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Case Report

Rapid aneuploidy diagnosis of partial trisomy 7q (7q34→qter) and partial monosomy 10q (10q26.12→qter) by array comparative genomic hybridization using uncultured amniocytes

Chih-Ping Chen [a,b,c,d,e,f,g,*], Shuan-Pei Lin [c,h], Yi-Ning Su [i], Fuu-Jen Tsai [e,j,k], Pei-Chen Wu [b], Dai-Dyi Town [b], Li-Feng Chen [b], Meng-Shan Lee [b], Wayseen Wang [c,l]

[a] *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*
[b] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*
[d] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[e] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[f] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[g] *Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[h] *Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan*
[i] *Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan*
[j] *Department of Medical Research, China Medical University Hospital, Taichung, Taiwan*
[k] *Department of Medical Genetics, China Medical University Hospital, Taichung, Taiwan*
[l] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

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Abstract

Objective: To present rapid aneuploidy diagnosis (RAD) of partial trisomy 7q (7q34→qter) and partial monosomy 10q (10q26.12→qter) by array comparative genomic hybridization (aCGH) using uncultured amniocytes.
Case Report: A 34-year-old, gravida 2, para 1, woman underwent amniocentesis at 20 weeks of gestation because of a previous mentally retarded child with an unbalanced reciprocal translocation inherited from the carrier father who had a karyotype of 46,XY,t(7;10) (q34;q26.12). Her first child was initially found to have a normal karyotype by routine cytogenetic analysis, but a cryptic chromosomal abnormality was subsequently diagnosed by aCGH. During this pregnancy, RAD by oligonucleotide-based aCGH using uncultured amniocytes revealed a 16.4-Mb duplication of 7q34–q36.3 and a 12.7-Mb deletion of 10q26.12–q26.3. Conventional cytogenetic analysis using cultured amniocytes revealed a karyotype of 46,XX,der(10)t(7;10)(q34;q26.12)pat. The parents elected to terminate the pregnancy. A malformed female fetus was delivered with a high prominent forehead, hypertelorism, epicanthic folds, a broad depressed nasal bridge, a prominent nose with anteverted nostrils, micrognathia, a short neck, large low-set ears, clinodactyly, small big toes, and normal female external genitalia.
Conclusion: aCGH is a useful tool for RAD of subtle chromosomal rearrangements in pregnancy, especially under the circumstance of a previous abnormal child with an unbalanced translocation derived from a parental subtle reciprocal translocation.

Keywords: chromosome 7 duplication; chromosome 10 deletion; monosomy 10q; rapid aneuploidy diagnosis; trisomy 7q; uncultured amniocytes

Introduction

Rapid aneuploidy diagnosis (RAD) using molecular cytogenetic techniques such as fluorescence *in situ* hybridization, quantitative fluorescent polymerase chain reaction, multiplex

* Corresponding author. Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

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ligation-dependent probe amplification, and/or array comparative genomic hybridization (aCGH) are currently available for rapid prenatal diagnosis of common aneuploidies as well as partial aneuploidies [1–3]. Here, we present a fetus with a subtle chromosomal rearrangement of partial trisomy 7q (7q34→qter) and partial monosomy 10q (10q26.12→qter) detected prenatally by aCGH.

Case report

A 34-year-old, gravida 2, para 1, woman underwent amniocentesis at 20 weeks of gestation because of a previous child with an unbalanced reciprocal translocation inherited from the carrier father. She had a 1-year-old son who had suffered from facial dysmorphism, lymphedema, microcephaly, developmental delay, severe mental retardation, and bilateral nephrocalcinosis. The infant was initially found to have a normal karyotype of 46,XY by routine cytogenetic analysis. A search of cryptic chromosomal abnormalities was made by the use of aCGH to investigate the genetic cause of the unexplained mental retardation in the infant. A deletion of 7q34-qter and a duplication of 10q26.12-qter were identified by aCGH. Cytogenetic analysis of the parents revealed that the mother had a karyotype of 46,XX, and the father had a karyotype of 46,XY,t(7;10)(q34;q26.12) (Fig. 1). During this pregnancy, ultrasound findings at 20 weeks of gestation were unremarkable, and approximately 38 mL amniotic fluid was aspired for prenatal diagnosis. RAD by oligonucleotide-based aCGH (Oligo HD Scan; CMDX, Irvine, CA, USA) was performed using 20 mL uncultured amniocytes. Within 6 days, aCGH revealed a 16.4-Mb duplication of 7q34–q36.3 and a 12.7-Mb deletion of 10q26.12–q26.3 [arr cgh 7q34q36.3 (142,467,856–158,821,424)×3, 10q26.12q26.3 (122,698,454–135,374,737)×1] (Fig. 2). Within 12 days, conventional cytogenetic analysis showed a karyotype of 46,XX,der(10) t(7;10) (q34;q26.12)pat (Fig. 3). The parents elected to terminate the pregnancy. A malformed female fetus was delivered with a high prominent forehead, hypertelorism, epicanthic folds, a broad depressed nasal bridge, a prominent nose with anteverted nostrils, micrognathia, a short neck, large low-set ears, clinodactyly, small big toes, and normal female external genitalia (Fig. 4).

Discussion

In the present case, the subtle chromosomal rearrangements in the father and the mentally retarded sib were not initially identified by conventional cytogenetic analysis. However, with the application of aCGH, the chromosomal rearrangements in the family were identified. The acquired information was helpful in genetic counseling of the following pregnancy. Mental retardation occurs in 1–3% of the general population [4]. Chromosome abnormalities can be identified by routine cytogenetic analysis in 40% of severe mental retardation and in 10–20% of mild mental retardation [5–7]. With the advent of molecular cytogenetic techniques, it has been reported that subtle chromosomal rearrangements can be detected in approximately 6–7% of children with moderate to severe mental retardation and in approximately 0.5% of children with mild mental retardation [5,8]. Wu et al [9] recently reported that submicroscopic subtelomeric aberrations were found in 5.1% (23/451) of Chinese children with clinically unexplained developmental delay and mental retardation. Such submicroscopic subtelomeric aberrations in children with mental retardation and/or developmental delay may be missed by G-banded conventional cytogenetic analysis [10]. In this

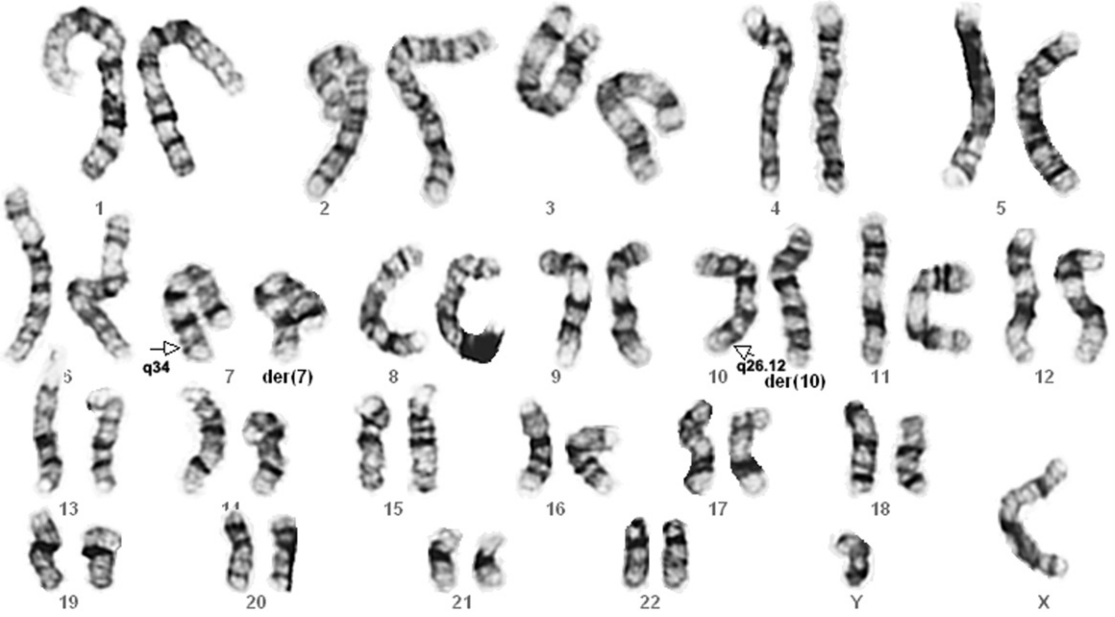

Fig. 1. The G-banded karyotype of the paternal blood lymphocytes shows a derivative chromosome 7, or der(7) and a der(10). The karyotype of the carrier father is 46,XY,t(7;10)(q34;q26.12). The arrows indicate the breakpoints.

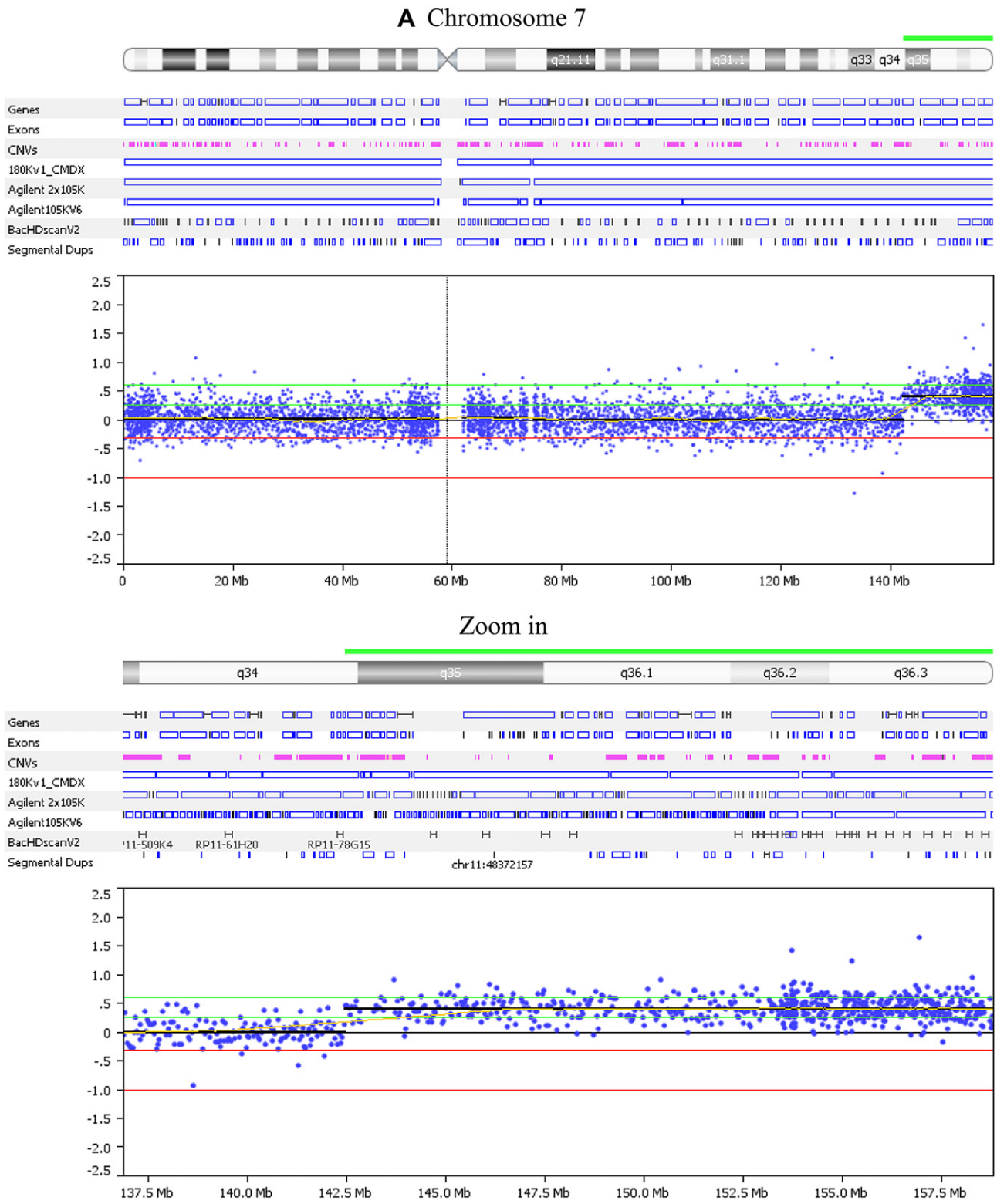

Fig. 2. Oligonucleotide-based array comparative genomic hybridization (aCGH) analysis using uncultured amniocytes shows (A) a 16.4-Mb duplication in 7q34→q36.3 [arr cgh 7q34q36.3 (142,467,856–158,821,424)×3] and (B) a 12.7-Mb deletion in 10q26.12→q26.3 [arr cgh 10q26.12q26.3 (122,698,454–135,374,737)×1]. (C) Whole genome view of partial trisomy 7q and partial monosomy 10q in the fetus.

regard, molecular cytogenetic techniques are very useful for rapid diagnosis of the genomic imbalance associated with subtle chromosomal rearrangements.

The present case was associated with partial monosomy 10q (10q26.12→qter). The distal 10q deletion syndrome includes distinctive clinical features of microcephaly at birth,

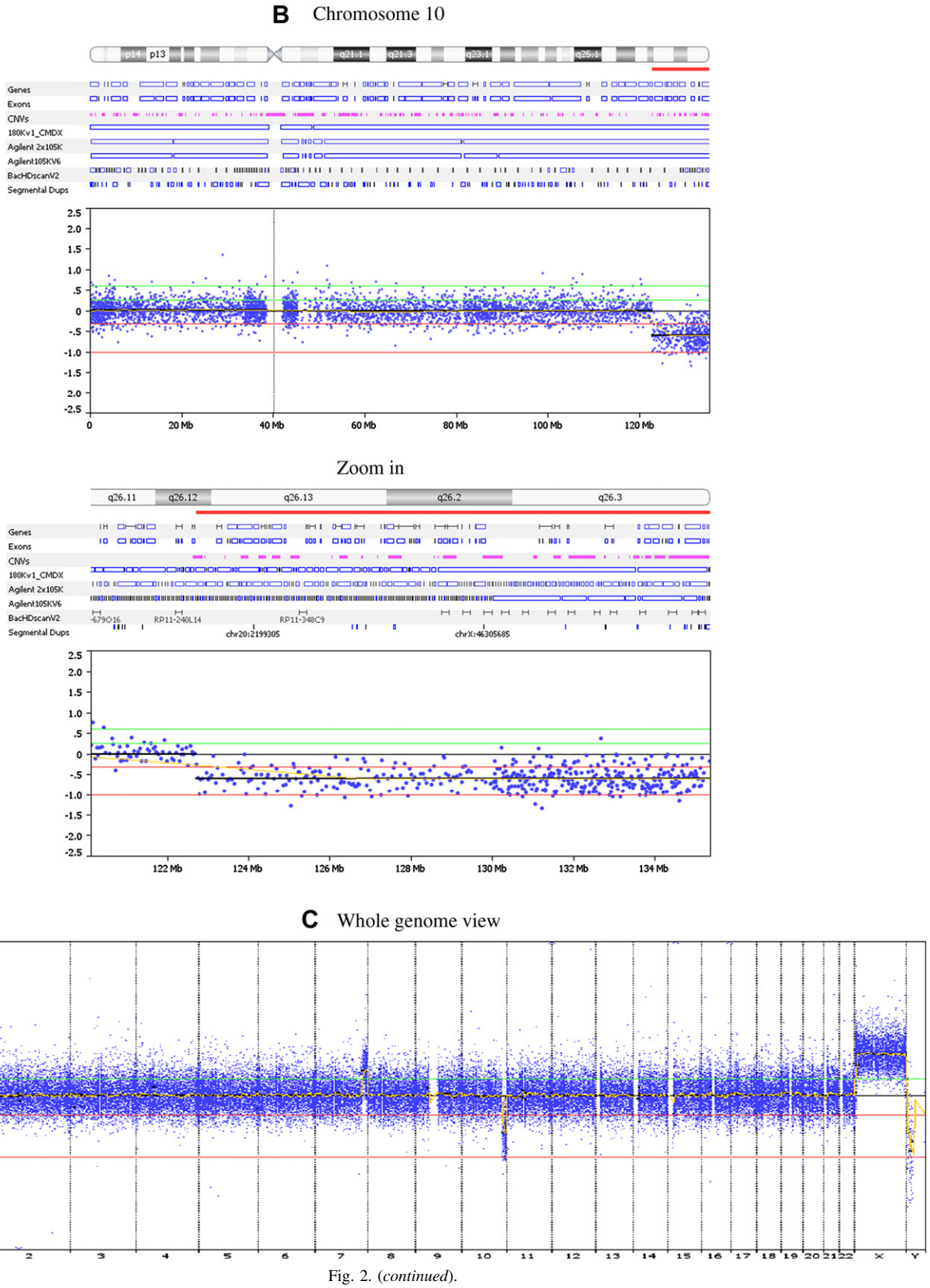

Fig. 2. (*continued*).

postnatal growth retardation, developmental and mental retardation, hypertelorism, strabismus, palpebral fissures, a prominent or broad nasal bridge, malformed low-set ears, a short neck, widely spaced nipples, joint abnormalities, syndactyly, hypotonia, hernia, congenital heart defects, urinary tract/renal anomalies, genital anomalies such as sex reversal,

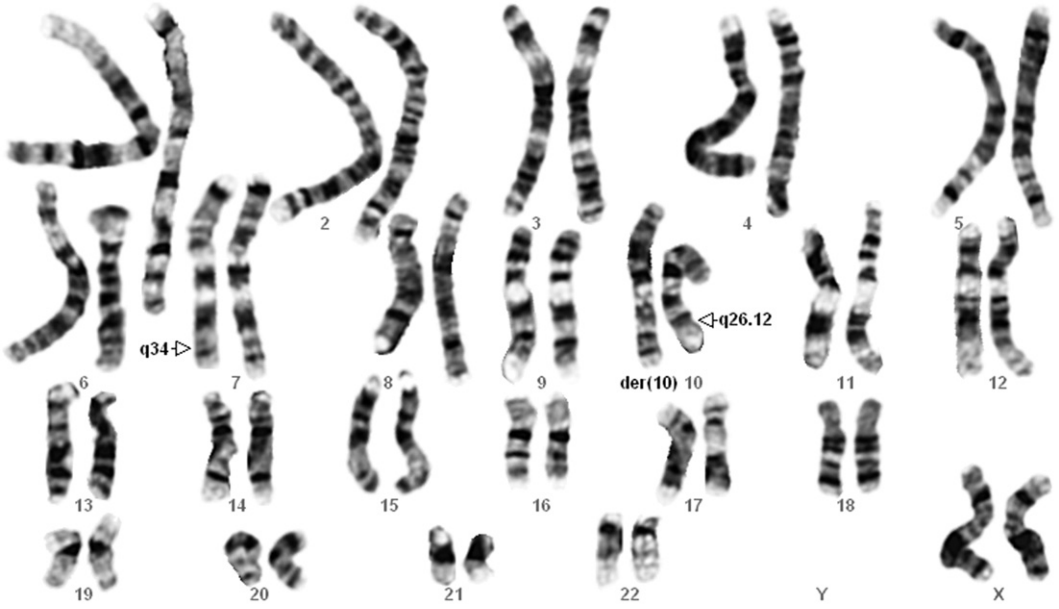

Fig. 3. The G-banded karyotype of the cultured amniocytes shows a der(10). The karyotype of the fetus is 46,XX,der(10)t(7;10)(q34;q26.12)pat.

undescended testis, micropenis and ambiguous genitalia, and neurobehavioral manifestations such as attention-deficit hyperactivity disorder (ADHD), disruptive and affectionate behavior, and bipolar-like syndrome [11–31]. The present case had haploinsufficiency of *DOCK1* and characteristic craniofacial dysmorphism associated with the distal 10q deletion syndrome. Yatsenko et al [31] defined an approximately 600-kb segment encompassing the genes of *DOCK1* and *C10orf90* at the 10q26.2 region that was associated with craniofacial dysmorphism, various degrees of mental retardation, and growth failure in five clinical cases of distal 10q deletions. Yatsenko et al [31] proposed that haploinsufficiency of *DOCK1* gene may play a critical role in the pathogenesis of the distal 10q deletion syndrome and can result in craniofacial dysmorphism, cardiac anomalies and urinary abnormalities associated with the distal 10q deletion syndrome.

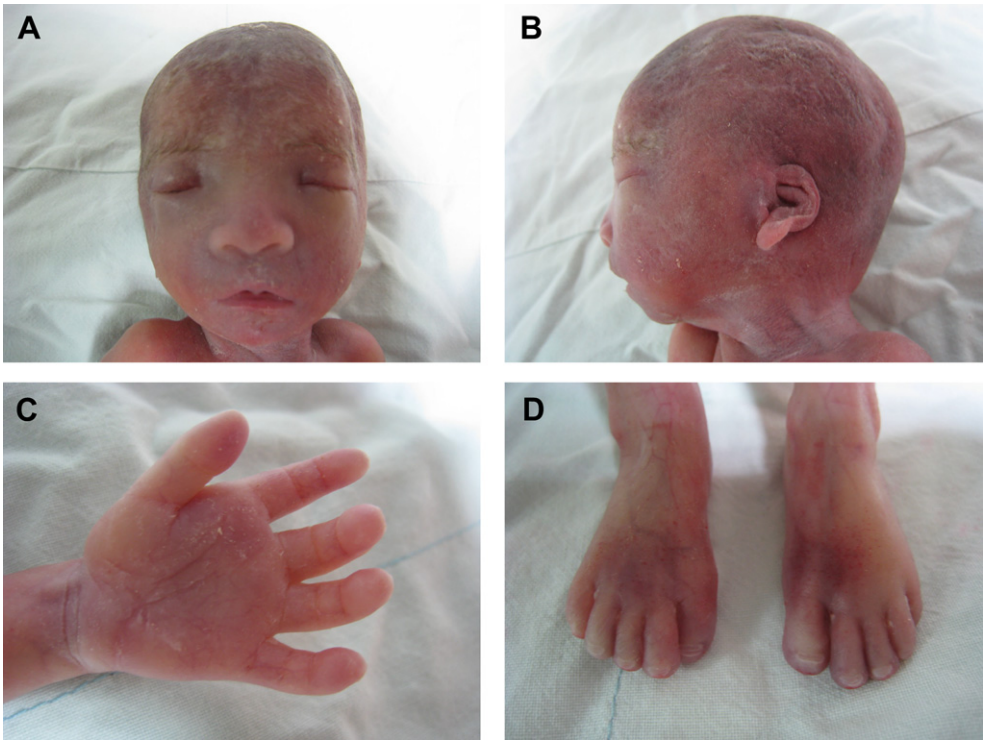

Fig. 4. (A, B) Craniofacial appearance, (C) the hand, and (D) the feet of the fetus at birth.

DOCK1 (dedicator of cytokinesis 1) (OMIM 601403) is involved in some cellular activities such as control of cell morphology, apoptosis, migration, polarity, phagocytosis, and vesicular transport [32−37]. The present case also had haploinsufficiency of *CTBP2* and *DRD1IP* which are involved in the pathogenesis of neurobehavioral disorders. *CTBP2* (c-terminal-binding protein 2) (OMIM 602619) (10q26.13) and *DRD1IP* (dopamine receptor D1-interacting protein) (calcyon) (OMIM 604647) (10q26.3) have been proposed as candidate genes associated with bipolar disorder [23,28] and *DRD1IP* is also associated with ADHD [27]. The present case did not have genital anomalies and the deleted segment did not involve the sex-determining candidate genes of *GFRA1* and *EMX2*. *GFRA1* [GDNF (glial cell line-derived neurotrophic factor) family receptor α-1] (OMIM 601496) (10q25.3) and *EMX2* (homolog of Drosophila empty spiracles 2) (OMIM 600035) (10q26.11) are located proximal to 10q26.12 and have been proposed as potential sex-determining candidate genes [22,31]. *GFRA1* is also associated with Hirschsprung disease. *EMX2* is critical for central nervous system and urogenital development.

The present case was associated with partial trisomy 7q (7q34→qter), a high prominent forehead and abnormalities of the hands and feet. Patients with terminal 7q duplication have been shown to manifest mental retardation, macrocephaly, frontal bossing, a low nasal bridge, large low-set ears, a short neck, single palmar crease, abnormalities of hands and feet, a large open fontanelle, epicanthic folds, down-slanting palpebral fissures, microretrognathia, hypotonia, congenital heart defects, and cleft palate [38−43]. Bartsch et al [39] reported two sibs with partial trisomy 7q (7q33→qter). The first child was a 9-month-old infant with frontal bossing, macrocephaly, a high prominent forehead, a large fontanelle, epicanthic folds, down-slanting palpebral fissures, a deep nasal bridge, low-set ears, slightly microretrognathia, and a short neck. The second child was the 17-gestational-week fetus with prenatal diagnosis of partial trisomy 7q (7q33→qter) by amniocentesis. The fetus manifested a high forehead, a broad flat nose with a depressed nasal bridge and anteverted nostrils, a prominent midface, a prominent philtrum, macrostomia, retrognathia and a short neck at birth. Romain et al [40] reported two first cousins with partial trisomy 7q (7q34→qter) and a phenotype of strabismus, low-set ears, a depressed nasal bridge, a small nose, hypotonia, and mental retardation. Speleman et al [41] reported partial trisomy 7q (7q35→qter) and partial monosomy 2q (2q37→qter) in two generations with macrocephaly, frontal bossing, and mental retardation. Morava et al [43] reported partial trisomy 7q (7q35→qter) and a partial monosomy 13q (13q34→qter) in an infant with hydrocephalus, cleft palate, joint contracture, a high prominent forehead, ptosis of the left eye, and hypotonia. Morava et al [43] suggested that overexpression of the gene of *SHH* (sonic hedgehog) (OMIM 600725) (7q36) may be responsible for the typical facial features and profound hypotonia observed in the distal 7q duplication syndrome.

In conclusion, aCGH is a useful tool for RAD of subtle chromosomal rearrangements in pregnancy, especially under the circumstance of a previous abnormal child with an unbalanced translocation derived from a parental subtle reciprocal translocation.

Acknowledgments

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