



Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Inv dup del(10p): Prenatal diagnosis and molecular cytogenetic characterization

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ARTICLE INFO

Article history:

Accepted 25 June 2019

Keywords:

Chromosome 10p

Deletion

Inverted duplication

Inv dup del(10p)

Prenatal diagnosis

ABSTRACT

Objective: We present molecular cytogenetic characterization of prenatally detected inverted duplication and deletion of 10p [inv dup del(10p)].**Case report:** A 39-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a derivative chromosome 10 with additional material at the end of the short arm of one chromosome 10. Simultaneous array comparative genomic hybridization (aCGH) analysis revealed the result of arr 10p15.3 (136,361–451,013) × 1, 10p15.3p12.1 (536,704–25,396,900) × 3 [GRCh37 (hg19)] with a 0.31-Mb deletion of 10p15.3 encompassing *ZMYND11* and *DIP2C*, and a 24.86-Mb duplication of 10p15.3p12.1. The pregnancy was subsequently terminated, and a female fetus was delivered with facial dysmorphism. Postnatal aCGH analysis showed that the umbilical cord had the same result as that of amniotic fluid, whereas the placenta had only the deletion of 10p15.3. Fluorescence *in situ* hybridization (FISH) analysis of the cord blood confirmed inverted duplication and deletion of 10p. The cord blood had a karyotype of 46,XX,der(10) del(10) (p15.3)dup(10) (p15.3p12.1)dn. Polymorphic DNA marker analysis confirmed a maternal origin of the chromosome 10 aberration.**Conclusion:** Prenatal diagnosis of inv dup del(10p) with haploinsufficiency of *ZMYND11* should include a genetic counseling of mental retardation and chromosome 10p15.3 microdeletion syndrome. aCGH, FISH and polymorphic DNA marker analysis are useful for perinatal investigation of inv dup del(10p).© 2019 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

An inverted duplication deletion with a terminal deletion (inv dup del) is a rare complex chromosomal rearrangement that involves an inverted duplication of a chromosome in association with a deletion distal to the site of duplication [1–4]. Proposed mechanism of the inv dup del include the U-type exchange model [5], the

non-allelic homologous recombination model [6] and the premeiotic non-homologous end joining model [7].

We previously reported molecular cytogenetic characterization of inv dup del(8p) [1], inv dup del(9p) [2], inv dup del(10q) [3] and inv dup del(14q) [4]. Here, we present an additional case of inv dup del(10p).

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Case Report

A 39-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a derivative chromosome 10, or der(10), with an additional material at the end of the short arm of one chromosome 10. Simultaneous array comparative genomic hybridization (aCGH) analysis revealed a result of arr 10p15.3 (136,361–451,013) \times 1, 10p15.3p12.1 (536,704–25,396,900) \times 3 [GRCh37 (hg19)] with a 0.31-Mb deletion of 10p15.3 and a 24.86-Mb duplication of 10p15.3p12.1. The karyotype was 46,XX,der(10)del(10) (p15.3) dup(10) (p15.3p12.1). The pregnancy was subsequently terminated, and a 342-g female fetus was delivered with facial dysmorphism of low-set ears, hypertelorism, frontal bossing, a large nose and a wide mouth (Fig. 1). Postnatal aCGH analysis on the umbilical cord revealed a result of arr 10p15.3 (136,361–451,013) \times 1.0, 10p15.3p12.1 (536,704–25,396,900) \times 3.0 [GRCh37 (hg19)] (Fig. 2). aCGH on the placental tissue revealed a result of arr 10p15.3 (136,361–451,013) \times 1.0 [GRCh37 (hg19)] (Fig. 3). The 0.31-Mb deletion of 10p15.3 encompasses two Online Mendelian Inheritance in Man (OMIM) genes of *ZMYND11* and *DIP2C*, and the 24.86-Mb duplication of 10p15.3p12.1 encompasses 87 OMIM genes. The parental karyotypes were normal. Metaphase fluorescence *in situ* hybridization (FISH) analysis on the cord blood lymphocytes using the bacterial artificial chromosome (BAC) probes confirmed a 10p15.3 deletion and an inverted duplication of 10p15.3p12.1 in the aberrant chromosome of der(10) (Fig. 4). Cytogenetic analysis of cord blood revealed a karyotype of 46,XX, inv dup del(10) (:p12.1 \rightarrow p15.3::p15.3 \rightarrow qter), or 46,XX,der(10) del(10) (p15.3) dup(10) (p15.3p12.1) (Fig. 5). Polymorphic DNA marker analysis confirmed a maternal origin of the chromosome 10 aberration (Figs. 6 and 7). Cytogenetic analysis of the umbilical cord revealed the same karyotype as that of cord blood.

Discussion

We have presented a rare case of inv dup del(10p) with prenatal diagnosis by amniocentesis and perinatal molecular cytogenetic analysis. The peculiar aspect of the present case is the maternal origin of the chromosomal aberration and the cytogenetic discrepancy between the placenta and the fetus. Our case shows that fetoplacental cytogenetic discrepancy may present in fetal inv

dup del(10p). Our finding implies the limitation of prenatal diagnosis of inv dup del(10p) by chorionic villus sampling (CVS) and non-invasive prenatal testing (NIPT) using maternal blood.

The present case has a microdeletion of 10p15.3 and haploinsufficiency of *ZMYND11*. Chromosome 10p15.3 microdeletion syndrome is characterized by neurodevelopmental disorder, characteristic dysmorphic features, behavioural disturbances, cognitive/developmental delay, speech delay, motor delay, brain anomalies, seizures, low birth weight and short stature, and in most cases the genes of *ZMYND11* and *DIP2C* are deleted [8–14]. Tumiene et al. [14] confirmed that the *ZMYND11* is the critical gene for the phenotype of chromosome 10p15.3 microdeletion syndrome. *ZMYND11* (OMIM 608668) encodes zinc finger MYND domain-containing protein 11, and mutations of *ZMYND11* are associated with autosomal dominant mental retardation 30 (OMIM 616083). Coe et al. [15] reported seven individuals from six families with loss-of-function variants in the gene of *ZMYND11* and the common features of intellectual disability, hypertelorism, ptosis and a wide mouth, and other problems of behavioural problems, aggressive behavior, social difficulty and speech delay.

The present case has a 10p12.1-p15.3 duplication. Partial trisomy 10pter \rightarrow p12.1 has been reported to be associated with multiple anomalies and mental retardation. Mihci and Lindo [16] reported a male with a 10p15.3 duplication and learning disability and melanoma. Dup(10) (pter \rightarrow p13) has been reported to be associated with motor and mental retardation, cleft palate, hydrocephalus, cerebral atrophy and cerebellar hypoplasia [17,18]. Fryns et al. [19] reported a 21-year-old mentally retarded female with 10p12 trisomy with slight craniofacial dysmorphism. Dup(10) (pter \rightarrow p12) has been reported to be associated with hydrocephalus [20]. Hoo et al. [21] reported a 21-year-old female with an inverted tandem duplication of dup(10) (pter \rightarrow p12.3) with prominent forehead, dolichocephaly and a ventricular septal defect.

In summary, we report prenatal diagnosis and molecular cytogenetic characterization of inv dup del(10p). Prenatal diagnosis of inv dup del(10p) should include a genetic counseling of mental retardation, facial dysmorphism, neurodevelopmental disorder, central nervous system (CNS) abnormalities and chromosome 10p15.3 microdeletion syndrome. Our case shows aCGH, FISH and polymorphic DNA marker analysis are useful for perinatal investigation of inv dup del(10p).



Fig. 1. The fetus at birth.

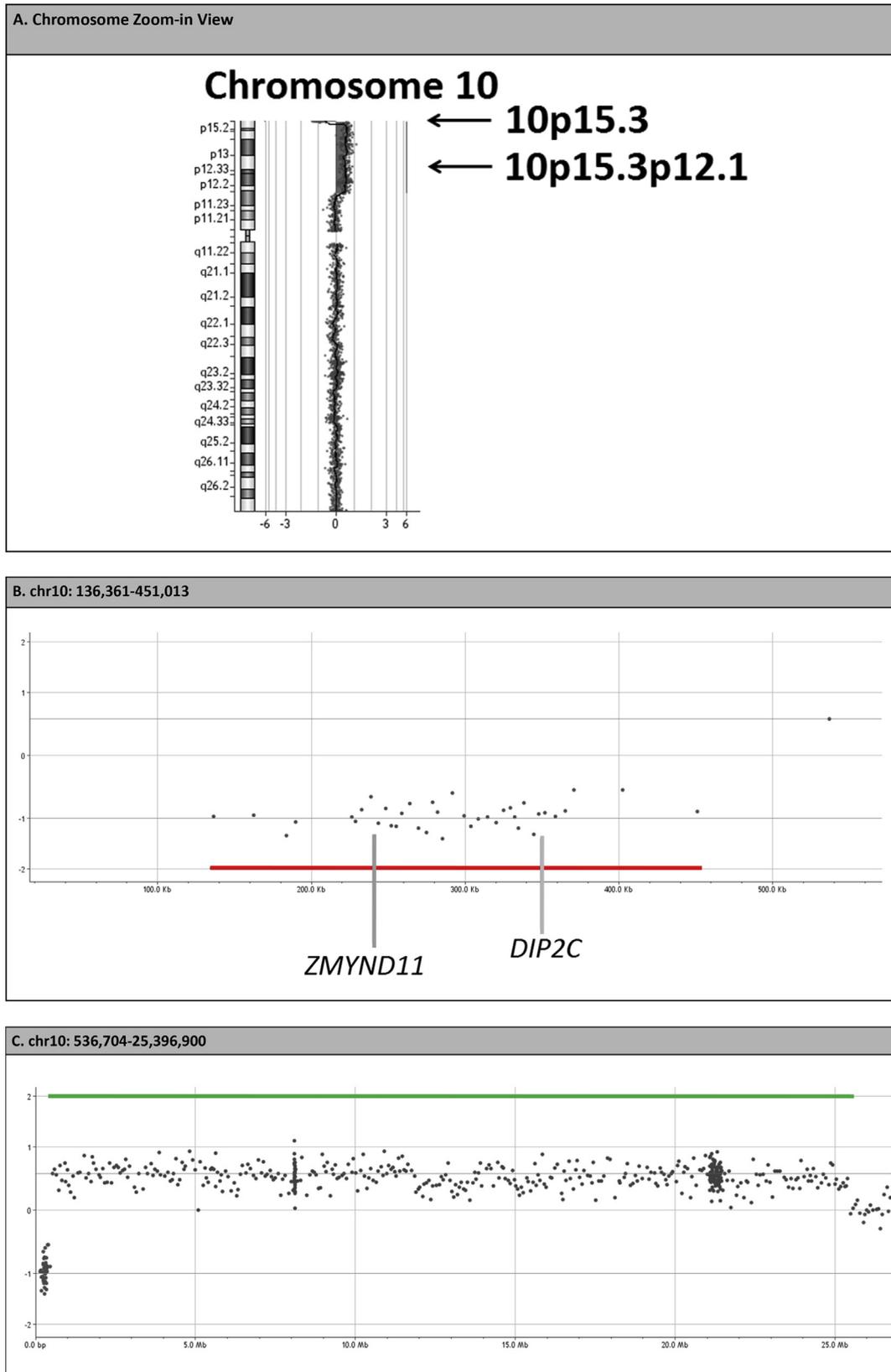


Fig. 2. Array comparative genomic hybridization (aCGH) of the DNA extracted from the umbilical cord using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60K (Agilent Technologies, Santa Clara, CA, USA) shows (A) a 10p15.3 deletion and a 10p15.3p12.1 duplication, (B) a 0.31-Mb deletion of 10p15.3 encompassing the genes of *ZMYND11* and *DIP2C*, and (C) a 24.86-Mb duplication of 10p15.3p12.1.

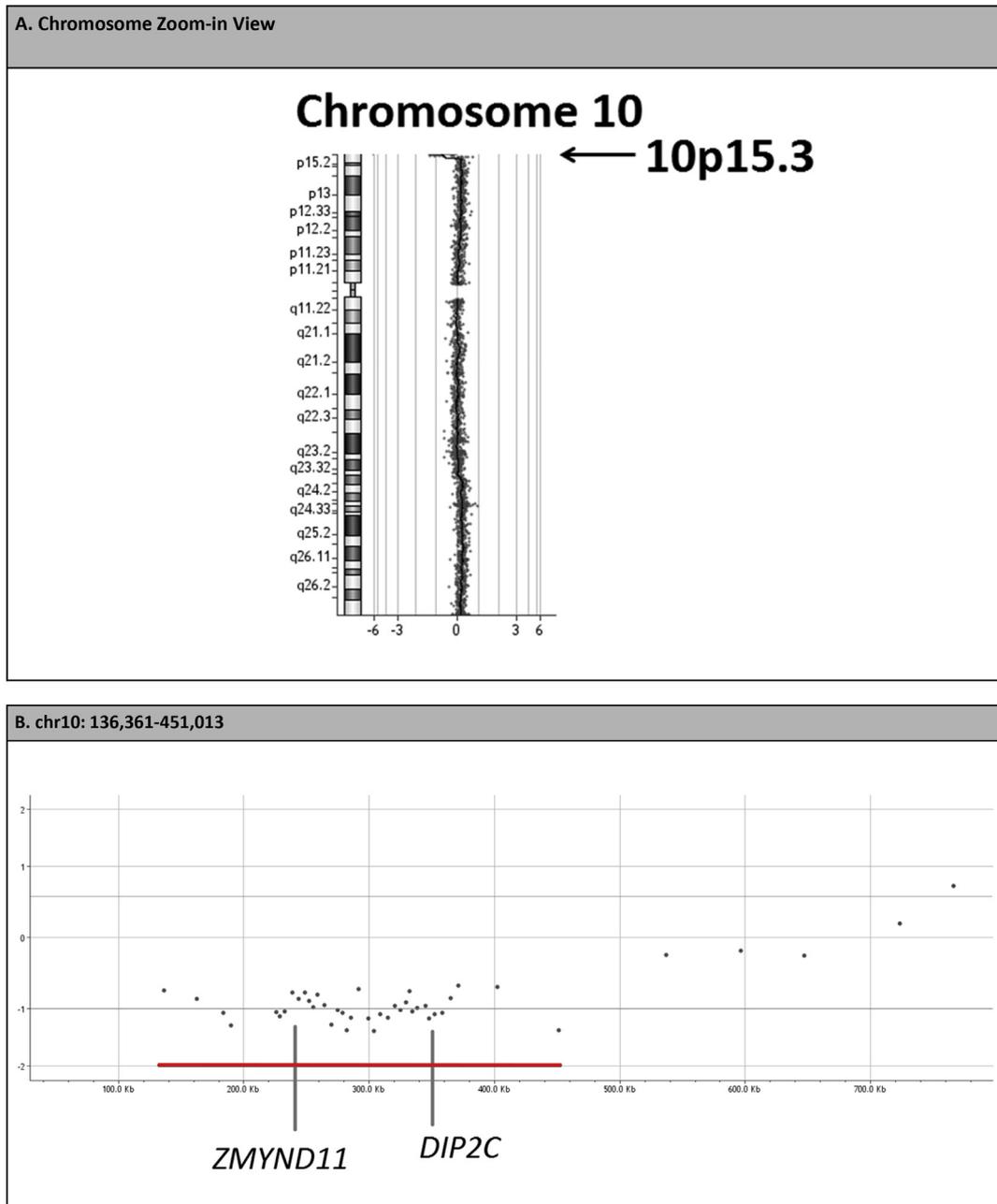


Fig. 3. aCGH of the DNA extracted from the placenta using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60K (Agilent Technologies, Santa Clara, CA, USA) shows (A) a 10p15.3 deletion and (B) a 0.31-Mb deletion of 10p15.3 encompassing the genes of *ZMYND11* and *DIP2C*.

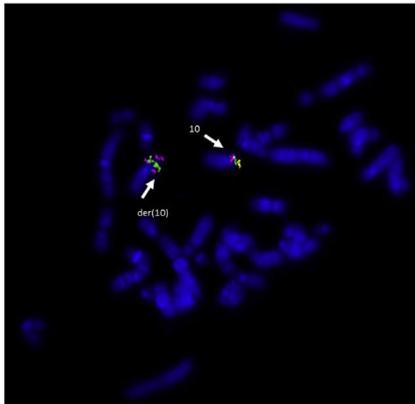


Fig. 4. Metaphase fluorescence *in situ* hybridization analysis on cord blood lymphocytes using the bacterial artificial chromosome (BAC) probes RP11-915J16 (10p12.3; 18,815,165–18,961,519; Texas Red, spectrum red), RP11-958E6 [10p15.1; 4,210,832–4,384,495; fluorescein isothiocyanate (FITC), spectrum green] and RP11-145I2 (10p15.3; 222,406–226,399; Cy5, spectrum yellow) shows that the normal chromosome 10 has three signals in the order of red-green-yellow (from centromere to telomere), and the aberrant derivative chromosome 10 [der(10)] has four signals in the order of red-green-green-red but without a yellow signal, indicating an inverted duplication and a deletion of 10p.

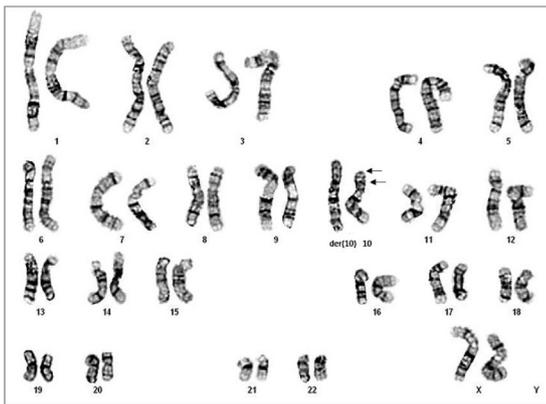


Fig. 5. A karyotype of 46,XX, inv dup del(10) (:p12.1 → p15.3::p15.3 → qter), or 46,XX,der(10)del(10) (p15.3) dup(10) (p15.3p12.1).

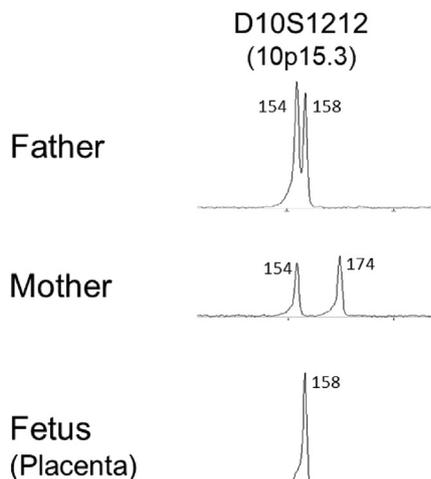


Fig. 6. Polymorphic DNA marker analysis on the DNAs extracted from the placenta and the parental bloods using the informative marker of D10S1212 (10p15.3; 160,005–160,326) (hg19) shows that the father has two alleles of 154 bp and 158 bp, and the mother has two alleles of 154 bp and 174 bp, but the placenta has only one allele of 158 bp inherited from the father, indicating a maternal origin of the 10p deletion.

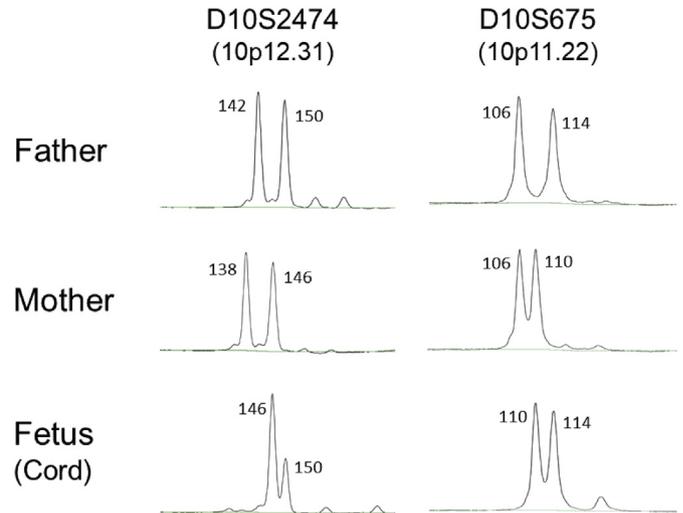


Fig. 7. Polymorphic DNA marker analysis on the DNAs extracted from the umbilical cord and the parental bloods using the informative marker of D10S2474 (10p12.31; 19,437,959–19,438,095) (hg19) shows that the father has two alleles of 142 bp and 150 bp, and the mother has two alleles of 138 bp and 146 bp, but the umbilical cord has two alleles of 146 bp: 150 bp (maternal allele: paternal allele) with a ratio of 2:1, indicating a maternal origin of the homozygous duplication.

Conflict of interest

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

Acknowledgements

This work was supported by research grants MOST-107-2314-B-195-005 from the Ministry of Science and Technology and MMH-E-108-04 from MacKay Memorial Hospital, Taipei, Taiwan.

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