we see an instance consistent with a balanced translocation in the father.

PWS is uniquely characterized by a hypoactive fetus, leading to a hypotonic baby failing to thrive. Feeding habits drastically change between the ages of 2 and 4, and the child becomes hyperphagic. Severe morbid obesity is common without lifestyle intervention.

It is recommended that parents lock food away and take other precautions.

Like most syndromes, there is no definitive cure for PWS; however, a multidisciplinary approach involving lifestyle management, nutrition, genetics, physical, speech, and occupational therapy is recommended for favorable outcomes. Of note, growth hormone therapy managed with endocrinology has been found to increase lean muscle mass, decrease fat mass, and lead to a more favorable BMI (Driscoll et al.).

"Like most syndromes, there is no definitive cure for PWS; however, a multidisciplinary approach involving lifestyle management, nutrition, genetics, physical, speech, and occupational therapy is recommended for favorable outcomes. Of note, growth hormone therapy managed with endocrinology has been found to increase lean muscle mass, decrease fat mass, and lead to a more favorable BMI (Driscoll et al.). "

15q11.2q13.1 Duplication: The 15q11.2q13.1 duplication detected in BB is within an imprinting region of the genome. Due to this, the phenotype is dependent on the inheritance. Maternally inherited 15q duplications are associated with hypotonia, motor delay, intellectual disability, autism, and epilepsy (Lusk et al.). Paternally inherited 15q duplications usually have milder phenotypes and have been reported in individuals with developmental delay, speech delay, and autism (Ageeli et al.). The inheritance of the 15q duplication in BB is expected to be paternal, so his phenotype is expected to be milder.

21q11.2q21.1 Deletion: The 21q11.2q21.1 deletion observed in BB is associated with variable phenotypes, which include developmental delay, short stature, microcephaly, clinodactyly, low set ears, scoliosis, and cardiac anomalies, (Jespersgaard et al.). The 21q deletion could account for some of BB's dysmorphic facial features. He is following up with cardiology for a hole in his heart that had reportedly closed.

Testing for the chromosome translocation was offered to the parents and declined at this time.

Take Away:

1.) **Carefully review genetic testing reports:** The mother was under the impression that both of the children had Prader Willi, which was reiterated during part of the appointment triage for the patients. A careful review of the genetic testing would have indicated two different diagnoses for the twins.

2.) **Balanced Translocations:** Balanced translocations in a parent may result in 4 chromosome arrangements in their children. The two unbalanced translocations in the offspring may be associated with two differing phenotypes, as observed in the twins.

Citations:

1. Ageeli, Essam Al, Séverine Drunat, Catherine Delanoë, Laurence Perrin, Clarisse Baumann, Yline Capri, Jennifer Fabre-Teste, Azzedine Aboura, Céline Dupont, Stéphane Auvin, Laila El Khattabi, Dominique Chantereau, Anne Moncla, Anne-Claude Tabet, Alain Verloes, Duplication of the 15q11-q13 region: Clinical and genetic study of 30 new cases, European Journal of Medical Genetics, Volume 57, Issue 1, 2014, Pages 5-14,ISSN 1769-7212, https://doi.org/10.1016/j.ejmg.2013.10.008. (https://www.sciencedirect.com/science/article/pii/S1769721213002437)

2. Driscoll DJ, Miller JL, Cassidy SB. Prader-Willi Syndrome. 1998 October 6 [Updated 2023 March 9]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1330/

3. Hiller B, Bradtke J, Balz H and Rieder H (2004): "CyDAS: a cytogenetic data analysis system," BioInformatics 2005 21(7):1282-1283; doi:10.1093/bioinformatics/bti146.Bioinformatics Advance Access originally published online on November 16, 2004

4. Jespersgaard C, Damgaard IN, Cornelius N, Bache I, Knabe N, Miranda MJ, Tümer Z. Proximal 21q deletion as a result of a de novo unbalanced t(12;21) translocation in a patient with dysmorphic features, hepatomegaly, thick myocardium and delayed psychomotor development. Mol Cytogenet. 2016 February 4;9:11. doi: 10.1186/s13039-016-0220-5. PMID: 26855673; PMCID: PMC4743331.

5. Lusk L, Vogel-Farley V, DiStefano C, Jeste S. Maternal 15q Duplication Syndrome. 2016 June 16 [updated 2021 July 15]. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. PMID: 27308687.

6. Olson LE, Richtsmeier JT, Leszl J, Reeves RH. A chromosome 21 critical region does not cause specific Down syndrome phenotypes. Science. 2004 Oct 22;306(5696):687-90. doi: 10.1126/science.1098992. PMID: 15499018; PMCID: PMC4019810.

7. Su, M.T.; Kuan, L.C.; Chou, Y.Y.; Tan, S.Y.; Kuo, T.C.; Kuo, P.L. Partial trisomy of chromosome 21 without the Down syndrome phenotype. *Prenat. Diagn.* **2016**, *36*, 492–495.

Disclosures: *There are no reported disclosures*

NT


Andrew Mueller, BS
Molecular and Cellular Biology
University of California, San Diego
San Diego, CA


Skylar Muchmore, OSM II
2023 ACMG Summer Genetics Scholar
College of Osteopathic Medicine of the Pacific
Western University of Health Science
Pomona, CA

Corresponding Author:


June-Anne Gold, MD, FACMG, DABOM, MBBS, MRCPCH, DCH,, RGN, RMN
Professor, Pediatrics, Genetics Division
Professor, Basic Sciences, Biochemistry Division
Loma Linda University School of Mediccine
Loma Linda, CA
Email: juneannegold@gmail.com