

Case Report

Array comparative genomic hybridization characterization of prenatally detected *de novo* apparently balanced reciprocal translocations with or without genomic imbalance in other chromosomes

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Abstract

We present our experience of array comparative genomic hybridization (aCGH) characterization of two cases of prenatally detected *de novo* simple and complex apparently balanced reciprocal translocations. Amniocentesis of the first case revealed a complex chromosome rearrangement and a karyotype of 46,XY,t(5;8;6)(q11.2;p23.1;q22.32)dn. aCGH of amniocytes revealed no genomic imbalance. Ultrasound findings were unremarkable. The pregnancy was carried to term, and pediatric follow-ups were normal at 3 months of age. Amniocentesis of the second case revealed a simple reciprocal translocation and a karyotype of 46,XY,t(3;11)(q14;q23)dn. aCGH of amniocytes revealed a 1.32-Mb microduplication in chromosome 2p12 [arr cgh 2p12 (75,245,747-76,563,965)×3] encompassing the genes of *TACR1*, *FAM176A*, *MRPL19*, and *C2orf3*. Ultrasound findings were unremarkable. The pregnancy was carried to term, and the pediatric follow-ups were normal at 8 months of age. In cases of prenatally detected *de novo* apparently balanced reciprocal translocations, cryptic intrachromosomal rearrangements may exist in addition to the cytogenetically visible structural chromosome aberrations. aCGH is useful not only in identifying the genomic imbalances at the breakpoints, but also in detecting unexpectedly complex rearrangements in other chromosomes. Copyright © 2012 Elsevier Taiwan LLC and the Chinese Medical Association. All rights reserved.

Keywords: array comparative genomic hybridization; complex chromosome rearrangement; cryptic genomic imbalance; *de novo* apparently balanced reciprocal translocations

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1. Introduction

Amniocentesis may detect *de novo* simple and complex apparently balanced reciprocal translocations that give rise to difficulties in genetic counseling and require molecular cytogenetic technologies to identify deletions or duplications at the breakpoints of the involved chromosomes as well as additional genomic imbalances in other chromosomes.^{1–3} A simple balanced reciprocal translocation is a two-way exchange between two chromosomes in which two chromosomal segments from two chromosomes break off, translocate, and unite. A balanced complex chromosome translocation (CCR) has three or more breakpoints. The most common type of CCR is three-way exchange CCR in which three chromosomal segments from three chromosomes break off, translocate, and unite. Here, we present our experience of array comparative genomic hybridization (aCGH) characterization of *de novo* simple and complex apparently balanced reciprocal translocations detected at amniocentesis.

2. Case reports

2.1. Case 1

A 41-year-old, gravida 2, para 0 woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Cytogenetic analysis revealed a karyotype of 46,XY,t(5;8;6) (q11.2;p23.1;q22.32)dn. The parental karyotypes were normal. Simultaneously, oligonucleotide-based aCGH analysis by SurePrint G3 Human CGH Microarray Kit 60K (Agilent Technologies, Santa Clara, CA, USA) using cultured amniocytes showed no genomic imbalance and no loss or increase in the dosage of genetic probes specific for chromosomes 5, 6, and 8. Level II ultrasound revealed no structural abnormalities. The parents decided to continue the pregnancy. At 38 weeks of gestation, a healthy male baby was delivered with a body weight of 3852 g. Pediatric examination of the infant during follow-up at 3 months of age showed normal psychomotor development without phenotypic abnormalities.

2.2. Case 2

A 39-year-old, gravida 2, para 1 woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Cytogenetic analysis revealed a karyotype of 46,XY,t(3;11) (q14;q23)dn. The parental karyotypes were normal. Repeated amniocentesis was performed at 22 weeks of gestation. Oligonucleotide-based aCGH analysis by CytoScan v3 Microarray Kit (Agilent Technologies, Santa Clara, CA, USA) using cultured amniocytes showed no loss or increase in the dosage of genetic probes specific for chromosomes 3 and 11 but a genomic imbalance in chromosome 2 (Fig. 1). There was a 1.32-Mb microduplication in chromosome 2p12 [arr cgh 2p12 (75,245,747-76,563,965)×3] encompassing the genes of *TACRI*, *FAM176A*, *MRPL19*, and *C2orf3*. Level II ultrasound revealed no structural abnormalities. After genetic counseling, the parents decided to continue

the pregnancy. At 38 weeks of gestation, a healthy male baby was delivered with a body weight of 3624 g. Pediatric examination of the infant during follow-up at 8 months of age showed no abnormal psychomotor development and no phenotypic abnormalities.

3. Discussion

The current cases of *de novo* apparently balanced reciprocal translocations did not have genomic imbalances at the breakpoints and manifested no phenotypic abnormalities at birth. Warburton⁴ reported that 6.1% of the cases (10 of 163) with prenatally detected balanced simple balanced reciprocal translocations were associated with serious congenital anomalies. Chen et al¹ reported that 55.6% of the cases (10 of 18) with prenatally detected *de novo* apparently balanced CCRs and multiple chromosome rearrangements (MCRs) manifested phenotypic abnormalities. Rapid genome-wide aneuploidy diagnosis can be achieved by aCGH using uncultured and/or cultured amniocytes.^{5–7} Precise definitions of *de novo* simple and complex apparently balanced reciprocal translocations should include rapid genome-wide aneuploidy diagnosis such as aCGH using uncultured and/or cultured amniocytes.

The peculiar aspect of Case 2 in this presentation is the prenatal detection of a *de novo* microduplication in chromosome 2 that was not involved in the translocation of t(3;11) (q14;q23). *De novo* apparently balanced reciprocal translocations have been reported to be associated with genomic imbalances in other chromosomes. Turleau et al⁸ reported mental retardation, bilateral glaucoma, hypospadias, and cryptorchidism in a patient with a deletion of 11p13 → p14 and a CCR involving chromosomes 4, 7, and 15. Gribble et al⁹ reported an 8-year-old girl with autism, dry skin, absent tears, developmental delay, and a *de novo* t(2;5)(q31.1;q23.2). aCGH analysis detected a *de novo* 2.2-3.4-Mb deletion of 6q21. Chen et al¹ reported a *de novo* apparently balanced CCR of t(2;18;14)(q33.1;q12.2;q31.2) associated with *de novo* duplication of 5q34, deletion of 7p21.1, and deletion of 10q25.3. The fetus had facial dysmorphism, clinodactyly, and hypoplasia of the great toe. In a study of 59 patients with *de novo* balanced chromosomal translocations including 41 *de novo* reciprocal translocations and 18 *de novo* CCRs, De Gregori et al¹⁰ found 42 deletions by aCGH in 27 cases, indicating 45.8% of the patients with an apparently balanced translocation were in fact unbalanced. De Gregori et al¹⁰ reported three patients with *de novo* balanced reciprocal translocations in association with *de novo* genomic imbalances in other chromosomes. In their report, one case was a female with growth retardation, ataxic gaits, absence of language, t(1;7)(q24;p13) and del(6)(q14.3-q15); the second case was a female with hypotonia, ataxic gait, facial dysmorphism, mental retardation, ventricle asymmetry, t(8;14)(q13;q13) and del(9)(pter-p24.2); and the third case was a female with mental retardation, facial dysmorphism, t(1;9)(q44;p13.3) and del(4)(p15.2). Baptista et al¹¹ reported a female with premature ovarian failure, a karyotype of 46,X,t(X;8)(q22.1;q24.13), and a 200-kb deletion in 2p13.2 detected by aCGH. Schluth-Bolard

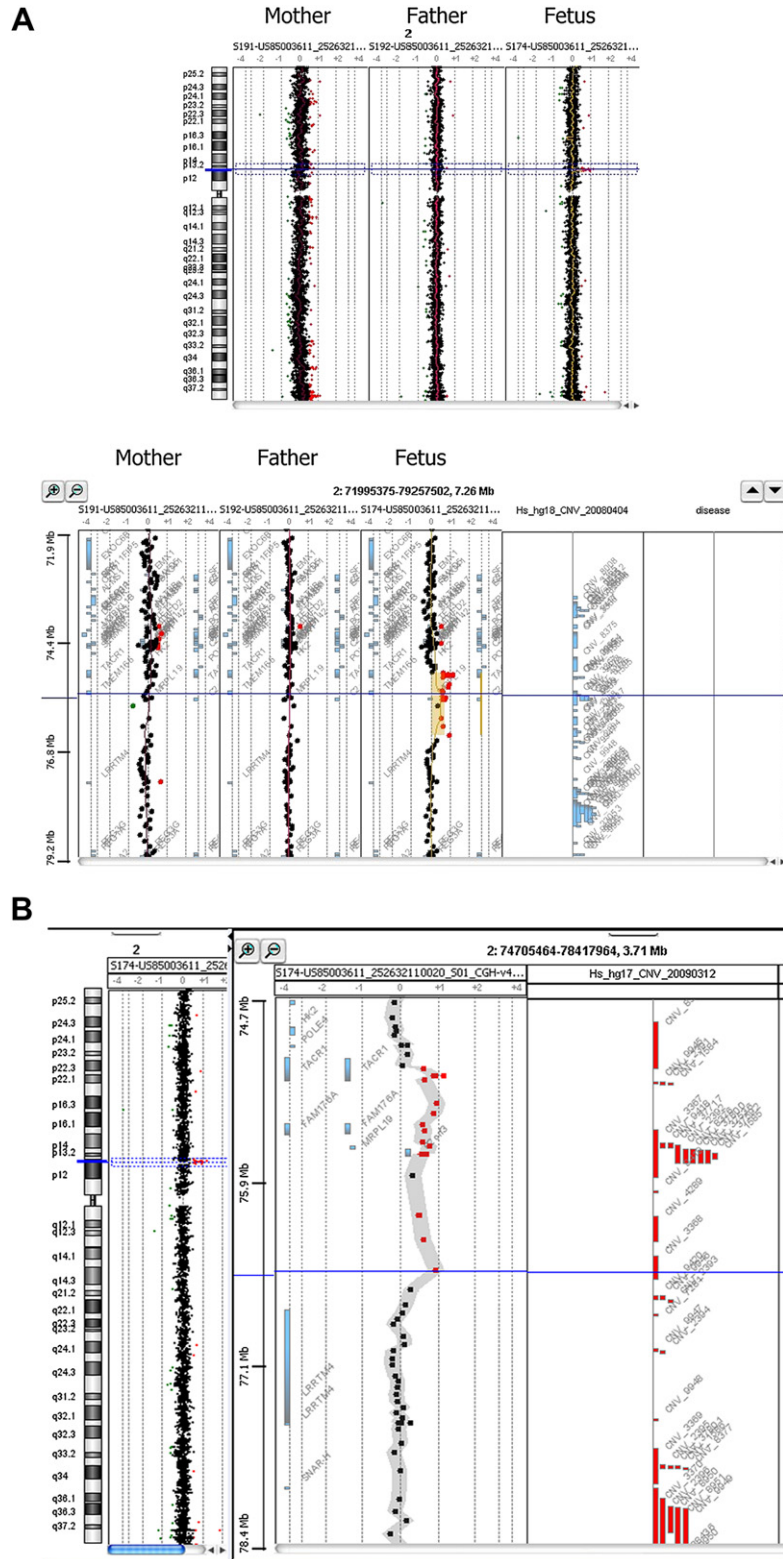


Fig. 1. (A) Oligonucleotide-based aCGH shows a *de novo* 1.32-Mb duplication in chromosome 2p12 [arr cgh 2p12 (75,245,747-76,563,965) $\times 3$] in the fetus. aCGH = array comparative genomic hybridization. (B) The duplicated region encompasses the genes of *TACR1*, *FAM176A*, *MRPL19*, and *C2orf3*.

et al¹² reported two patients with *de novo* balanced reciprocal translocations in association with *de novo* genomic imbalances in other chromosomes. In their report, one case was a male with mental retardation, macrosomia, leukodystrophy, hexadactyly, t(1;18)(q11.1;q12.1) and del(14)(q32.3q32.3); the other case was a male with mental retardation, autistic troubles, growth retardation, t(7;12)(p11;p11), and del(2)(q33.1q33.1). Tzschach et al¹³ reported a female patient with mental retardation, psychosis, obesity, facial dysmorphism, strabismus, t(2;5)(p21;q12.1), and an interstitial 4q32 deletion.

The current Case 2 had a *de novo* 1.32-Mb microduplication in 2p12 encompassing the genes *TACR1*, *FAM176A*, *MRPL19*, and *C2orf3*. *TACR1* [Online Mendelian Inheritance in Man (OMIM) 162323], or tachykinin receptor 1, is a neurokinin 1 receptor mediating behavioral stress responses. *FAM176A*, or family with sequence similarity 176, member A, is a regulator of programmed cell death mediating both autophagy and apoptosis. *MRPL19* (OMIM 611832), or mitochondrial ribosomal protein L19, participates in mitochondrial energy metabolism. *C2orf3* (OMIM 189901), or chromosome 2 open reading frame 3, or transcription factor 9 (TCF-9) acts as a factor that represses transcription. *MRPL19* and *C2orf3* have been associated with dyslexia. Association studies of positional candidate genes have implicated *MRPL19* and *C2orf3* as relevant candidates for the *DYX3* locus,^{14,15} although recently, some data did not support *MRPL19/C2orf3* as a locus involved in reading abilities.¹⁶ At least 2–3 years are needed to follow up the psychomotor development of Case 2 to define the 1.32-Mb microdeletion in 2p12 as a copy number variation of benign nature.

In conclusion, the current cases provide evidence that in cases of prenatally detected *de novo* apparently balanced reciprocal translocations, cryptic intrachromosomal rearrangements may exist in addition to the cytogenetically visible structural chromosome aberrations. In this regard, aCGH is useful not only in identifying the genomic imbalances at the breakpoints but also in detecting unexpectedly complex rearrangements in other chromosomes.

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