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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of *de novo* partial monosomy 3p (3p26.3→pter) and partial trisomy 16q (16q23.1→qter)

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ABSTRACT

Objective: To present the prenatal diagnosis and molecular cytogenetic characterization of a *de novo* unbalanced reciprocal translocation.

Case Report: A 37-year-old woman, G3P1, underwent amniocentesis at 17 weeks of gestation because of her advanced maternal age. Her husband was 38 years old. Amniocentesis revealed a derivative chromosome 3 with the deletion of terminal 3p and the addendum of an unknown extra chromosomal segment on the distal 3p. The parental karyotypes were normal. Prenatal ultrasound findings were unremarkable. Array comparative genomic hybridization (aCGH) analysis using cultured amniocytes revealed a 2.38-Mb deletion in 3p26.3 [arr 3p26.3 (1-2,380,760)×1] encompassing 15 genes, which included 3 OMIM genes *CHL1*, *CNTN6*, and *CNTN4*, and a 13.17-Mb duplication in 16q23.1-q24.3 [arr 16q23.1q24.3 (76,999,082-90,170,596)×3] encompassing 207 genes, which included 81 OMIM genes. The pregnancy was subsequently terminated, and a malformed fetus was delivered with facial dysmorphism. Postnatal cord blood analysis revealed a karyotype of 46,XY,der(3)t(3;16)(p26.3;q23.1)dn. Polymorphic DNA marker analysis by quantitative fluorescent polymerase chain reaction (QF-PCR) on the DNAs extracted from the placenta and parental blood showed a paternal origin of the aberrant chromosome.

Conclusion: The aCGH and QF-PCR analyses helped in delineating the genomic imbalance and parental origin of prenatally detected *de novo* unbalanced reciprocal translocation.

Introduction

Concomitant partial monosomy 3p and partial trisomy 16q is very unusual. To our knowledge, only one case has been previously reported [1]. Dikmetas et al [1] reported an infant with the karyotype of 46,XY,der(3)t(3;16)(p25;q13)mat associated with partial trisomy 16q (16q13→qter) and partial monosomy 3p (3p25→pter), anterior segment dysgenesis with iris hypoplasia on the right and glaucoma on the left, facial dysmorphism of synophrys, high prominent forehead, bitemporal narrowing, depressed nasal bridge, long philtrum and lingual phrenulum, atrial septal defect, patent ductus arteriosus, buphthalmos, stromal edema of the left eyes, right-sided atypical iris coloboma, and mild delay in growth and mental development.

In this paper, we also report the prenatal diagnosis and molecular cytogenetic characterization of a fetus with the karyotype of

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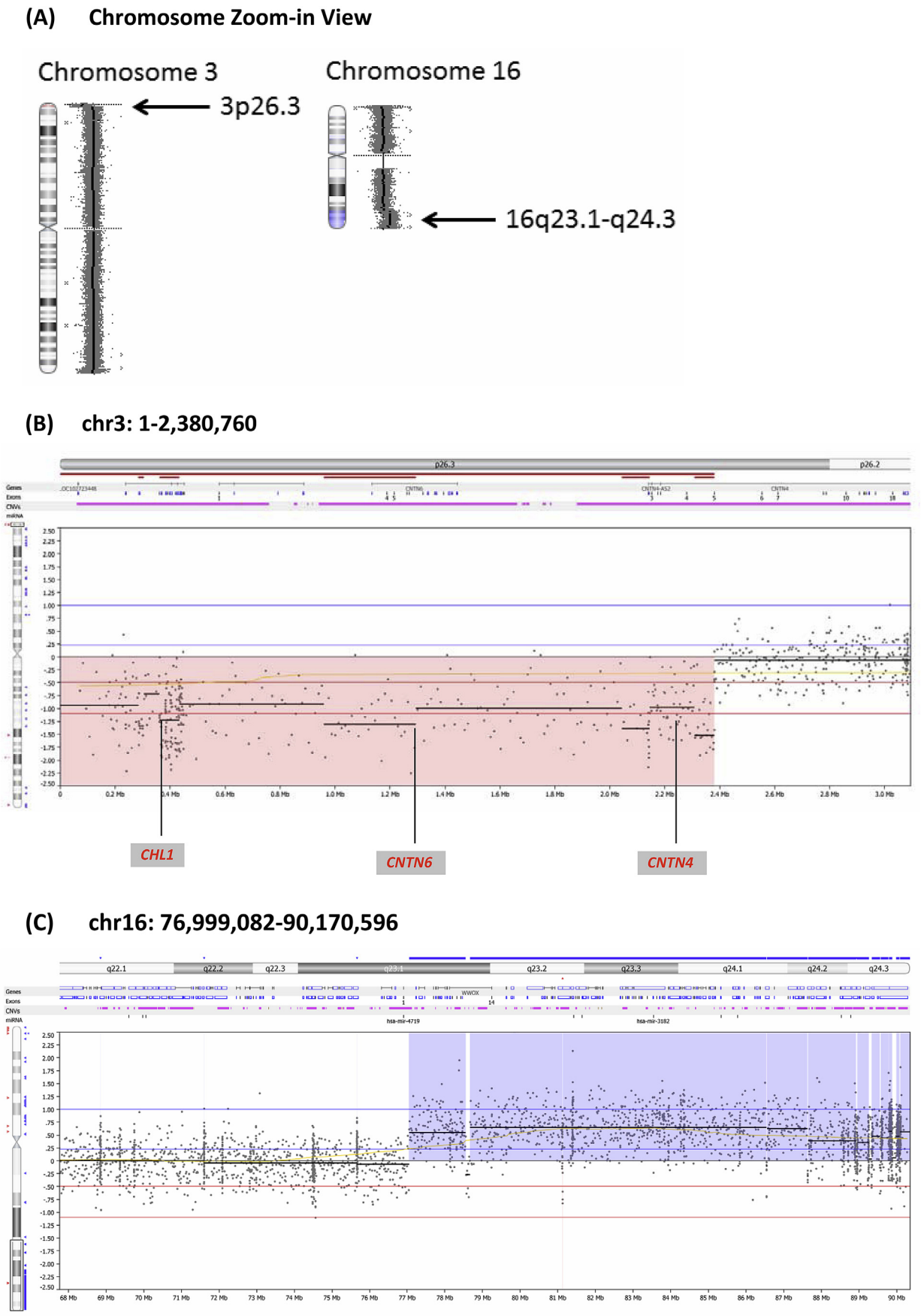

Figure 1. Array comparative genomic hybridization of uncultured amniocytes shows a 2.38-Mb deletion in 3p26.3 [arr 3p26.3 (1-2,380,760)×1] and a 13.17-Mb duplication in 16q23.1-q24.3 [arr 16q23.1q24.3 (76,999,082-90,170,596)×3]. (A) Chromosome zoom-in view. (B) Chromosome 3. (C) Chromosome 16.

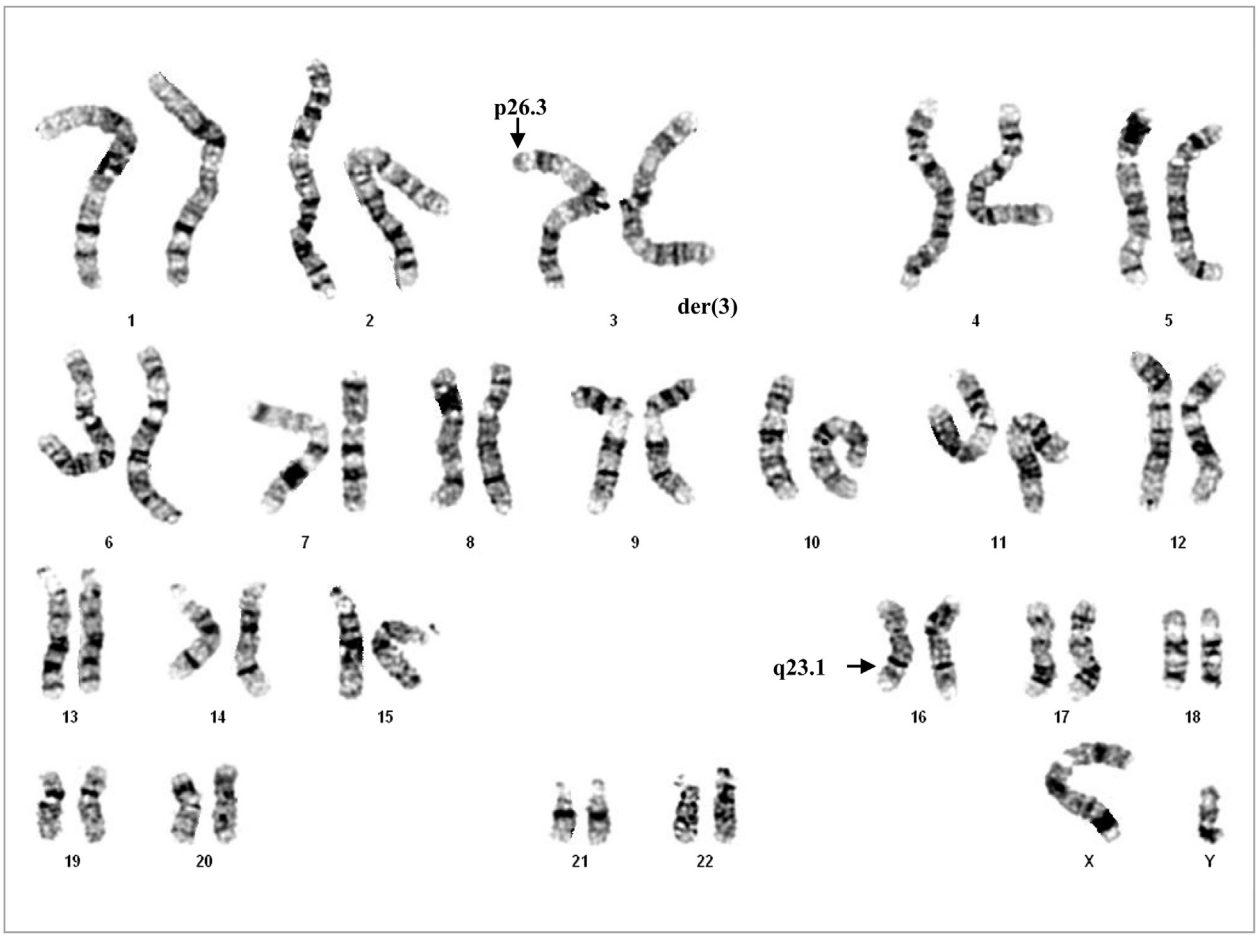

Figure 2. The karyotype of 46,XY,der(3)t(3;16) (p26.3;q23.1). The arrows indicate the breakpoints. der = derivative.

46,XY,der(3)t(3;16)(p26.3;q23.1)dn with partial monosomy 3p (3p26.3→pter) and partial trisomy 16q (16q23.1→qter). In this presentation, we demonstrate the usefulness of array comparative genomic hybridization (aCGH) and quantitative fluorescent polymerase chain reaction (QF-PCR) in delineating the genomic imbalance and parental origin of a prenatally detected *de novo* unbalanced reciprocal translocation. Information acquired by molecular cytogenetic techniques is very helpful in genetic counseling.

Case Report

A 37-year-old, gravida 3, para 1 woman underwent amniocentesis at 17 weeks of gestation because of her advanced maternal age. Her husband was 38 years old. The couple had a 3-year-old healthy boy, the woman had experienced one abortion, and there was no family history of congenital malformations. Amniocentesis during this pregnancy revealed a derivative chromosome 3 with the deletion of terminal 3p and the addendum of an unknown extra chromosomal segment on distal 3p. The parental karyotypes were normal. Prenatal ultrasound findings were unremarkable. The aCGH analysis by Roche ISCA Plus Cytogenetic Array kit (Roche NimbleGen, Madison, WI, USA) using cultured amniocytes showed arr 3p26.3 (1-2,380,760)×1, 16q23.1q24.3 (76,999,082-90,170,596) ×3 with a 2.38-Mb deletion in 3p26.3 encompassing 15 genes, which included three OMIM genes (i.e., *CHL1*, *CNTN6* and *CNTN4*) and a 13.17-Mb duplication in 16q23.1-q24.3 encompassing 207 genes, which included 81 OMIM genes (Figure 1). The pregnancy was subsequently terminated, and 454 g malformed fetus was delivered at 21 weeks of gestation with facial dysmorphism of brachycephaly, hypertelorism, a short thick nose, micrognathia, and large low-set ears. Postnatal cord blood analysis revealed a karyotype of 46,XY,der(3)t(3;16) (p26.3;q23.1)dn (Figure 2). Polymorphic DNA marker analysis by QF-PCR on the DNA extracted from the placenta and parental blood showed a paternal origin for the chromosome aberration (Figure 3).

Discussion

Chromosome 3pter-p25 deletion syndrome (OMIM 613792) is characterized by low birth weight, microcephaly, trigonocephaly, hypotonia, psychomotor and growth retardation, ptosis, telecathus, down-slanting palpebral fissures and micrognathia, and variable features of postaxial polydactyly, renal anomalies, cleft palate, congenital heart defects, preauricular pits, sacral dimple, and gastrointestinal anomalies. The present case was associated with a 2.38-Mb deletion in 3p26.3, which encompassed three OMIM genes: *CHL1*, *CNTN6*, and *CNTN4*. We previously reported two cases of prenatally detected partial monosomy 3p, [i.e., del(3)(p26.1) and del(3)(p25.3), respectively] [2,3]. Neither of these two fetuses manifested prominent ultrasound abnormalities. The present patient had a terminal 3p26.3 deletion and presented no major ultrasound abnormalities. Moghadasi et al [4] reported a 2.6-Mb

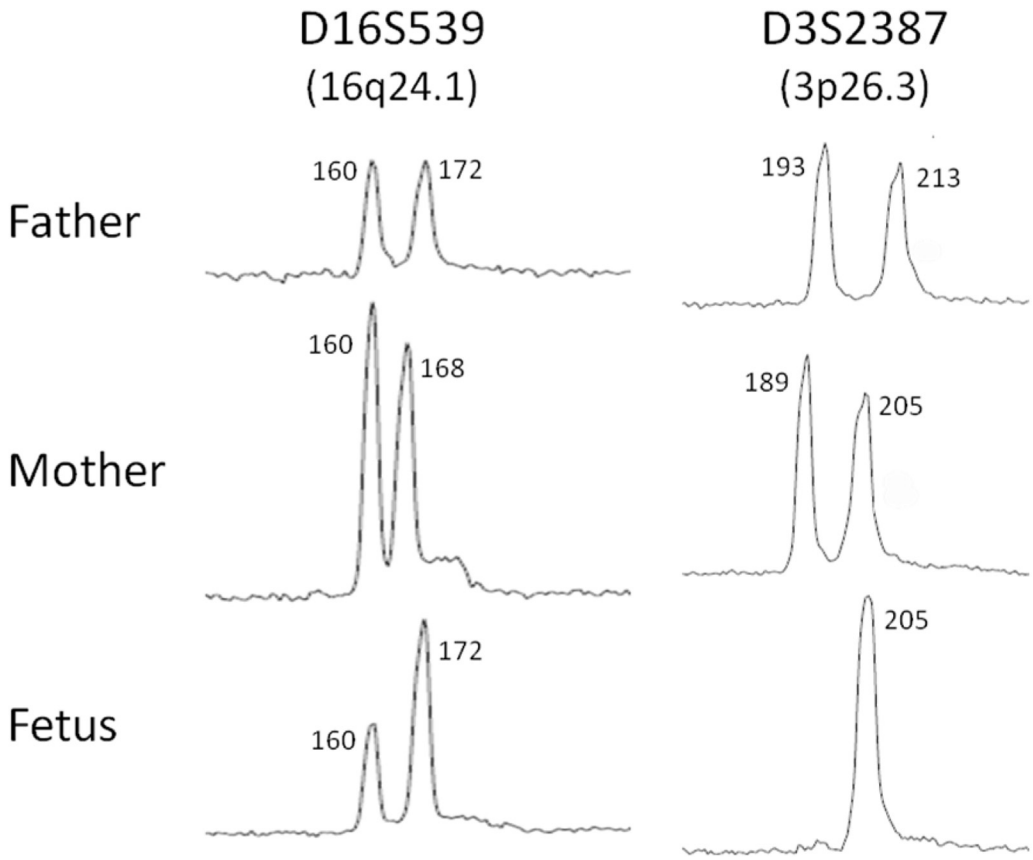

Figure 3. Polymorphic DNA marker analysis by quantitative fluorescent polymerase chain reaction shows that the fetus has a duplication of the paternal allele of 172bp in the informative marker of D16S539 (16q24.1), and a deletion of the paternal allele with the presence of only the maternal allele of 205bp in the informative marker of D3S2387 (3p26.3). This finding indicates a paternal origin of the 3p deletion and 16q duplication in the fetus.

terminal 3p26.3 deletion encompassing *CHL1*, *CNTN6*, and *CNTN4* in a four-generation family associated with no dysmorphic features or intellectual disability; they suggested that such a microdeletion occurs in 1% of the general population and is a benign variant. Various clinical reports concerning a deletion of the distal 3p region without apparent phenotypic effects have been described [5–13]. *CHL1* (OMIM 607416) belongs to the L1 gene family of neural cell adhesion molecules and is expressed on thin axonal neurites. *CNTN4* (OMIM 607280) and *CNTN6* (OMIM 607220) belong to axon-associated cell adhesion molecules of the immunoglobulin superfamily and are important in the formation, maintenance, and plasticity of functional neuronal networks. Knight et al [5] reported a baby girl and her mother who had del(3)(p25.3) but no apparent phenotypic abnormalities. Jervis et al [6] reported a 3p25.3 deletion in a mother and daughter with a normal phenotype. Sklower-Brooks et al [7] reported a 3p25.3 deletion in a mother and child without significant clinical features. Shrimpton et al [8] reported a patient with 3p26 deletion and 8q24.3 duplication with a virtually normal phenotype and mild cognitive deficit. Takagishi et al [9] reported a 3p25.3-pter deletion in a mother and daughter with minimal phenotypic effect. Hoo and Shrimpton [10] suggested that distal 3p deletion is not necessarily associated with dysmorphic features or psychomotor delay. Gijsbers et al [11] reported an apparently healthy boy with a 3p26.3-pter deletion and a 21q22.3-qter duplication. Pohjola et al [12] reported a 3p25.3 deletion in a mother and daughter with an extremely mild phenotypic effect. Cuoco et al [13] reported a terminal 3p26.3 deletion, which contained only the *CHL1* gene, in a normal father and his two children who were affected with microcephaly, mental retardation, and learning and language difficulties, but without the typical phenotypic manifestations described in the 3p deletion syndrome.

Prenatal diagnosis of trisomy 16 or partial trisomy 16 is uncommon, and the reported abnormal ultrasound findings include hydrocephalus [14], intrauterine growth restriction, micrognathia, congenital heart defects, clinodactyly, and abnormal external genitalia [15–17]. The phenotypic effects of partial trisomy 16q may be influenced by the secondary chromosomal rearrangement resulting from concurrent partial monosomy or trisomy.

The present case had a 13.17-Mb duplication in 16q23.1-q24.3. Brisset et al [18] suggest the following genotype–phenotype correlations of partial trisomy 16q: distinctive facial dysmorphism of high and prominent forehead and bitemporal narrowing; periorbital edema in the neonatal period; severe mental retardation; and vertebral, genital, and anal anomalies to 16q24; distal joint contractures and clinodactyly to 16q23; cleft palate and renal anomalies to 16q22; gut malrotation and lung and liver anomalies to 16q13; and behavior abnormalities to 16q11-q13. Quéméner-Redon [19] reported 16q24.1 microduplication in a woman, which was associated with mental retardation, spastic paraplegia, severe epilepsy, a narrow arched palate, malar hypoplasia, and arachnodactyly.

In summary, we described the prenatal diagnosis and molecular cytogenetic characterization of *de novo* partial monosomy 3p (3p26.3→pter) and partial trisomy 16q (16q23.1→qter). We demonstrated the usefulness of aCGH and QF-PCR in the prenatal identification of a *de novo* chromosome aberration, and the information acquired by molecular cytogenetic analyses was very helpful in genetic counseling.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

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