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Short Communication

Inv dup del(10q): Identification by fluorescence *in situ* hybridization and array comparative genomic hybridization in a fetus with two concurrent chromosomal rearrangements

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Abstract

Objective: To present molecular cytogenetic characterization of an inverted duplication with terminal deletion of 10q, or inv dup del(10q) in a fetus with two concurrent chromosomal rearrangements.

Materials, Methods and Results: A 39-year-old woman underwent amniocentesis at 20 weeks of gestation because of advanced maternal age. Amniocentesis revealed a der(10) with additional material at the end of the long arm of chromosome 10, a der(9) and a der(22). Parental karyotypes were normal. A *de novo* unbalanced complex chromosomal rearrangement (CCR) was diagnosed by conventional cytogenetics, but the breakpoints could not be defined. The pregnancy was subsequently terminated, and a malformed fetus was delivered with facial dysmorphism. Postnatal analysis of fetal tissues using spectral karyotyping, fluorescence *in situ* hybridization, multicolor banding, and array-comparative genomic hybridization identified an inv dup del(10q) with an inverted duplication of 10q25.1→q26.2 and a terminal deletion of 10q26.2→qter, and a balanced reciprocal translocation between chromosomes 9 and 22. Microsatellite analysis determined a paternal origin of the inv dup del(10q). The karyotype of the fetus was 46,XX,t(9;22)(p23;q13),der(10)del(10)(q26.2) dup(10)(q26.2q25.1)dn.

Conclusion: A *de novo* inv dup del(10q) can be associated with a concurrent *de novo* balanced reciprocal translocation and should be differentiated from an unbalanced CCR by molecular cytogenetic techniques.

Keywords: 10q; aCGH; deletion; FISH; inv dup del(10q); inverted duplication

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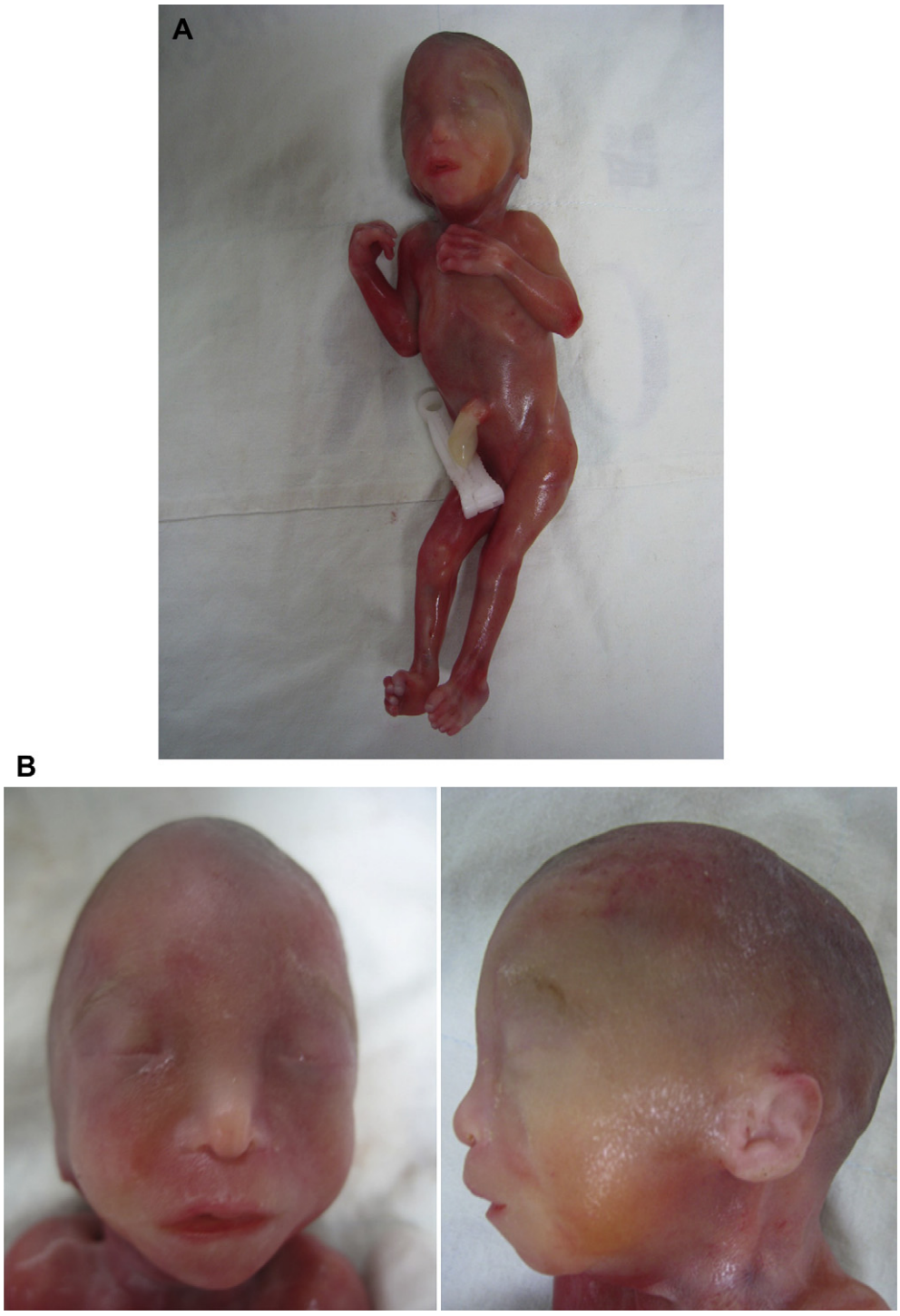

Fig. 1. (A) Whole body view; (B) the craniofacial appearance of the fetus at birth.

Introduction

An inverted duplication with a terminal deletion (inv dup del) is a rare chromosome rearrangement that has been reported to be associated with chromosomes 1p, 1q, 2p, 2q, 3p, 4p, 4q, 5p, 6p, 7q, 8p, 8q, 9p, 9q, 10q, 11p, 13q, 14q, 15q, 18q, 20p, 21q, and Xp [1–4]. Many reported cases of inverted duplication may be in fact "inv dup del" with a subtle terminal deletion that can be identified only by advanced molecular cytogenetic techniques. Proposed mechanisms of inv dup del include the U-type exchange model [5], the nonallelic homologous recombination model [6], and the premeiotic nonhomologous end-joining model [7]. Recently, Yu and Graf [3] suggested that a telomere capture mechanism is a frequent mechanism for stabilization of the terminal chromosomal deletion associated with inverted duplication. We previously reported inv dup del(14q) in

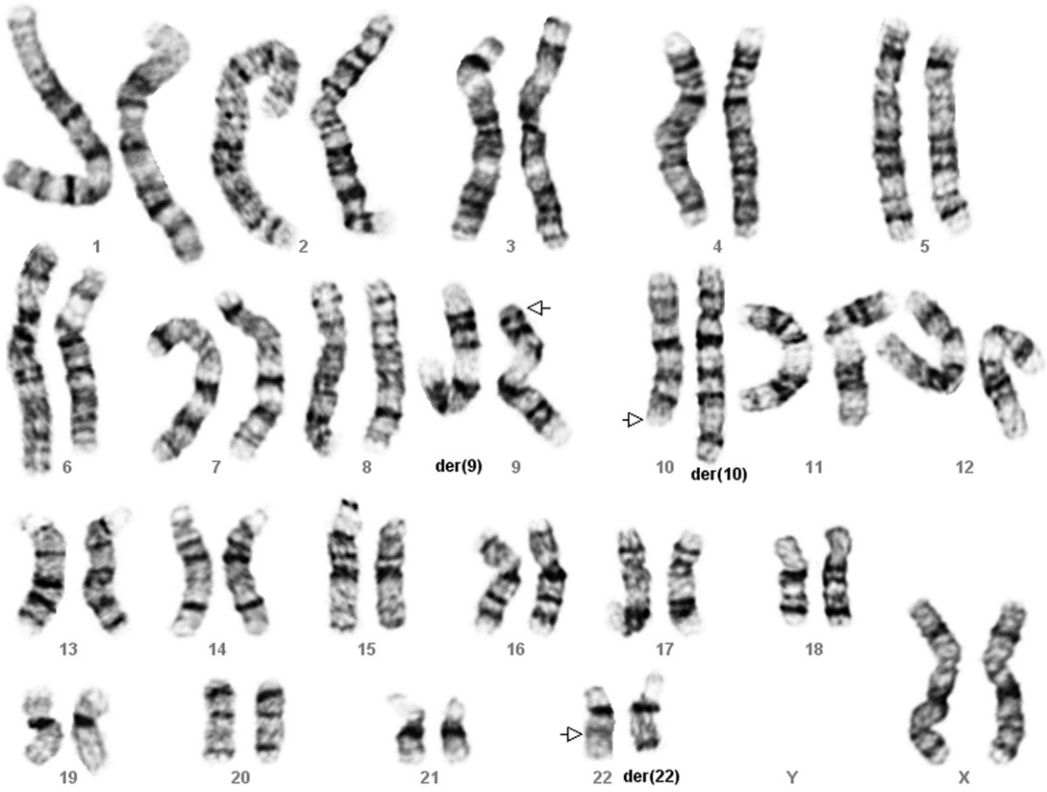

Fig. 2. A karyotype of 46,XX,t(9;22)(p23;q13),der(10)del(10)(q26.2)dup(10)(q26.2q25.1). der = derivative chromosome. The arrows indicate the breakpoints.

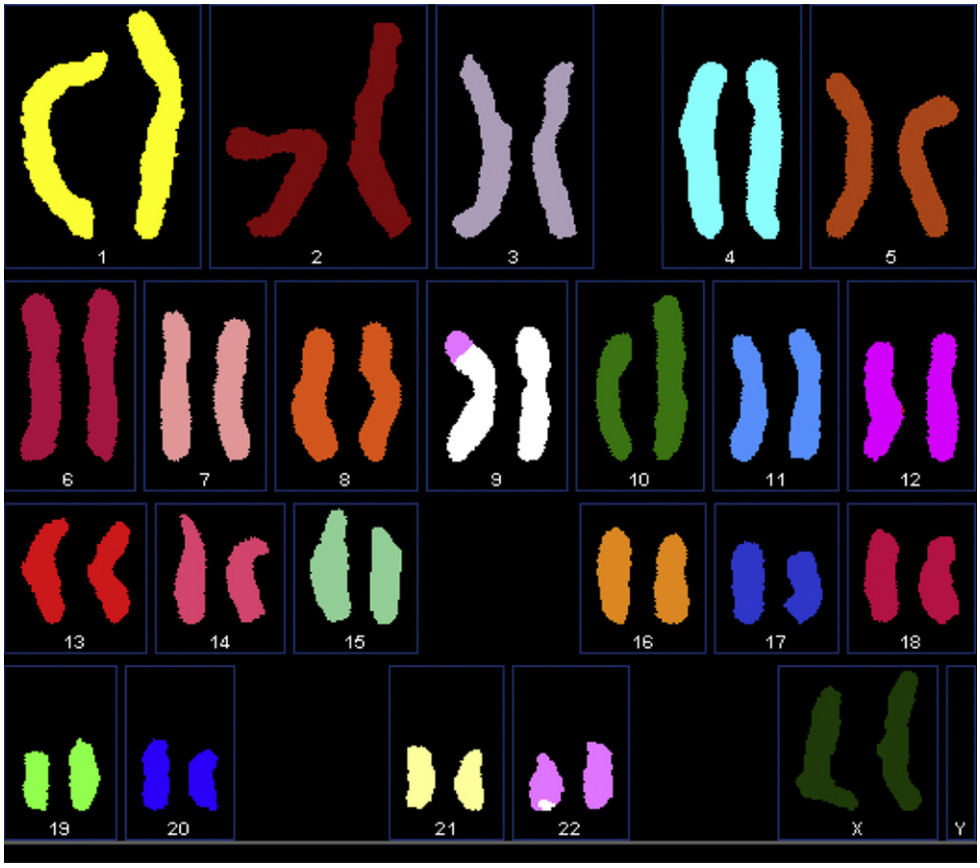

Fig. 3. SKY using 24-color SKY probes shows a der(9) and a der(22) derived from a reciprocal translocation between chromosomes 9 and 22, and a der(10) with an additional chromosomal material derived from chromosome 10. der = derivative chromosome; SKY = spectral karyotyping.

a child [1] and inv dup del(9p) in a fetus [2]. Here, we additionally report our experience of inv dup del(10q) in a fetus.

Materials, methods and results

Case

A 39-year-old, gravid 2, para 1, woman underwent amniocentesis in a clinic at 20 weeks of gestation because of advanced maternal age. Cytogenetic analysis revealed a derivative chromosome 9, or der(9), a der(10) and a der(22). The parental karyotypes were normal. A diagnosis of *de novo* unbalanced complex chromosomal rearrangement (CCR) such as 46,XX, der(9)t(9;?)(p22;?),der(10)t(10;?3)(q26.3;?p23),der(22)t(22;?)(q12.2;?)dn was made, but the breakpoints could not be defined. The parents elected to terminate the pregnancy at 22 weeks of gestation, and a 314-g malformed female fetus was delivered with hypertelorism, bilateral epicanthic folds, blepharophimosis, a small nose with flat nasal bridge, long philtrum, micrognathia, a short neck, low-set malformed ears, clenched hands with long fingers, and hyperextensible joints (Fig. 1). Postnatally, we investigated the chromosome aberration in the fetus by molecular cytogenetic techniques. By applying spectral karyotyping (SKY), fluorescence *in situ* hybridization (FISH), multicolor banding (mBand), and array-comparative genomic hybridization (aCGH) in cord blood and placental tissues, we identified an inverted duplication of the distal interstitial portion of the long arm of chromosome 10 (10q25.1→q26.2) and a deletion of the terminal 10q (10q26.2→qter), and a balanced reciprocal translocation between chromosomes 9 and 22 in the fetus. The prenatally detected chromosome aberration should be interpreted as 46,XX,t(9;22)(p23;q13),der(10)del(10)(q26.2)dup(10)(q26.2q25.1)dn (Fig. 2).

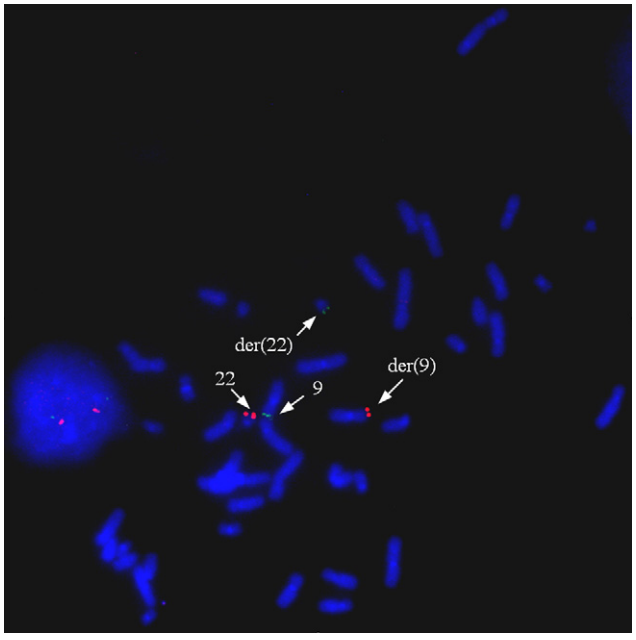

Fig. 4. FISH using the Telomere 9p probe (spectrum green) and the Telomere 22q probe (spectrum red) shows absence of the red signal and presence of the green signal on der(22), and absence of the green signal and presence of the red signal on der(9), indicating a reciprocal translocation between chromosomes 9p and 22q. der = derivative chromosome; FISH = fluorescence *in situ* hybridization.

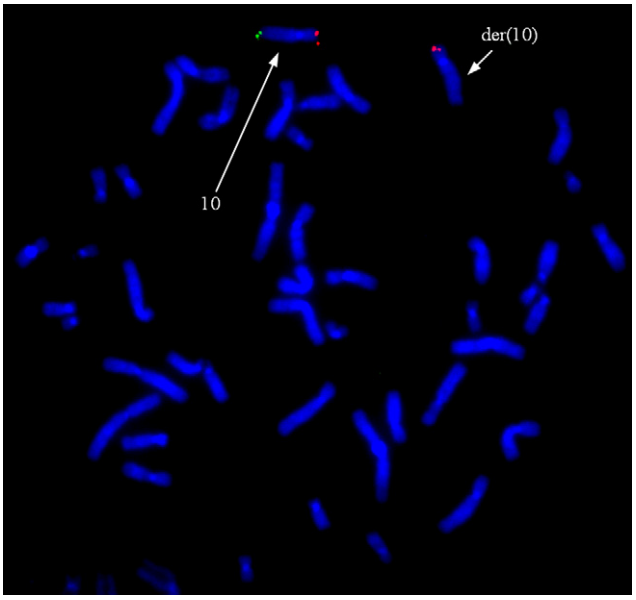

Fig. 5. FISH using the Telomere 10p probe (spectrum red) and the Telomere 10q probe (spectrum green) shows absence of the green signal on the der(10), indicating a terminal 10q deletion on the der(10). der = derivative chromosome; FISH = fluorescence *in situ* hybridization.

SKY

The der(9), der(10) and der(22) were characterized by SKY using 24-color SKY probes (Applied Spectral Imaging,

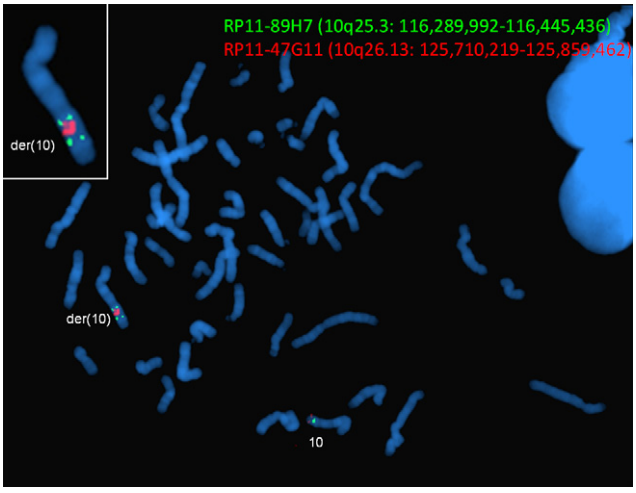

Fig. 6. FISH using BAC probe RP11-89H7 (spectrum green) at 10q25.3 and the BAC probe RP11-47G11 (spectrum red) at 10q26.13 shows an inverted duplication of distal 10q with an inverted duplication orientation of green-red-red-green on the der(10). BAC = bacterial artificial chromosome; der = derivative chromosome; FISH = fluorescence *in situ* hybridization.

Carlsbad, CA, USA). The SKY results revealed that the additional chromosomal material on der(10) was derived from chromosome 10, the der(9) contained a chromosome 22 segment in the end of the shortened short arm, and the der(22) contained a chromosome 9 segment in the end of the shortened long arm, indicating a reciprocal translocation between chromosomes 9 and 22 and an intrachromosomal rearrangement in chromosome 10 (Fig. 3).

FISH

FISH using the Telomere 9p probe (Cytocell, Adderbury, UK; spectrum green) and the Telomere 22q probe (Cytocell, Adderbury, UK; spectrum red) showed absence of the red signal and presence of the green signal on der(22), and absence of the green signal and presence of the red signal on der(9), indicating a reciprocal translocation between chromosomes 9p and 22q (Fig. 4).

FISH using the Telomere 10p probe (Cytocell, Adderbury, UK; spectrum red) and the Telomere 10q probe (Cytocell, Adderbury, UK; spectrum green) showed presence of both the red and green signals on a chromosome 10 but only the red signal on the der(10) indicating a terminal 10q deletion on the der(10) (Fig. 5).

FISH using the bacterial artificial chromosome (BAC) probe RP11-89H7 (116,289,992–116,445,436 bp; spectrum green) at 10q25.3 and the BAC probe RP11-47G11 (125,710,219–125,859,462 bp; spectrum red) at 10q26.13 showed an inverted duplication of distal 10q with an inverted duplication orientation of green-red-red-green on the der(10) (Fig. 6).

The results of FISH confirmed inv dup del(10q) and t(9p;22q).

mBand

The multicolor banding (mBand; MCB; Metasystems, Altlussheim, Germany) analysis was applied to investigate the structural aberration of the der(10). The result showed an inverted duplication of distal 10q on the der(10) (Fig. 7).

aCGH

Oligonucleotide-based aCGH (CytoScan v3 Human CGH Microarray kit 60K; Agilent Technologies, Santa Clara, CA, USA) using placental DNA demonstrated a 21.1-Mb copy number increase at 10q25.1→q26.2 (108,044,044–129,103498 bp) and a 5.7-Mb copy number decrease at 10q26.2→q26.3 (129,599,530–135,254,513 bp) (National Center for Biotechnology Information (NCBI) build 36 March 2006). These results are shown in Fig. 8. There was no genomic imbalance in either chromosome 9 or chromosome 22.

Microsatellite analysis

Microsatellite analysis using the fetal and parental DNA demonstrated that the deletion and duplication were paternal in origin. In the duplicated segment of 10q, all the informative microsatellites were homozygous indicating an intrachromosomal event.

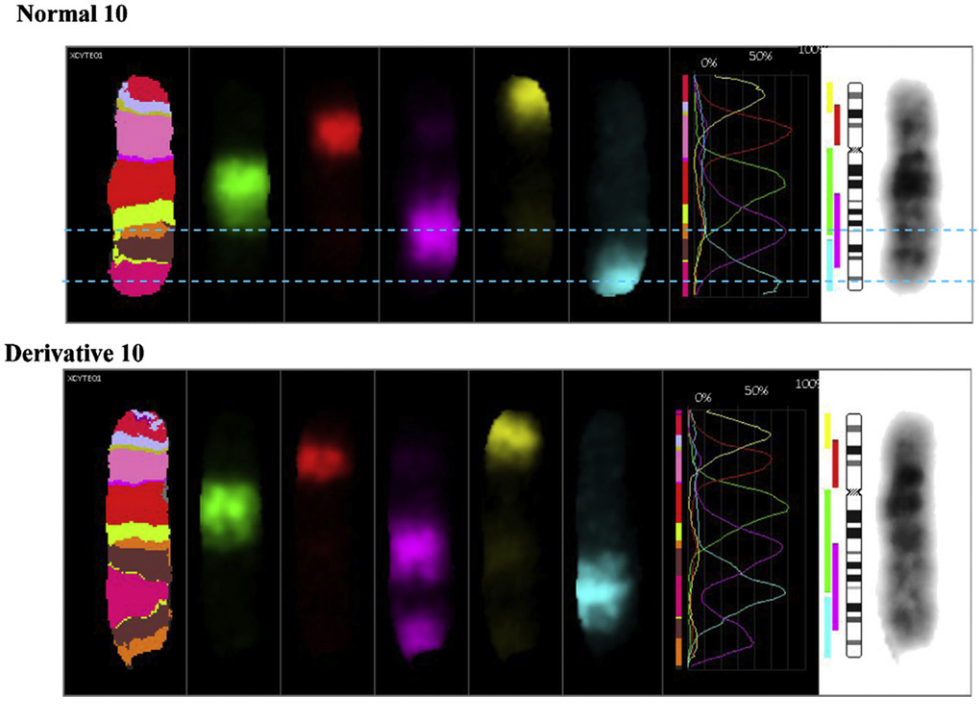

Fig. 7. The mBand shows an inverted duplication of distal 10q on the der(10). mBand = multicolor banding, der = derivative chromosome.

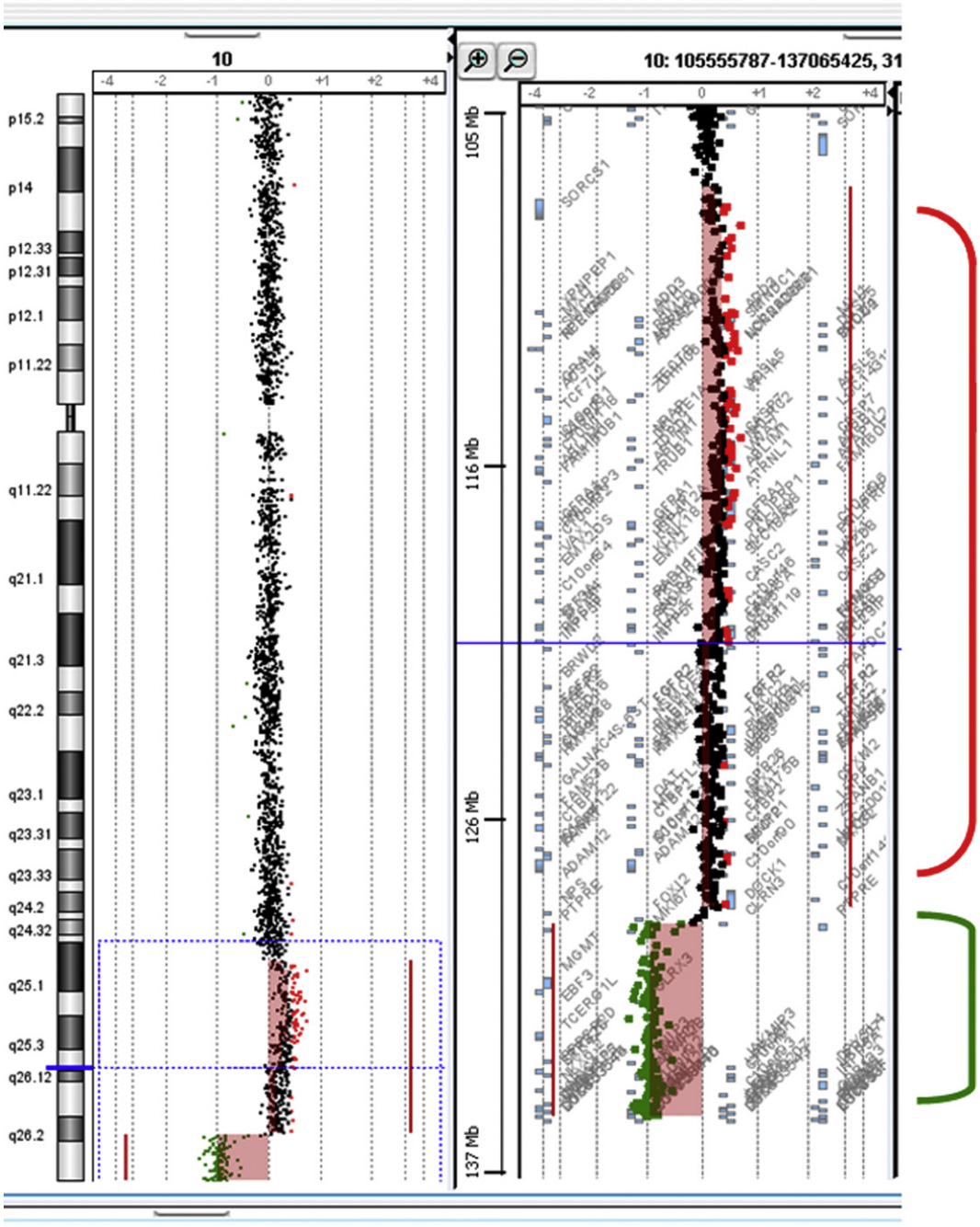

Fig. 8. Oligonucleotide-based aCGH shows a 21.1-Mb copy number increase at 10q25.1→q26.2 and a 5.7-Mb copy number decrease at 10q26.2→q26.3. aCGH = array-comparative genomic hybridization.

Discussion

Very few individuals with inv dup del(10q) have been described. In this presentation, we report a very rare case of inv dup del(10q) with an inverted duplication of the distal interstitial portion of the long arm of chromosome 10 (10q25.1→q26.2), a deletion of the 10q terminal portion (10q26.2→qter), and facial dysmorphism. The inv dup del(10q) in this case was paternal in origin and intra-chromosomal. The homozygosity throughout the duplicated segment implicates a possible U-type exchange mechanism of inv dup del(10q).

Cases with a pure distal 10q duplication have been reported [8–13]. However, none of these cases have been well investigated for the status of terminal 10q, and a microdeletion in terminal 10q might have been overlooked. With the advent of molecular cytogenetic techniques, it is possible to better delineate the region involved and to reveal a previously undetected telomeric deletion of 10q in cases of *de novo* inverted duplication of chromosome 10q. To date, only two cases with 10q-inverted duplication/deletion have previously been reported, and both were females. Carter and colleagues [14] first reported a 7-year-old girl with a 25.4-Mb inverted interstitial duplication of distal 10q (10q25.1→q26.3) and

a 1.6-Mb deletion of terminal 10q (10q26.3→qter). The girl manifested intrauterine growth restriction (IUGR), postnatal developmental delay, mental retardation, blepharophimosis, low-set ears, a short neck, scoliosis, pectus excavatum, thin fingers, sandal gap, hypermobility, hip dysplasia/coax valga, and conductive hearing loss. Kibe and colleagues [15] reported a 6-year, 11-month-old girl with inverted duplication and deletion in 10q26 region, and a microdeletion in the 1q24.2q25.2 region. The girl manifested IUGR, postnatal developmental delay, anal atresia, antithrombin deficiency, patent foramen ovale, mental retardation, generalized shortening of the long bones, arched eyebrows, a depressed nasal bridge, bilateral blepharophimosis, epicanthus, anteverted nares, and microcephaly. Our case is the third case and adds to the literature list of inv dup del(10q).

The peculiar aspect of the present case is two concurrent chromosomal rearrangements. Kibe and colleagues [15] estimated that the frequency of two or more concurrent chromosomal rearrangements is 2%–4%. Inv dup del(10q) has been reported to be associated with concurrent chromosomal rearrangements. Kibe and colleagues [15] reported inv dup del(10q) associated with cryptic concurrent microdeletion of 1q24.2q25.2 in a patient with stroke, antithrombin deficiency and patent foramen ovale. In that case, both chromosomal rearrangements occurred in the paternal allele. Yu and Graf [3] reported inv dup del(13q) associated with cryptic concurrent microdeletion of 4p16.3p15.33. In that case, an unbalanced chromosomal translocation was previously noted as 46, XX,der(13) (13pter→q34::13q34→q22::4p16.3→pter) .ish der(13)t(4;13)(pter+;qter-)(D4S3359+;D13S327-). Yu and Graf [3] suggested that the deleted terminal end of inv dup del(13q) was healed by capturing a 13.22-Mb terminus from 4p terminus.

A simple reciprocal translocation is a two-way exchange between two chromosomes [16]. A multiple chromosome rearrangement (MCR) is a double chromosome rearrangement with two separate simple translocations with double two-way exchanges [16]. A complex chromosome rearrangement (CCR) has three or more breakpoints located on two or more chromosomes, and the most common type of CCR is a three-way exchange [16]. Prenatal diagnosis by amniocentesis may detect balanced or unbalanced *de novo* CCRs [16,17]. The present case shows that an inv dup del with a concurrent balanced reciprocal translocation may be interpreted as an unbalanced CCR by conventional cytogenetics and will require molecular cytogenetic techniques for further delineation. The facial dysmorphism seen in this patient is characteristic for partial trisomy 10q [9–11,13–15]. Duplication of 10q25.1→q26 can be associated with mental retardation, growth retardation, blepharophimosis, palpebral ptosis, hypertelorism, epicanthus, flat nasal bridge, small nose, micrognathia, high-arched palate, short neck, low-set ears, wide spaced toes, joint laxity, scoliosis, hypotonia, cardiac malformations, and renal malformations [15,18]. However, clinical findings in the present case show that the terminal 10q deletion contributes little to the phenotype of this case. The 10q distal deletion syndrome consists of facial asymmetry, prominent nose and ears, strabismus, developmental delay, behavior problems, digital anomalies, growth delay, and short stature [19,20].

In summary, we report a 22-gestational-week female fetus with two concurrent chromosomal rearrangements that were previously interpreted as a *de novo* unbalanced CCR by G-banded karyotype at amniocentesis. FISH and aCGH helped to better delineate the region involved and revealed a balanced reciprocal translocation and an inv dup del. Our presentation provides evidence that a *de novo* inv dup del(10q) can be associated with a concurrent *de novo* balanced reciprocal translocation and should be differentiated from an unbalanced CCR by molecular cytogenetic techniques.

Acknowledgments

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