Inheritance of a Balanced t(12;20)(q24.33;p12.2) and Unbalanced der(13)t(7;13)(p21.3;q33.2) from a Maternally Derived Double Balanced Translocation Carrier

Jess F. Peterson¹ Gabrielle C. Geddes² Donald G. Basel^{2,3} Dana Schippman² John W. Grignon Jr.⁴
Peter vanTuinen¹ Ulrike P. Kappes^{3,5}

¹ Department of Pathology, Medical College of Wisconsin, Milwaukee, Wisconsin, United States

² Department of Pediatrics, Section of Genetics, Medical College of Wisconsin, Milwaukee, Wisconsin, United States

³ Human and Molecular Genetics Center, Medical College of Wisconsin, Milwaukee, Wisconsin, United States

⁴ Wisconsin Diagnostic Laboratories, Milwaukee, Wisconsin, United States

⁵ The Advanced Genomics Laboratory at Children's Research Institute, Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Address for correspondence Jess F. Peterson, MD, Froedtert/MCW Laboratory Building, 9200 W Wisconsin Avenue, Milwaukee, WI 53226, United States (e-mail: jepeterson@mcw.edu).

J Pediatr Genet 2018;7:35–39.

Abstract

Keywords

- 7p21.3-p22.3 duplication
- 13q33.2-q34 deletion
- unbalanced translocation
- double balanced translocation carrier
- fluorescence in situ hybridization
- array comparative genomic hybridization

We report a 4-month-old male proband with a history of prominent forehead, hypertelorism, ear abnormalities, micrognathia, hypospadias, and multiple cardiac abnormalities. Initial microarray analysis detected a concurrent 7p21.3-p22.3 duplication and 13q33.2-q34 deletion indicating an unbalanced rearrangement. However, subsequent conventional cytogenetic studies only revealed what appeared to be a balanced t(12;20)(q24.33;p12.2). Fluorescence in situ hybridization (FISH) using chromosome-specific subtelomere probes confirmed the presence of an unbalanced der(13)t(7;13)(p21.3;q33.2) and balanced t(12;20)(q24.33;p12.2), both of maternal origin. In addition to our unique clinical findings, this case highlights the benefits and limitations of both conventional cytogenetic studies and microarray analysis and how FISH complements each methodology.

Introduction

Balanced translocations are commonly observed in humans, occurring in approximately 0.16 to 0.20% (1/625–1/500) of live births.^{1,2} Importantly, balanced translocation carriers are at an increased risk of having recurrent spontaneous abortions and/or having children with congenital abnormalities, in addition to neurodevelopmental disorders (mostly when de novo in origin), particularly autism spectrum dis-

order and intellectual disability.^{2,3} Numerous causes for these abnormal clinical features have been described, including large segmental aneusomies that may or may not be compatible with life; submicroscopic deletion, duplication, disruption, dysregulation; and fusion of genes at or near the translocation breakpoints.^{2,4} Complex chromosomal rearrangements (CCRs), defined here as structural abnormalities involving more than two chromosomes with exchanges of chromosomal segments, are rare and mostly de novo in

received

June 21, 2017

accepted after revision

July 10, 2017

published online

August 14, 2017

Copyright © 2018 by Georg Thieme
Verlag KG, Stuttgart · New York

DOI <https://doi.org/10.1055/s-0037-1605592>.
ISSN 2146-4596.

origin.^{1,5–7} Carriers of CCRs can harbor two or three independent translocations, thus increasing the likelihood of having offspring with segmental aneusomies.^{2,5–7}

Clinical Report

We present a 4-month-old male patient who was born to a 22-year-old, G3P1A1 mother and a 21-year-old father. Labor was induced at 39^{3/7} weeks of gestation due to a 3-week low baseline fetal heart rate. He was delivered vaginally, with Apgar scores of 7 and 8 at 1 and 5 minutes, respectively, and placed on continuous positive airway pressure via mask for respiratory distress. His birth weight was 2.49 kg, length was 47 cm, and occipital–frontal circumference (OFC) was 32 cm. Notable physical exam findings at birth included a recessed hair line, a sloped and prominent forehead, malar flattening, a broad and prominent nasal bridge, hypertelorism, low-set ears with prominent antihelix, micrognathia, neck webbing with additional skin folds, and hypospadias (→Fig. 1A, B). Multiple cardiac abnormalities were also diagnosed, including noncompaction cardiomyopathy, ventricular and atrial septal defects, bicuspid aortic valves, patent ductus arteriosus, and congenital dilation of the aortic arch. Pyloric stenosis was diagnosed at 1 month and surgically corrected via laparoscopic pyloromyotomy.

Our genetic service reevaluated the proband at 4 months of age. His body mass index (BMI) was 14.4 kg/m², weight was 4.92 kg (<1% for boys aged 0–2 years, WHO), height was 58.4 cm (<1% for boys aged 0–2 years, WHO), and head circumference was 39 cm (1% for boys aged 0–2 years, WHO). Additional dysmorphic features noted were downslanting palpebral fissures and posteriorly rotated ears.

The maternal side of the family was of African American, Italian, and Greek descent. The mother had two full brothers, a maternal half-brother who was reported healthy, and two maternal half-sisters, one of whom reportedly carried two balanced translocations. The paternal side of the family was of African American and Caucasian descent. The proband had one maternal half-brother who was reportedly healthy. Family history of birth defects, intellectual disability, developmental disorders, or consanguinity was not reported.

Fig. 1 Proband at the age of 4 months. (A, B) Note the recessed hair line, prominent forehead, malar flattening, a broad and prominent nasal bridge, hypertelorism, downslanting palpebral fissures, low-set posteriorly rotated ears with prominent antihelix, and micrognathia.

Materials and Methods

Conventional cytogenetic studies were performed on phytohemagglutinin (PHA)-stimulated peripheral blood specimens collected from the proband and each parent. A total of 20 metaphase cells were analyzed per case by ASCP-certified cytogenetic technologists and captured using CytoVision software (Leica Biosystems, Buffalo Grove, Illinois, United States). Array comparative genomic hybridization (aCGH) analysis was performed on purified DNA from the proband using the CytoScan HD microarray platform (Affymetrix, Santa Clara, California, United States), and scanned with a GeneChip Scanner 3000 (Affymetrix). The reported nucleotide coordinates were based on UCSC hg19 (NCBI Build 37, Feb. 2009). FISH analysis was performed on both proband and maternal metaphase cells using subtelomere-specific probes for 7p (VIJyRM2185), 12q (VIJyRM2196), 13q (D13S327), and 20p (D20S1157, Abbott Laboratories, Abbott Park, Illinois, United States). Representative metaphase cells were captured using CytoVision software (Leica Biosystems). All aCGH and FISH procedures were performed as per the manufacturer's protocol.

Results

Microarray analysis on the proband revealed a concomitant 8.4-Mb duplication of 7p21.3–p22.3 (→Fig. 2A) and a 9.6-Mb heterozygous 13q33.2–q34 deletion (→Fig. 2B). The 7p21.3–p22.3 duplication contained 144 genes (58 of them OMIM genes), while the 13q33.2–q34 deletion contained 94 genes (34 of them OMIM genes). Subsequent conventional cytogenetic studies in 20 metaphase cells of the proband only revealed what appeared to be a reciprocal t(12;20)(q24.33;p12.2; →Fig. 3A, C). The partial 7p duplication and partial 13q deletion seen on microarray were not readily detected by conventional cytogenetic studies.

To confirm the presence of an unbalanced translocation between 7p and 13q as indicated by microarray analysis, FISH was performed on metaphase cells obtained from the proband. Positive hybridization for 7p (VIJyRM2185) was observed on the distal short arms of both copies of chromosome 7, in addition to the distal long arm of one copy of chromosome 13 (→Fig. 2C, D). Positive hybridization for 13q (D13S327) was only observed on the distal long arm of one copy of chromosome 13 (→Fig. 2E, F). FISH analysis was also performed on metaphase cells from the proband to confirm the balanced translocation between 12q and 20p as seen by conventional cytogenetic studies. Positive hybridization for 12q (VIJyRM2196) was observed on the distal long arm of one copy of chromosome 12, in addition to the distal short arm of one copy of chromosome 20 (→Fig. 3B). Positive hybridization for 20p (D20S1157) was observed on the distal short arm of one copy of chromosome 20, in addition to the distal long arm of one copy of chromosome 12 (→Fig. 3D). The final proband karyotype was 46,XY,t(12;20)(q24.33;p12.2)mat, der(13)t(7;13)(p21.3;q33.2)mat.ish t(12;20)(qter,pter + ;pter,qter +)(VIJyRM2196,-D20S1157 + ;D20S1157,-VIJyRM2196 +), der(13)t(7;13)(qter,-pter +)(D13S327,-VIJyRM2185 +).arr

Fig. 2 Array CGH profile showing (A) 8.4-Mb duplication of the 7p21.3-p22.2 chromosomal region and (B) 9.6-Mb heterozygous deletion of the 13q33.2-q34 chromosomal region. (C) Representative metaphase cell showing the derivative chromosome 13 (long black arrow) along with both normal copies of chromosome 7 (short black arrows). (D) Sequential FISH analysis (see image C) using a 7p subtelomere probe (green). Positive hybridization was observed on both short arms of chromosome 7 in addition to the distal long arm of the derivative chromosome 13. (E) Representative metaphase cell showing the derivative chromosome 13 (long black arrow) along with the normal copy of chromosome 13 (short black arrows). (F) Sequential FISH analysis (see image E) using a 13q subtelomere probe (red). Positive hybridization was only observed on the distal long arm of the normal copy of chromosome 13 (white arrow).

[GRCh37] 7p21.3p22.3(43360_8489911)x3,13q33.2q34(105499026_115107733)x1.

In addition, conventional cytogenetic studies were performed on the parents to determine the carrier status of each translocation observed in the proband. Maternal metaphase cell analysis detected the presence of a balanced $t(12;20)(q24.33;p12.2)$ and was confirmed by FISH. Sequential FISH analysis using 7p and 13q subtelomeric probes also revealed a balanced $t(7;13)(p21.3;q33.2)$, thus confirming the maternal origin of both balanced translocations. The final maternal karyotype was 46,XX, $t(7;13)(p21.3;q33.2)$, $t(12;20)(q24.33;p12.2)$.ish $t(7;13)(pter-,qter+;qter-,pter+)(VIJyRM2185-,D13S327+;D13S327-,VIJyRM2185+)$, $t(12;20)(qter-,pter+;pter-,qter+)(VIJyRM2196-,D20S1157+;D20S1157-,VIJyRM2196+)$. Paternal metaphase cell analysis yielded a normal male karyotype.

Discussion

While both chromosomal microarray analysis (CMA) and conventional cytogenetic studies (G-banding) can be utilized to detect copy number changes, the detection of truly balanced rearrangements can only be observed by G-banding.^{3,4,8} However, subtle rearrangements, particularly when similar banding patterns are involved, may go undetected.

Our case is unique in that microarray studies initially detected a likely unbalanced $der(13)t(7;13)(p21.3;q33.2)$ resulting in partial trisomy 7p and partial monosomy 13q (confirmed by FISH), while G-banding studies only detected a balanced $t(12;20)(q24.33;p12.2)$. The $der(13)t(7;13)$ was not observed by G-banding due to the small size and similar banding patterns between distal 7p and 13q. The $t(12;20)$ was not observed by microarray because it was balanced. The detection of balanced rearrangement carriers is significant, particularly for individuals planning to have children. Balanced rearrangement carriers may benefit from prenatal genetic counseling or preimplantation genetic testing, as they are at an increased risk of recurrent spontaneous abortions and/or having children with congenital abnormalities.^{2,5,9} If a balanced rearrangement is inherited, appropriate genetic testing could also be valuable to immediate family members.^{2,5} In our case, a maternal half-sister was also reported to be a double balanced translocation carrier. This demonstrates that half-siblings need to be equally considered as potential balanced translocation carriers.

Of additional interest in this case was the clinical presentation of our patient. The inheritance of the $der(13)t(7;13)(p21.3;q33.2)$ resulted in a 8.4-Mb duplication of 7p21.3-p22.3 and a 9.6-Mb heterozygous deletion of

Fig. 3 (A) Representative metaphase cell showing the derivative chromosome 20 along with the normal copy of chromosome 12. (B) Sequential FISH analysis (see image A) using a 12q subtelomere probe (red). Positive hybridization was observed on both the distal long arm of the normal chromosome 12 in addition to the distal short arm of the derivative chromosome 20. (C) Representative metaphase cell showing the derivative chromosome 12 along with the normal copy of chromosome 20. (D) Sequential FISH analysis (see image C) using a 20p subtelomere probe (green). Positive hybridization was observed on both the distal short arm of the normal chromosome 20 in addition to the distal long arm of the derivative chromosome 12.

13q33.2-q34. Distal 7p duplications spanning the 7q22.1 chromosomal region are associated with developmental and speech delays, skeletal abnormalities (scoliosis, leg length differences, mild kyphosis), and craniofacial dysmorphisms (macrocephaly, ocular hypertelorism, down-slanting palpebral fissures, micrognathia, low-set and/or malformed ears, and high or prominent forehead).^{10–14} Distal 13q deletions spanning the 13q33–q34 chromosomal region are associated with intellectual disability, congenital heart defects, craniofacial dysmorphisms, and genital malformations in males (ambiguous genitalia and hypospadias).^{15–19} Our patient presented with overlapping clinical features of both 7p22.1 duplication and 13q33–q23 deletion, including a prominent forehead, hypertelorism, low-set ears with prominent antihelix, micrognathia, hypospadias, and multiple cardiac abnormalities, including noncompaction cardiomyopathy, ventricular and atrial septal defects, bicuspid aortic valves, patent ductus arteriosus, and congenital dilation of the aortic arch. Interestingly, emerging data indicate that sequence-level resolution using next-generation sequencing dramatically improves prediction of clinical outcomes for balanced rearrangements, particularly for de novo rearrangements that may disrupt clinically significant

genes or disrupt topologically associated domains (TADs) that encompass known syndromic loci.^{3,4} Given that both rearrangements were maternally inherited, it is unlikely that the balanced $t(12;20)(q24.33;p12.2)$ contributed to the clinical features of our patient.

In conclusion, we report a 4-month-old male patient that inherited both unbalanced and balanced rearrangements that resulted in a partial 7p duplication and a heterozygous partial 13q deletion. Clinical features associated with both copy number variations were observed in our patient, including a prominent forehead, hypertelorism, ear abnormalities, micrognathia, hypospadias, and multiple cardiac abnormalities. Importantly, the detection of two maternally inherited balanced translocations may have reproductive implications for the parents and potentially to the mother's siblings. This case demonstrates the limitations of both microarray analysis and G-banding in the detection of both unbalanced and balanced rearrangements.

Conflict of Interest
None.

References

- 1 Chen CP, Wu PC, Lin CJ, et al. Balanced reciprocal translocations detected at amniocentesis. *Taiwan J Obstet Gynecol* 2010;49(04): 455–467
- 2 Gardner RJM, Sutherland GR, Shaffer LG. *Chromosome Abnormalities and Genetic Counseling*. 4th ed. New York City: Oxford University Press; 2012
- 3 Redin C, Brand H, Collins RL, et al. The genomic landscape of balanced cytogenetic abnormalities associated with human congenital anomalies. *Nat Genet* 2017;49(01):36–45
- 4 Ordulu Z, Kammin T, Brand H, et al. Structural chromosomal rearrangements require nucleotide-level resolution: lessons from next-generation sequencing in prenatal diagnosis. *Am J Hum Genet* 2016;99(05):1015–1033
- 5 Bowser-Riley SM, Griffiths MJ, Creasy MR, et al. Are double translocations double trouble? *J Med Genet* 1988;25(05):326–331
- 6 Simioni M, Steiner CE, Gil-da-Silva-Lopes VL. De novo double reciprocal translocations in addition to partial monosomy at another chromosome: a very rare case. *Gene* 2015;573(01): 166–170
- 7 Uysal A, Uludağ A, Silan F, Erçelen N, Zafer C, Ozdemir O. Double translocation: an interesting family history. *Balkan J Med Genet* 2013;16(01):77–80
- 8 Martin CL, Warburton D. Detection of chromosomal aberrations in clinical practice: from karyotype to genome sequence. *Annu Rev Genomics Hum Genet* 2015;16:309–326
- 9 Treff NR, Zimmerman RS. Advances in preimplantation genetic testing for monogenic disease and aneuploidy. *Annu Rev Genomics Hum Genet* 2017. Doi: 10.1146/annurev-genom-091416-035508
- 10 Caselli R, Ballarati L, Vignoli A, et al. 7p22.1 microduplication syndrome: clinical and molecular characterization of an adult case and review of the literature. *Eur J Med Genet* 2015;58(11):578–583
- 11 Cox DM, Butler MG. A case of the 7p22.2 microduplication: refinement of the critical chromosome region for 7p22 duplication syndrome. *J Pediatr Genet* 2015;4(01):34–37
- 12 Pebrel-Richard C, Rouzade C, Kemeny S, et al. Refinement of the critical region in a new 7p22.1 microduplication syndrome including craniofacial dysmorphism and speech delay. *Am J Med Genet A* 2014;164A(11):2964–2967
- 13 Preiksaitiene E, Kasnauskienė J, Ciuladaite Z, Tumienė B, Patsalis PC, Kučinskas V. Clinical and molecular characterization of a second case of 7p22.1 microduplication. *Am J Med Genet A* 2012;158A(05):1200–1203
- 14 Ronzoni L, Grassi FS, Pezzani L, et al. 7p22.1 microduplication syndrome: Refinement of the critical region. *Eur J Med Genet* 2017;60(02):114–117
- 15 Andresen JH, Aftimos S, Doherty E, Love DR, Battin M. 13q33.2 deletion: a rare cause of ambiguous genitalia in a male newborn with growth restriction. *Acta Paediatr* 2010;99(05):784–786
- 16 Huang C, Yang YF, Yin N, et al. Congenital heart defect and mental retardation in a patient with a 13q33.1-34 deletion. *Gene* 2012; 498(02):308–310
- 17 McMahon CJ, Breathnach C, Betts DR, Sharkey FH, Grealley MT. De novo interstitial deletion 13q33.3q34 in a male patient with double outlet right ventricle, microcephaly, dysmorphic craniofacial findings, and motor and developmental delay. *Am J Med Genet A* 2015;167A(05):1134–1141
- 18 Walczak-Sztulpa J, Wisniewska M, Latos-Bielenska A, et al. Chromosome deletions in 13q33-34: report of four patients and review of the literature. *Am J Med Genet A* 2008;146A(03):337–342
- 19 Yang YF, Ai Q, Huang C, et al. A 1.1Mb deletion in distal 13q deletion syndrome region with congenital heart defect and post-axial polydactyly: additional support for a CHD locus at distal 13q34 region. *Gene* 2013;528(01):51–54