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Case Report

Prenatal diagnosis of a distal 3p deletion associated with fetoplacental chromosomal discrepancy and confined placental mosaicism detected by array comparative genomic hybridization

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Abstract

Objective: This study is aimed at prenatal diagnosis of a distal 3p deletion associated with fetoplacental chromosomal discrepancy and confined placental mosaicism, and providing evidence for the limitation of array comparative genomic hybridization (aCGH) on placental tissues for molecular cytogenetic characterization of prenatally detected aneuploidy.

Case Report: A 30-year-old woman underwent amniocentesis at 18 weeks of gestation because of maternal anxiety. Results of amniocentesis revealed a distal deletion of chromosome 3p. A malformed female fetus was delivered at 20 weeks of gestation with brachycephaly and facial dysmorphisms, and a cytogenetic analysis of the cord blood revealed a karyotype of 46,XX,del(3)(p26.1),inv(9)(p12q13). A whole-genome aCGH on uncultured cord blood and placental tissue was performed. The aCGH on cord blood revealed a 7.4-Mb deletion at 3p26.3-p26.1. However, the aCGH on placental tissue revealed a 32.42-Mb gene dosage increase at 3p26.1-p22.1 and a 26.28-Mb gene dosage increase at 1p36.33-p36.11 in addition to a 7.4-Mb deletion at 3p26.3-p26.1, indicating confined placental mosaicism for partial trisomy 3p (3p26.1→p22.1) and mosaicism for partial trisomy 1p (1p36.33→p36.11). The 7.4-Mb deleted region of 3p26.3-p26.1 contained the following genes: *CHL1*, *CNTN4*, *CRBN*, *LRRN1,* and *ITPR1*.

Conclusion: Fetal tissue and amniocytes offer more reliable resources for aCGH characterization of prenatally detected aneuploidy compared with placental tissues. A molecular cytogenetic evaluation of prenatally detected aneuploidy using placental tissue should raise concerns of confined placental mosaicism and fetoplacental chromosomal discrepancy.

Keywords: 3p deletion; aCGH; confined placental mosaicism; fetoplacental chromosomal discrepancy

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Introduction

Confined placental mosaicism is defined as a fetoplacental cytogenetic discrepancy with chromosomal aberrations in the placenta, which is absent from the fetal tissues [1]. The occurrence rate of confined placental mosaicism by chorionic villus sampling has been estimated to be 1–2% [2,3]. Recent studies have shown that comparative genomic hybridization (CGH) and array CGH (aCGH) are the most effective molecular cytogenetic methods for investigating confined placental mosaicism at multiple sites in postdelivery placentas [4–9]. Confined placental mosaicism may be associated with intrauterine growth restriction (IUGR) [10], congenital anomalies [11,12], and false-positive fetal aneuploidy scre ening by maternal plasma DNA sequencing at noninvasive prenatal diagnosis [13,14].

Here, we present our experience of prenatal diagnosis of a distal 3p deletion associated with fetoplacental chromosomal discrepancy and confined placental mosaicism detected by aCGH.

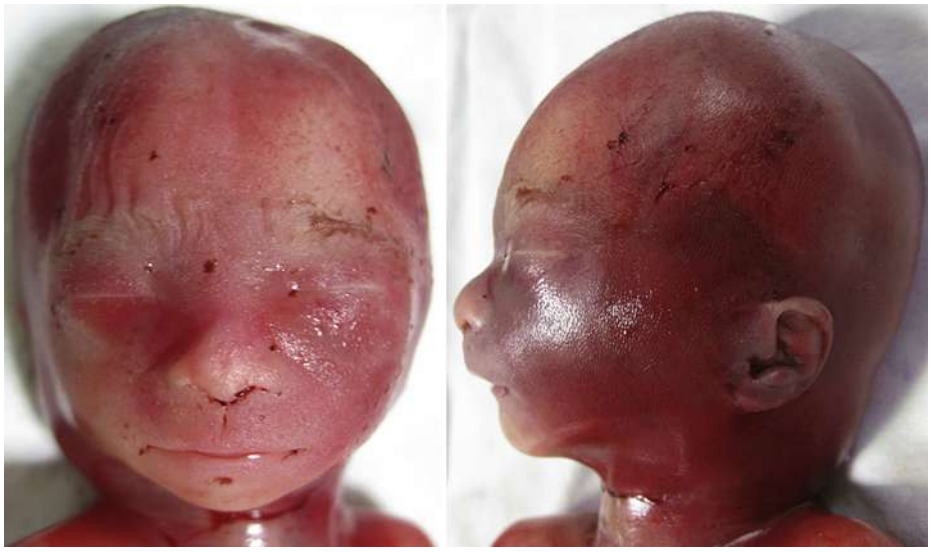

Fig. 1. Craniofacial appearance of the fetus at birth.

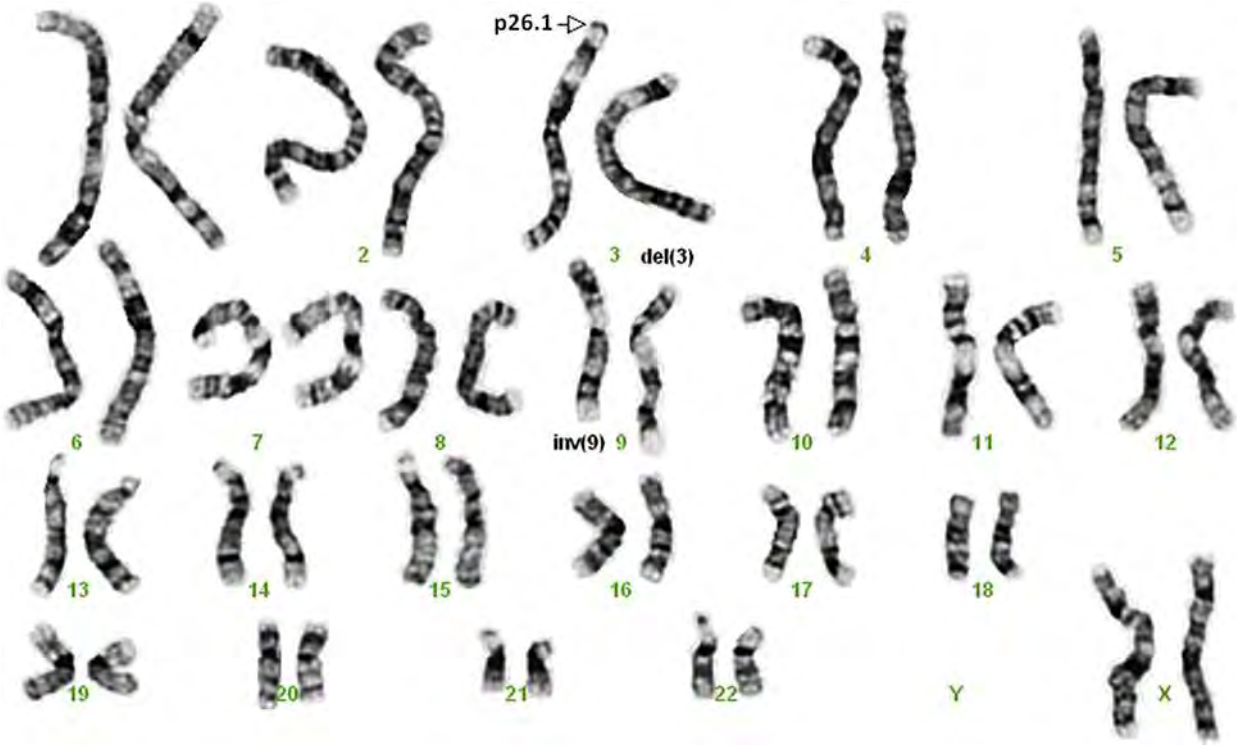

Fig. 2. A karyotype of 46,XX,del(3)(p26.1),inv(9)(p12q13).

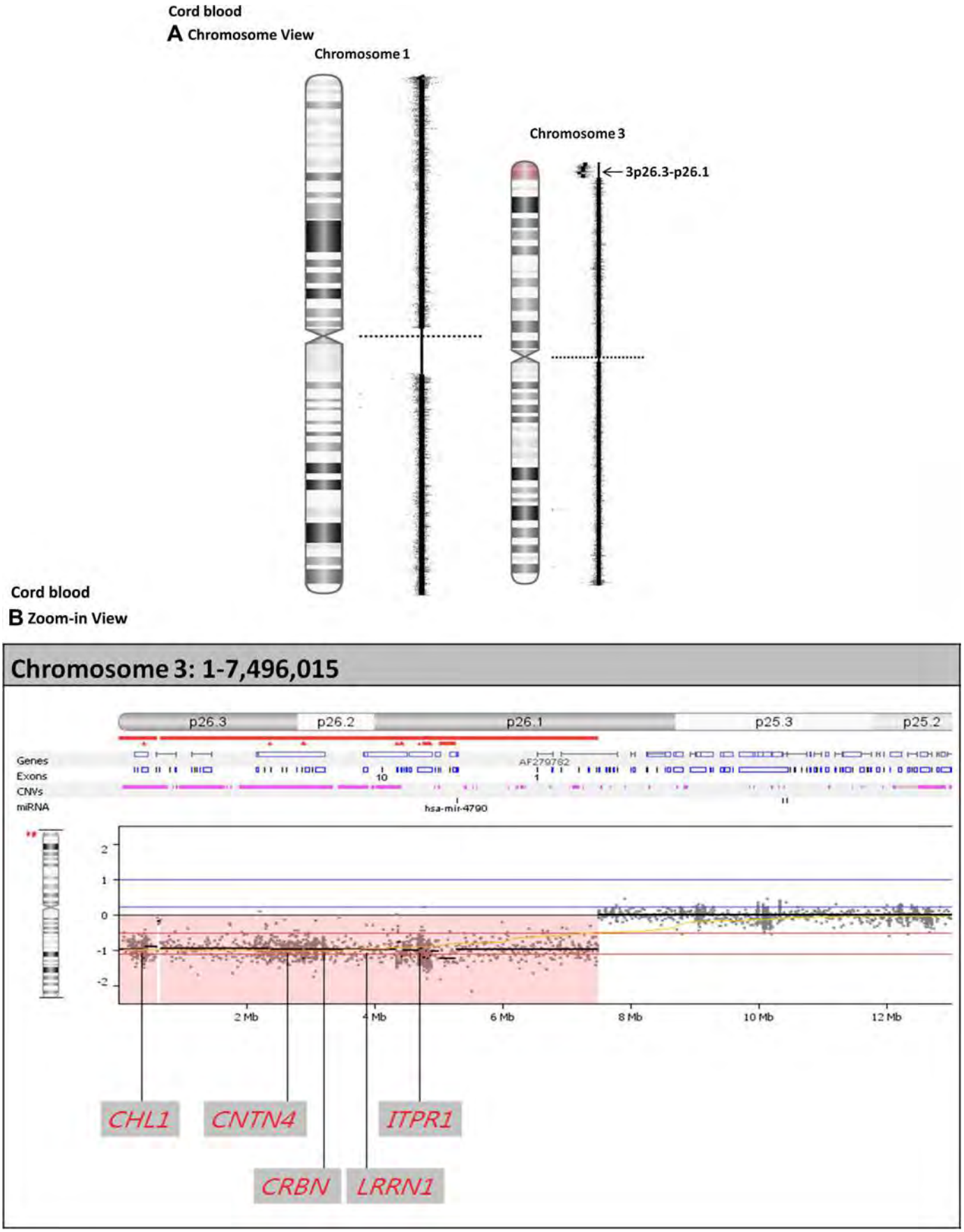

Fig. 3. Whole-genome array comparative genomic hybridization on cord blood shows a 7.4-Mb deletion at 3p26.3-p26.1 [arr 3p26.3p26.1 (1–7,496,015) × 1] (NCBI build 37).

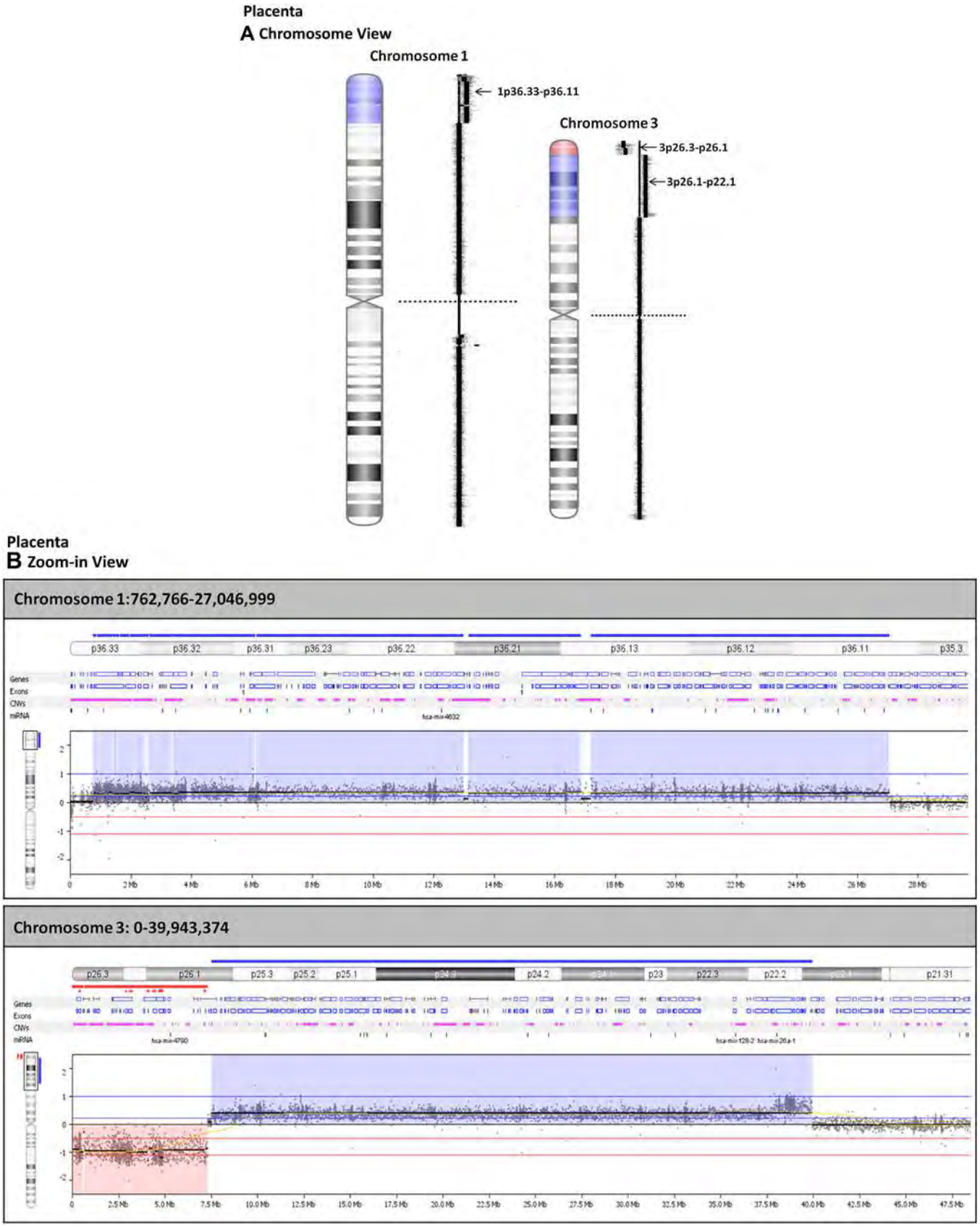

Fig. 4. Whole-genome array comparative genomic hybridization on placenta shows a 7.4-Mb deletion at 3p26.3-p26.1 [arr 3p26.3p26.1 (1–7,496,015) × 1], a 32.42-Mb gene dosage increase at 3p26.1-p22.1 [arr 3p26.1p22.1 (7,520,750–39,943,374) × 2.64], and a 26.28-Mb gene dosage increase at 1p36.33-p36.11 [arr 1p36.33p36.11 (762,766–27,046,999) × 2.55] (NCBI build 37), indicating mosaicism for partial trisomy 3p (3p26.1→p22.1) and 1p (1p36.33→p36.11) in the placenta in addition to constitutional partial monosomy 3p (3p26.3→p26.1).

Case report

A 30-year-old, gravida 2, para 1, woman underwent amniocentesis at 18 weeks of gestation because of maternal anxiety. She had experienced preterm labor with neonatal death. Amniocentesis during this pregnancy revealed a distal deletion of chromosome 3p. Prenatal ultrasound findings were unremarkable. Premature rupture of the membranes occurred at 20 weeks of gestation, and a 295-g malformed female fetus was delivered with brachycephaly, hypertelorism, a flat nose, micrognathia, low-set ears, and neonatal death occurred (Fig. 1). A cytogenetic analysis of the cord blood revealed a karyotype of 46,XX,del(3)(p26.1),inv(9)(p12q13) (Fig. 2). The maternal karyotype was 46,XX,inv(9)(p12q13). The paternal karyotype was 46,XY. Whole-genome aCGH on uncultured cord blood and placental tissue was performed using NimbleGen ISCA Plus Cytogenetics Array (Roche NimbleGen, Madison, WI, USA). An aCGH analysis on cord blood revealed a 7.4-Mb deletion at 3p26.3-p26.1 [arr 3p26.3p26.1 (1−7,496,015) × 1] (NCBI build 37) (Fig. 3). The 7.4-Mb deleted region of 3p26.3-p26.1 contains the following genes: *CHL1*, *CNTN4*, *CRBN*, *LRRN1,* and *ITPR1* (Fig. 3). However, an aCGH analysis on placental tissue revealed a 32.42-Mb gene dosage increase at 3p26.1-p22.1 [arr 3p26.1p22.1 (7,520,750−39,943,374) × 2.64] (NCBI build 37) and a 26.28-Mb gene dosage increase at 1p36.33-p36.11 [arr 1p36.33p36.11 (762,766−27,046,999) × 2.55] in addition to a 7.4-Mb deletion at 3p26.3-p26.1 [arr 3p26.3p26.1 (1−7,496,015) × 1] (Fig. 4), indicating a mosaicism for partial trisomy 3p (3p26.1→p22.1) and 1p (1p36.33→p36.11) in the placenta in addition to a constitutional partial monosomy 3p (3p26.3→p26.1). Mosaicism of a derivative chromosome 3 carrying partial 1p duplication and partial 3p deletion was noted in 28% (7/25 cells) of the cultured chorionic villi cells (Fig. 5).

Discussion

The 3p deletion syndrome [Online Mendelian Inheritance in Man (OMIM) ID 613792] is a contiguous gene syndrome associated with del(3)(p25→pter) and the phenotype of mental retardation, IUGR, developmental delay, and craniofacial

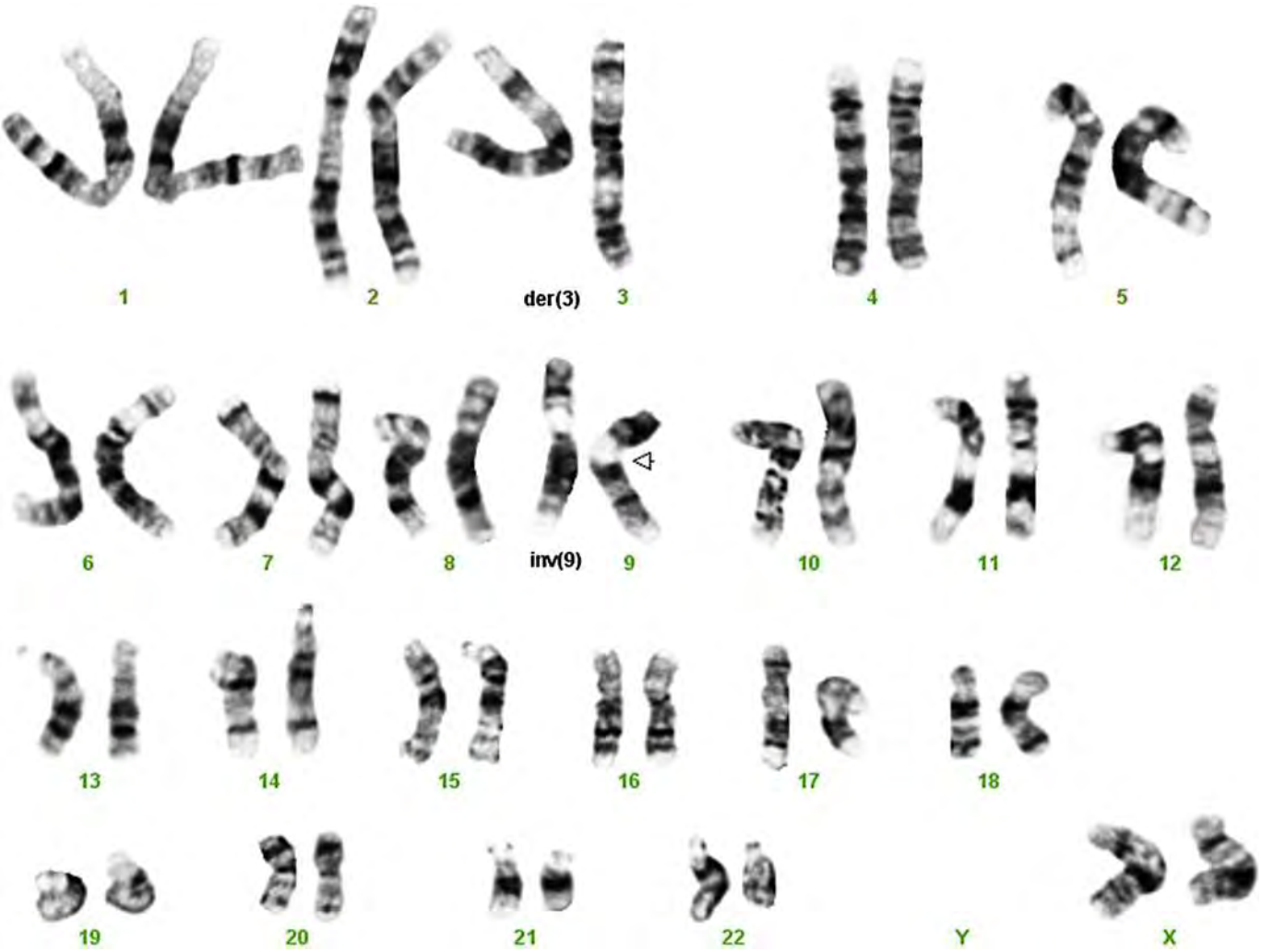

Fig. 5. A cultured chorionic villi cell with a derivative chromosome 3 [der(3)] carrying partial 1p duplication and partial 3p deletion.

dysmorphisms of microcephaly, brachycephaly, frontal bossing, triangular face, hypertelorism, palpebral ptosis, hypertrichosis, synophrys, short and thick nose, long philtrum, micrognathia, and low-set ears; and variable abnormalities of optic atrophy, hypoplastic clavicles, pectus excavatum, scoliosis, polydactyly, syndactyly, congenital heart defects, hiatal hernia, polycystic renal dysplasia, and hypogenitalia [15–21].

The present case had haploinsufficiency of several important genes responsible for the 3p deletion syndrome such as *CHL1* (OMIM ID: 607416), *CNTN4* (OMIM ID: 607280), *CRBN* (OMIM ID: 609262), and *LRRN1* and *ITPR1* (OMIM ID: 147265). Pohjola et al [22] suggested that haploinsufficiency of *CHL1* may cause mild mental retardation, learning difficulty, and IUGR but not profound mental retardation and dysmorphisms. Cuoco et al [23] suggested that *CHL1* is a candidate gene for nonspecific mental retardation. It was suggested that haploinsufficiency of *CNTN4* and *CRBN* is sufficient to cause mental retardation in the 3p deletion syndrome [23,24]. Fernandez et al [25,26] suggested that haploinsufficiency of *CNTN4* is associated with developmental delay, growth retardation, and dysmorphisms in the 3p deletion syndrome. *LRRN1* is related to formation of the midbrain–hindbrain boundary during neuronal development and may be associated with mental disturbance in the 3p deletion syndrome [19,27,28]. Cargile et al [29] suggested that *ITPR1* is a candidate gene for mental retardation in the 3p deletion syndrome.

The peculiar aspect of this presentation is the chromosomal discrepancy between the fetus and placenta. In the present case, confined placental mosaicism for 3p duplication and 1p duplication was incidentally identified by aCGH on placental tissues. Fetoplacental chromosomal discrepancy remains a concern for a potential difference between the chorionic villus sampling and the fetal and amniocyte karyotyping [12]. The present case used direct uncultured chorionic villi cells for aCGH analysis. Filges et al [8] further found that confined placental mosaicism may cause misinterpretations of aCGH analysis on direct chorionic villi cells due to chromosomal discrepancy between cytotrophoblasts and mesenchymal villus core. Conventional cytogenetics for culturing chorionic villi cells requires additional chopping and enzymatic digestion, and therefore allows the assessment of both cytotrophoblast tissue and mesenchymal tissue; by contrast, the major proportion of the extracted DNA from direct uncultured chorionic villi cells used for aCGH analysis may originate from the cytotrophoblasts only [8,30]. Chen et al [17] previously reported fetoplacental discrepancy in prenatally detected mosaic deletion–duplication syndrome of chromosome 3 and suggested a limitation of using placenta as a diagnostic tool for prenatal diagnosis of mosaic chromosome rearrangements. Our case reinforces the notion that fetal tissue and amniocytes offer more reliable resources for aCGH characterization of prenatally detected aneuploidy compared with placental tissues. Therefore, a molecular cytogenetic evaluation of prenatally detected aneuploidy using placental tissue should raise concerns of confined placental mosaicism and fetoplacental chromosomal discrepancy.

Acknowledgments

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