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Case Report

Molecular genetic characterization of a prenatally detected *de novo* interstitial deletion of chromosome 2q (2q31.1-q32.1) encompassing *HOXD13*, *ZNF385B* and *ZNF804A* associated with syndactyly and increased first-trimester nuchal translucency

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ABSTRACT

Objective: We present prenatal diagnosis and molecular genetic characterization of a *de novo* interstitial deletion of 2q (2q31.1-q32.1) and discuss the genotype–phenotype correlation.

Case report: A 34-year-old, primigravid woman was referred to the hospital at 20 weeks of gestation for genetic counseling because of a prenatally detected *de novo* interstitial deletion of chromosome 2q (2q31.1-q32.1). She underwent amniocentesis at 17 weeks of gestation because of advanced maternal age and an increased first-trimester nuchal translucency (NT) thickness of 3.6 mm. Amniocentesis revealed a karyotype of 46,XY. However, array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniotic fluid and amniocytes revealed a 13.29-Mb deletion at chromosome 2q31.3-q32.1. The parents did not have such a deletion. Prenatal ultrasound findings were unremarkable. After counseling of the genotype–phenotype correlation of such a chromosome aberration with congenital malformations, the parents elected to terminate the pregnancy. The fetus postnataly manifested hypertelorism and syndactyly of the second and third toes of bilateral feet. Cytogenetic analysis of the umbilical cord revealed a karyotype of 46,XY,del(2)(q31q32). aCGH analysis on the DNA extracted from the cord blood confirmed a 13.35-Mb deletion of 2q31.1-q32.1 encompassing *HOXD13*, *ZNF385B*, *ITGA4*, *CERKL*, *PDE1A*, *FRZB* and *ZNF804A*. Polymorphic DNA marker analysis revealed a paternal origin of the deletion.

Conclusion: Fetuses with an interstitial deletion of 2q31.1-q32.1 may be associated with increased first-trimester NT. Haploinsufficiency of *HOXD13* is associated with syndactyly. Genomic microarray is useful in detecting subtle chromosomal abnormalities in fetuses with increased NT and normal karyotype.

Introduction

The chromosome 2q31.1 microdeletion syndrome is a well-defined and clinical recognizable contiguous gene syndrome characterized by limb defects due to hemizygosity of the *HOXD* genes, and craniofacial dysmorphism of a narrow forehead, prominent metopic suture, a small nose with a bulbous tip, long and

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smooth philtrum, down-slanting palpebral features, thin upper lip, thick and everted lower lip, low-set and dysplastic ears, and micrognathia [1].

The chromosome 2q31.2q32.3 deletion syndrome is characterized by multiple dysmorphisms, developmental delay, mental retardation and behavioral disturbances, and various candidate genes such as *ZNF385B* at 2q31.2-q31.3; *ITGA4* and *CERKL* at 2q31.3; *PDE1A*, *ZNF804A* and *FRZB* at 2q32.1; *MSTN* and *GLS* at 2q32.2; and *MYO1B* at 2q32.3 have been suggested to be responsible for the genotype–phenotype correlation [2–5]. Here, we present our experience of prenatal diagnosis of 2q31.1-q32.1 deletion associated with increased first-trimester nuchal translucency (NT) thickness and syndactyly.

Case report

A 34-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age and an increased first-trimester NT thickness of 3.6 mm. Her husband was 34 years old, and there was no family history of congenital malformations. Amniocentesis revealed a karyotype of 46,XY. However, array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniotic fluid and amniocytes revealed a 13.29-Mb deletion at chromosome 2q31.3-q32.1. The parents did not have such a deletion. Prenatal ultrasound findings were unremarkable. After counseling of the genotype–phenotype correlation of the chromosome aberration with congenital malformations, the parents elected to terminate the pregnancy, and a 348-g malformed male fetus was delivered with hypertelorism and syndactyly of the second and the third toes of bilateral feet. Cytogenetic analysis of the umbilical cord revealed a karyotype of 46,XY,del(2)(q31q32) (Fig. 1). aCGH analysis on the DNA extracted from the cord blood by CytoChip ISCA Array (Illumina, San Diego, CA, USA) revealed a result of arr 2q31.1q32.1 (174,506,070–187,858,552) × 1.0 with a 13.35-Mb deletion of 2q31.1-q32.1 encompassing 53 Online Mendelian Inheritance in Man (OMIM) genes including *HOXD13*, *ZNF385B*, *ITGA4*, *CERKL*, *PDE1A*, *FRZB* and *ZNF804A* (Fig. 2). Metaphase fluorescence *in situ* hybridization analysis of the umbilical cord fibroblasts confirmed an interstitial deletion of chromosome 2q32.1 (Fig. 3). Polymorphic DNA marker analysis revealed a paternal origin of the deletion (Table 1).

Discussion

The present case had an interstitial deletion of chromosome 2q (2q31.1-q32.1) encompassing *HOXD13*, *ZNF385B*, *ITGA4*, *CERKL*, *PDE1A*, *ZNF804A* and *FRZB*. *HOXD13* (OMIM 142989) is located at 2q31.1 and encodes homeobox D13 which is a master regulator of autopod skeletal morphogenesis [6]. Deletions or loss-of-function mutations of *HOXD13* cause autosomal dominant brachydactyly type D (OMIM 113200) brachydactyly type E (OMIM 113300), syndactyly type V (OMIM 186300) and synpolydactyly type 1 (OMIM 18600), and brachydactyly–syndactyly syndrome (OMIM 610713). Digital abnormalities such as brachydactyly, syndactyly, camptodactyly, clinodactyly and ectrodactyly have been well observed in patients with a 2q31.1 microdeletion with haploinsufficiency of *HOXD13* [1,7–11].

ZNF385B (OMIM 612344) is located at 2q31.2-q31.3 and encodes zinc finger protein 385B which is expressed in the brain. Monfort et al. [12] reported mental retardation and dysmorphism in a 14-year-old boy with an interstitial deletion at 2q31.2 encompassing *ZNF385B*. Monfort et al. [12] suggested that loss-of-function mutations in zinc finger genes play a role in human cognitive process. *ITGA4* (OMIM 192975) is located at 2q31.3 and encodes α4 integrin. Correia et al. [13] suggested an association of *ITGA4* with autism. However, Cochrane et al. [14] did not find such an association in an Irish sample. *CERKL* (OMIM 608381) is located at 2q31.3 and encodes ceramide kinase-like protein which is associated with autosomal recessive retinitis pigmentosa [15]. *PDE1A* (OMIM 171890) is located at 2q32.1 and encodes phosphodiesterase 1A which has been associated with major depression [16]. However, recent studies did not support such a correlation [17,18]. *ZNF804A* (OMIM 612282) is located at 2q32.1 and encodes zinc finger protein 804A

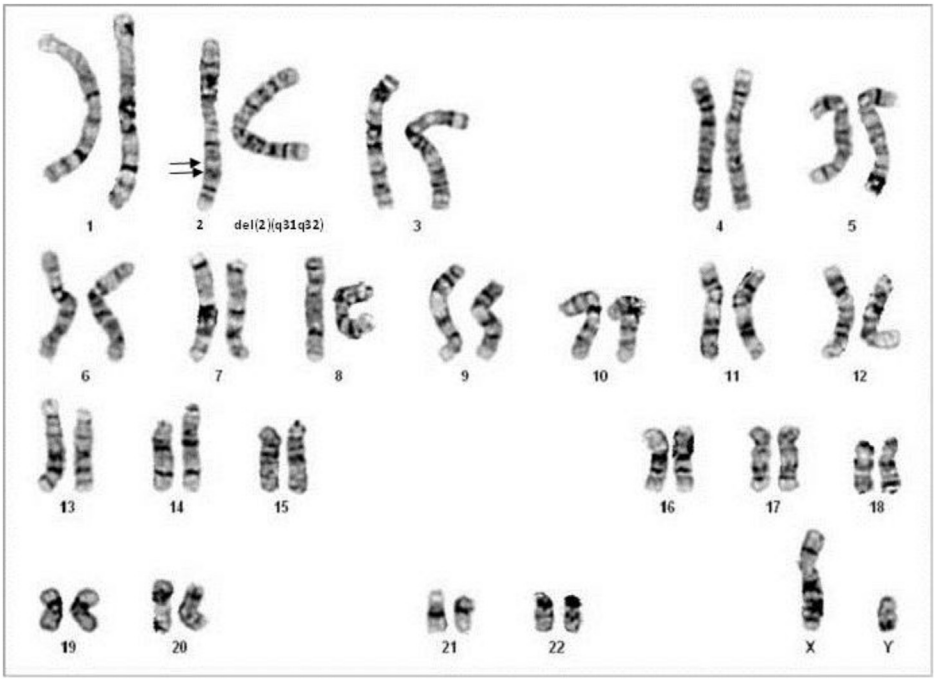

Fig. 1. A karyotype of 46,XY,del(2)(q31q32). The arrows on the normal chromosome 2 indicate the breakpoints. del = deletion.

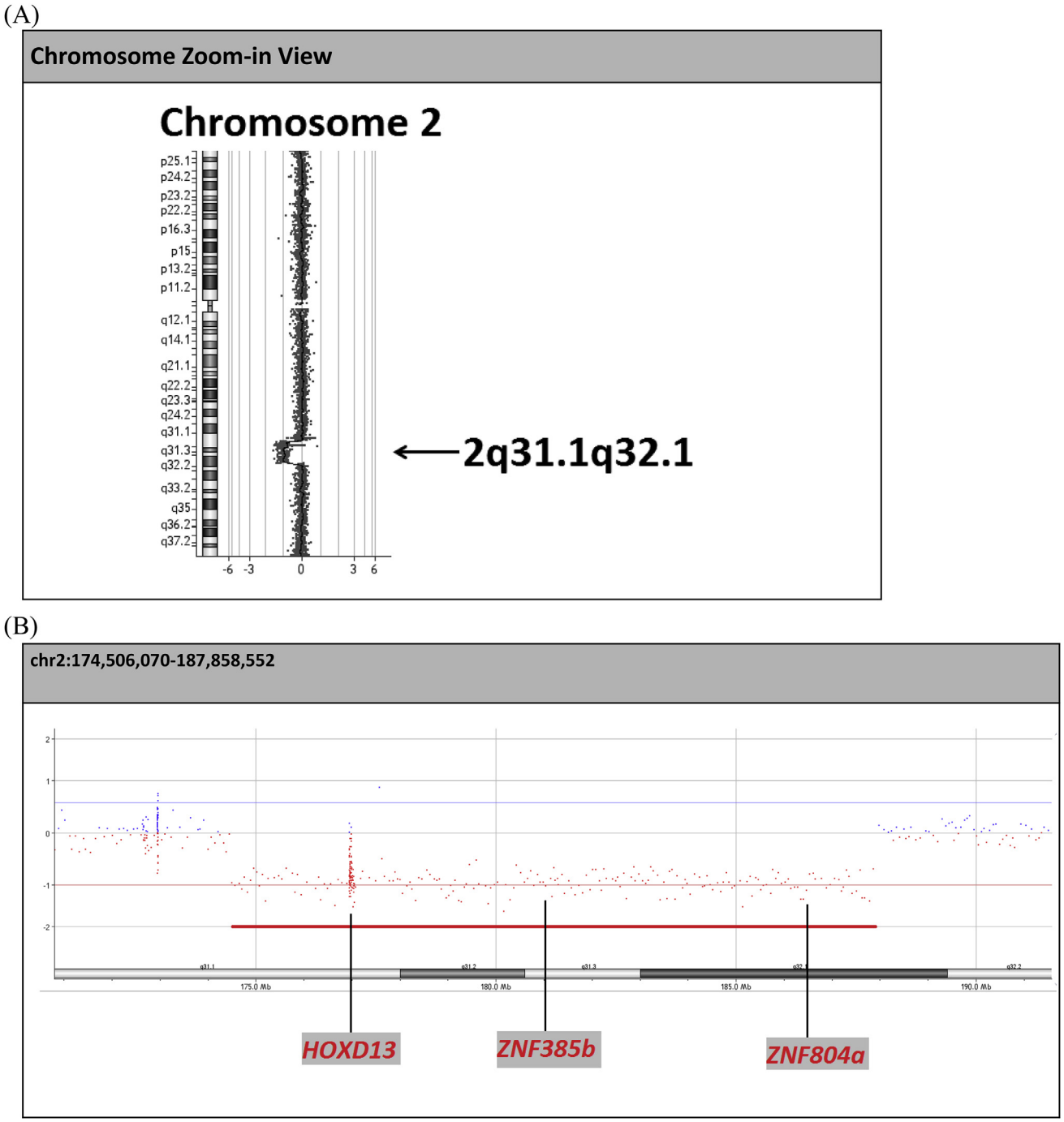

Fig. 2. (A) and (B). The fetus carries a 13.35-Mb deletion at 2q31.11-q32.1 encompassing *HOXD13*, *ZNF385B* and *ZNF804A*.

which regulates neurite formation and dendritic spine structure [19]. *ZNF804A* is a candidate gene for cognitive and behavioral disturbances such as psychosis, schizophrenia and bipolar disorders [19–21]. *FRZB* (OMIM 605083) is located at 2q32.1 and encodes frizzled-related protein which is associated with skeletal morphogenesis [22].

The peculiar aspect of the present case is the association of increased first-trimester NT with del(2)(q31.1q32.1). The present case provides evidence for the usefulness of application of genomic microarray in fetuses with increased NT and normal karyotype. In a systemic review and meta-analysis, Grande et al. [23] concluded that the use of genomic microarray provides a 5% increased yield of detecting copy number variants (CNVs) in fetuses with increased NT and normal karyotype. Yang et al. [24] detected 9.1% (20/220) fetuses with submicroscopic chromosomal abnormalities in fetuses with increased NT and normal karyotype, and found that these fetuses with abnormal prenatal morphology had a significantly higher chromosomal abnormality rate of 26.9% compared with 6.7% of chromosomal abnormality rate in fetuses with normal prenatal morphology.

In summary, we present prenatal diagnosis and molecular cytogenetic characterization of a *de novo* interstitial deletion of 2q (2q31.1-q32.1) associated with increased first-trimester NT and syndactyly, and discuss the genotype–phenotype correlation. Our

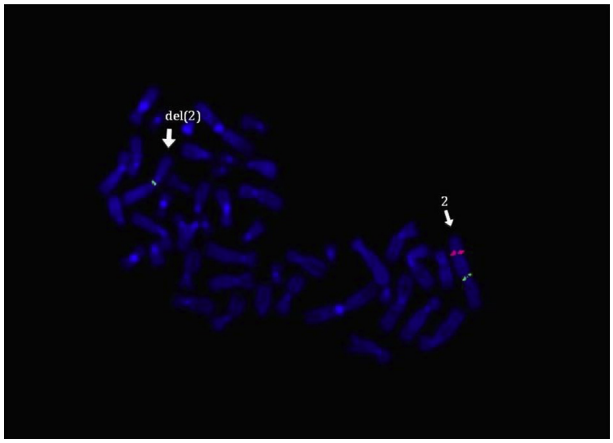

Fig. 3. Metaphase fluorescence *in situ* hybridization analysis of cultured umbilical cord fibroblasts using the bacterial artificial chromosome probes RP11-979L17 (2q32.1; 182,632,464–182,816,988; Texas Red, spectrum red) and RP11-973B20 [2q11.2; 97,747,200–97,919,415; fluorescein isothiocyanate (FITC), spectrum green] shows one red signal and one green signal in a normal chromosome 2, and only one green signal in the del(2) chromosome with interstitial deletion of 2q32.1 del = deletion.

Table 1
Genotypic information of the fetus and the parents at short tandem repeat markers specific for chromosome 2q obtained by quantitative fluorescent polymerase chain reaction assays.[a]

Markers	Locus	Father	Mother	Fetus	Inheritance
D2S1379	2q24.1	140, 148	148, 148	148, 148	Non-informative
D2S1372	2q24.2	138, 142	130, 138	130, 142	Biparental
D2S2978	2q31.3	126, 135	129, 135	129	Maternal
D2S1347	2q31.3	166, 166	163, 163	163	Maternal
D2S2979	2q32.1	114, 114	118, 118	118	Maternal
D2S248	2q32.2	287, 287	287, 287	287, 287	Non-informative

[a] Alleles (basepair sizes) are listed below each individual.

case demonstrates that a fetus with del(2)(q31.1q32.1) may present increased first-trimester NT and the phenotype of syndactyly, and provides evidence that genomic microarray is useful in detecting subtle chromosomal abnormalities in fetuses with increased NT and normal karyotype.

Conflict of interest

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

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