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Short Communication

Prenatal diagnosis of a 1.6-Mb 4p16.3 interstitial microdeletion encompassing *FGFRL1* and *TACC3* associated with bilateral cleft lip and palate of Wolf-Hirschhorn syndrome facial dysmorphism and short long bones

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ABSTRACT

Objective: We present prenatal diagnosis of a 4p16.3 interstitial microdeletion associated with bilateral cleft lip and palate and short long bones on prenatal ultrasound, and we discuss the genotype–phenotype correlation.

Materials and methods: A 32-year-old woman underwent amniocentesis at 22 weeks of gestation because of bilateral cleft lip and palate and short limbs on prenatal ultrasound. Conventional cytogenetic analysis was performed on cultured amniocytes and parental bloods. Oligonucleotide array comparative genomic hybridization (aCGH) was performed on the DNAs extracted from uncultured amniocytes, parental bloods and umbilical cord. Metaphase fluorescence *in situ* hybridization (FISH) was performed on cultured amniocytes.

Results: Amniocentesis revealed a karyotype of 46,XY. The parental karyotypes were normal. aCGH analysis on uncultured amniocytes revealed a 1.66-Mb interstitial microdeletion at 4p16.3 encompassing 23 Online Mendelian Inheritance of in Man (OMIM) genes including *FGFRL1* and *TACC3*. The parents did not have such a deletion. The pregnancy was subsequently terminated, and a malformed fetus was delivered with typical Wolf-Hirschhorn syndrome (WHS) facial appearance and bilateral cleft lip and palate. aCGH analysis of the umbilical cord confirmed the prenatal diagnosis with a result of arr 4p16.3 (72,447–1,742,649) × 1.0 [GRCh37 (hg19)]. Metaphase FISH analysis of cultured amniocytes confirmed a 4p16.3 microdeletion.

Conclusion: Haploinsufficiency of *FGFRL1* and *TACC3* at 4p16.3 can be associated with bilateral cleft lip and palate of WHS facial dysmorphism and short long bones. Prenatal diagnosis of facial cleft with short long bones should raise a suspicion of chromosome microdeletion syndromes.

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Introduction

Wolf-Hirschhorn syndrome (WHS) [Online Mendelian Inheritance of in Man (OMIM) 194190] is a contiguous gene deletion syndrome that was first described by Wolf et al. [1] and Hirschhorn et al. [2] independently as a syndrome with multiple congenital anomalies and mental retardation caused by partial deletion of 4p, especially 4p16.3. WHS is characterized by the "Greek warrior helmet" facial appearance of wide nose bridge continuing to the forehead, high arched eyebrows, widely spaced eyes, microcephaly, distinct mouth, short philtrum, micrognathia, intrauterine growth restriction (IUGR), postnatal growth deficiency, intellectual disability, hypotonia, muscle hypotrophy, seizures, feeding difficulties and abnormal ears in exceeding 75% of the cases; distinctive electroencephalogram (EEG) abnormalities, skeletal anomalies, skin changes, craniofacial asymmetry, abnormal teething, ptosis and antibody deficiency in 50–75% of the cases; heart defects, hearing defects, eye and optic nerve defects, cleft lip and palate, stereotypies, structural brain anomalies and genitourinary tract defects in 25–50% of the cases; and anomalies of liver, gallbladder, gut, diaphragm, esophagus, lung and aorta in less than 25% of the cases [3–6].

The WHS critical regions at 4p16.3 include WHS candidate genes of *WHSC1* (OMIM 602952), *WHSC2* (OMIM 606026) and *LETM1* (OMIM 604407). WHS patients with a microdeletion of 4p16.3 less than 5 Mb are uncommon and represent less than 3% of all reported cases [4]. Here, we present a very rare case of 1.6-Mb 4p16.3 interstitial microdeletion which is telomeric to *WHSC1*, *WHSC2* and *LETM1* and is associated with bilateral cleft lip and palate of WHS facial dysmorphism and short long bones. Our presentation helps to elucidate the critical regions responsible for the core WHS phenotype.

Materials and methods

Clinical description

A 32-year-old, grvida 2, para 1, woman was referred for genetic counseling and amniocentesis at 22 weeks of gestation because of short long bones with a fetal long bone biometry equivalent to 20 weeks, and bilateral cleft lip and palate on prenatal ultrasound (Fig. 1). Her husband was 33 years old, and there was no family history of congenital malformations. Her previous pregnancy ended in preterm labor because of cervical incompetence. During this pregnancy, she underwent a surgery of cervical circlage to prevent preterm labor. However, irregular uterine contractions occurred off and on. Level II ultrasound at 22 weeks of gestation revealed bilateral cleft lip and palate and short long bones, but other internal organs were unremarkable. Conventional cytogenetic analysis was performed on cultured amniocytes and parental bloods. Array comparative genomic hybridization (aCGH) was performed on the DNAs extracted from uncultured amniocytes, parental bloods and umbilical cord. Metaphase fluorescence *in situ* hybridization (FISH) was performed on cultured amniocytes.

Conventional cytogenetic analysis

Routine cytogenetic analysis by G-banding techniques at the 550 bands of resolution was performed on cultured amniocytes and parental bloods according to the standard cytogenetic protocol.

aCGH

Oligonucleotide aCGH on the DNAs extracted from uncultured amniocytes, parental bloods and umbilical cord was performed

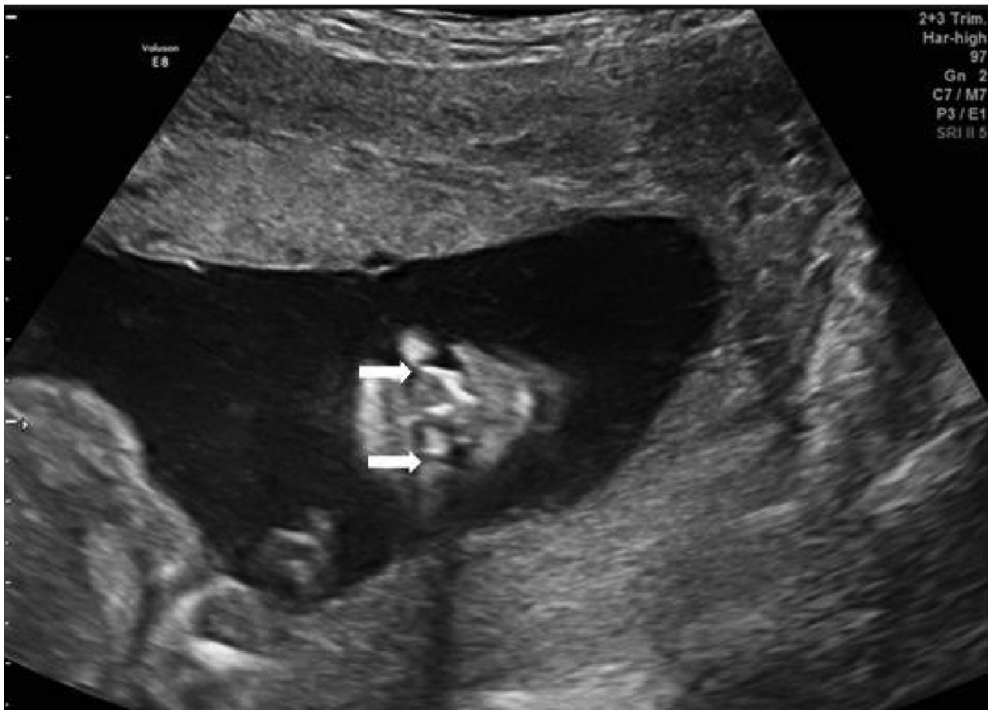

Fig. 1. Prenatal ultrasound at 22 weeks of gestation shows bilateral cleft lip and palate. The arrows indicate facial cleft.

using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K Array (Agilent Technologies, Santa Clara, CA, USA). The array has 60,000 probes and a median resolution of 60 kb across the entire genome according to the manufacturer's instruction.

FISH

Metaphase FISH analysis on cultured amniocytes was performed using the bacterial artificial chromosome (BAC) probes of RP11-939A10 [4p16.3; fluorescein isothiocyanate (FITC), spectrum green] and RP11-924O4 (4q12; Texas red, spectrum red) according to the standard FISH protocol.

Results

Cytogenetic analysis of cultured amnioyctes revealed a karyotype of 46,XY (Fig. 2). The parental karyotypes were normal. aCGH analysis on uncultured amniocytes detected a result of arr [GRCh37] 4p16.3 (78,470–1,742,649) × 1 (X,Y) × 1 dn with a 1.66-Mb interstitial microdeletion encompassing 23 OMIM genes. The parents did not have such a deletion. Metaphase FISH analysis of cultured amniocytes confirmed the 4p16.3 microdeletion (Fig. 3). The pregnancy was subsequently terminated, and a malformed fetus was delivered with typical WHS facial appearance of "Greek warrior helmet" facial appearance of nose, high forehead, prominent glabella, hypertelorism, high-arched eyebrows epicanthic folds, short philtrum, micrognathia, low-set ears, and bilateral cleft lip and palate (Fig. 4). aCGH analysis on umbilical cord confirmed the prenatal diagnosis with a result of arr 4p16.3 (72,447–1,742,649) × 1.0 [GRCh37 (hg19)] with a 1.67-Mb deletion encompassing 23 OMIM genes of *ZNF141*, *PIGG*, *PDE6B*, *ATP5I*, *MYL5*,

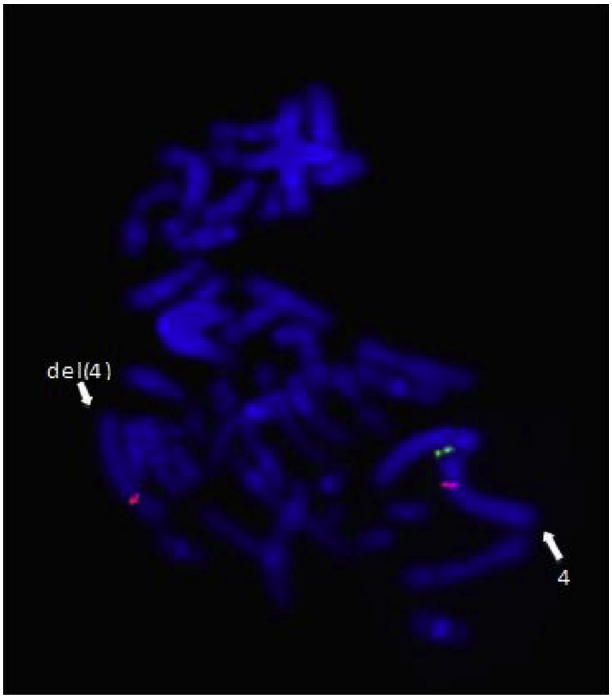

Fig. 3. Metaphase fluorescence *in situ* hybridization analysis on cultured amniocytes using the 4p16.3-specific probe of RP11-939A10 (spectrum green) and the 4q12-specific probe of RP11-924O4 (spectrum red) shows one red signal and one green signal in a normal chromosome 4, and only one red signal in the chromosome with 4p distal deletion [del(4)]. The result is consistent with a 4p16.3 microdeletion.

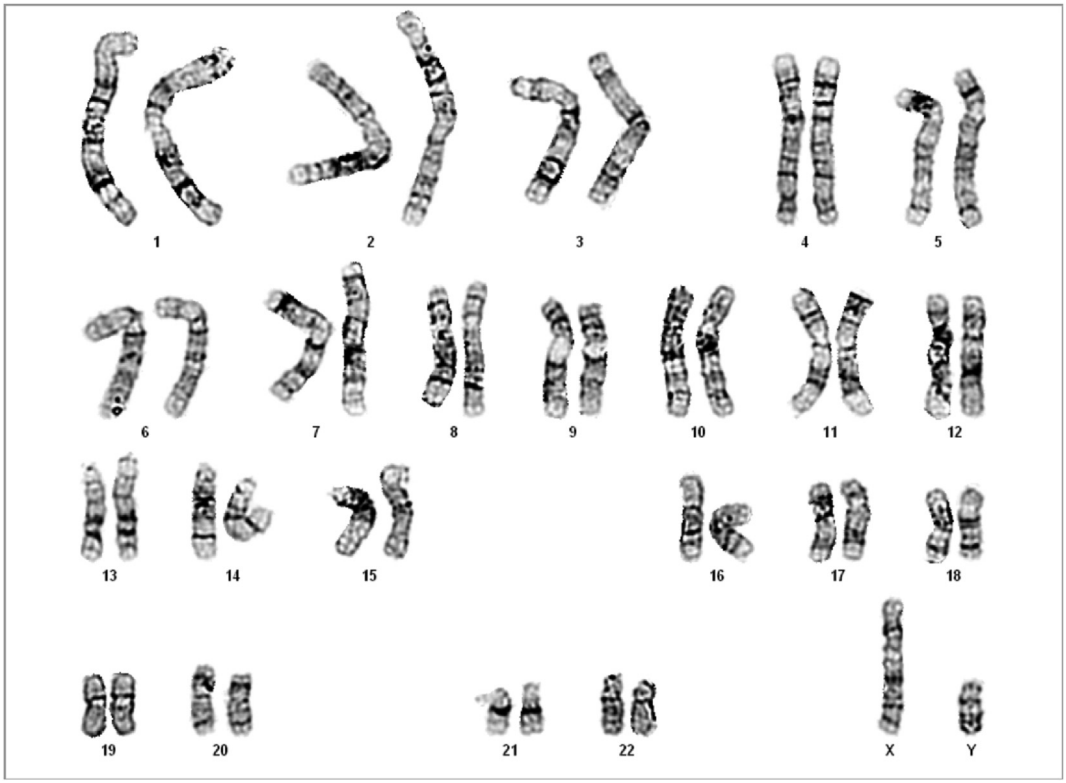

Fig. 2. A karyotype 46,XY in cultured amniocytes.

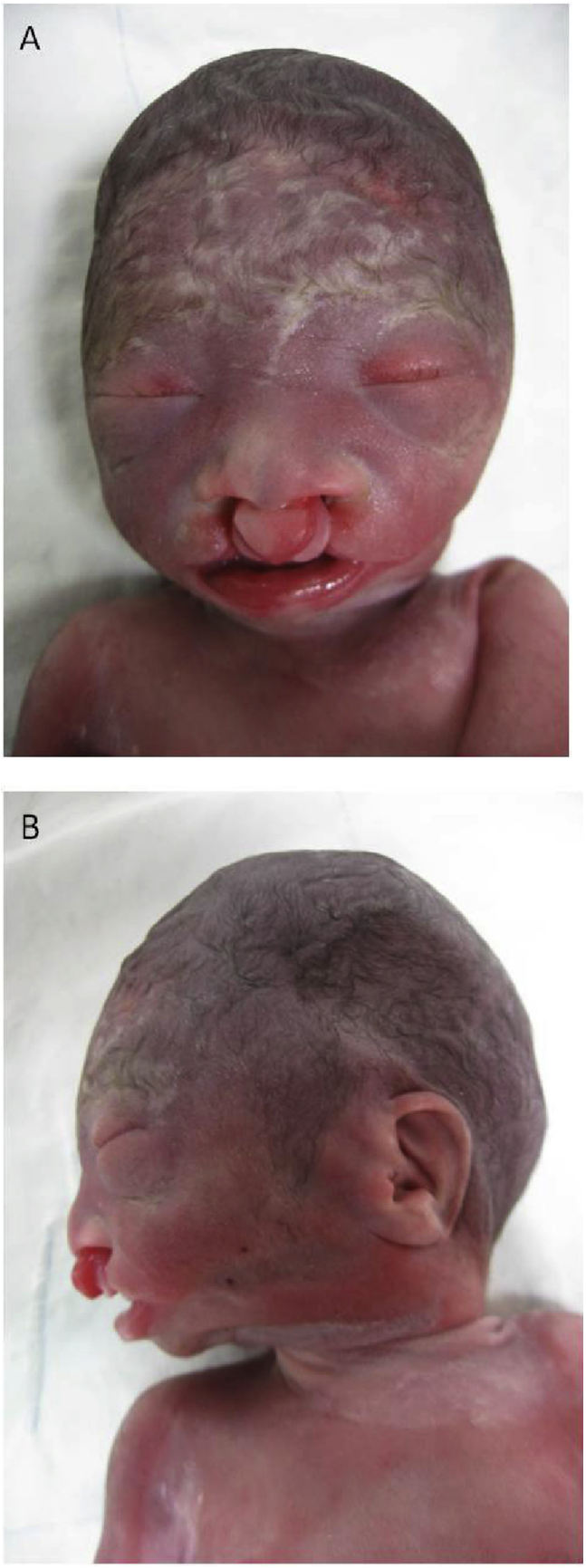

Fig. 4. (A) Anterior view and (B) lateral view of the facial profile of the fetus at birth.

PCGF3, *CPLX1*, *GAK*, *TMEM175*, *DGKQ*, *SLC26A1*, *IDUA*, *FGFRL1*, *RNF212*, *SPON2*, *CTBP1*, *MAEA*, *UVSSA*, *CRIPAK*, *FAM53A*, *SLBP*, *TMEM129* and *TACC3* (Fig. 5).

Discussion

The present case manifested bilateral cleft lip and palate on prenatal ultrasound. Uni- and bilateral cleft lip and palate are reported in about one third of the patients with WHS of whom the 4p deletions are usually larger than 3.5-Mb [4]. Prenatal diagnosis of WHS has been well described [7–24]. The reported abnormal findings associated with WHS on prenatal ultrasound include IUGR, midface hypoplasia, "Greek warrior helmet" appearance of the nose, facial cleft, hypospadias, agenesis of the corpus callosum, cardiac septal defects, congenital diaphragmatic hernia, renal hypoplasia, foot deformity, increased nuchal translucency and cystic hygroma.

The present case had a 1.6-Mb 4p16.3 interstitial microdeletion encompassing the genes of *PIGG*, *PCGF3*, *CPLX1*, *GAK*, *DGKQ*, *FGFRL1*, *CTBP1* and *TACC3*. Such a microdeletion is telomeric to the known WHS critical regions of *WHSC1*, *WHSC2* and *LETM1*. Among these genes, *PIGG*, *PCGF3*, *CPLX1*, *GAK*, *DGKQ* and *CTBP1* have all been proposed to be associated with seizures/epilepsy susceptibility and intellectual disability in WHS [25–33].

Of interest is the association of haploinsufficiency of *FGFRL1* and *TACC3* with bilateral cleft lip and palate, and short long bones in the present case. Haploinsufficiency of *FGFRL1* associated with 4p16.3 deletions has been suggested to contribute to the WHS craniofacial phenotype and other skeletal features [34–36]. *FGFRL1* (OMIM 605830) encodes fibroblast growth factor receptor-like 1. During late stage of the mouse development, *Fgfrl1* is prominent in the primordia of maxilla, mandible and the permanent cartilage of trachea, rib and nose, and is preferentially expressed in the skeletal tissues [37,38]. Depletion of *Fgfrl1* in zebrafish results in the craniofacial phenotype of lower jaw malformation and inhibition of the cartilage formed by the branchial arches [39]. Catela et al. [34] reported multiple congenital WHS malformations such as abnormal craniofacial development, axial and appendicular skeletal anomalies and congenital heart defects in *Fgfrl1* null mice.

TACC3 deficiency is related to craniofacial malformation in mice [40–43]. *TACC3* (OMIM 605303) encodes transforming acidic coiled-coil-containing protein 3, and *TACC3* mRNA is highly expressed in migratory neural crest cells in the *Xenopus laevis* pharyngeal arches [42]. Rutherford and Lowery [43] proposed a correlation of WHS pathophysiology with defects in neural crest cell motility and migration during development. Piekorz et al. [40] found that *TACC3* homozygous null embryonic mice exhibited facial defects and growth restriction. Yao et al. [41] found that mice with *TACC3* homozygous mutations and *TACC3* deficiency exhibited IUGR and defects in formation of the axial skeleton. Our case provides evidence that the deletion of 4p16.3 involving *FGFRL1* and *TACC3* without involving *WHSC1*, *WHSC2*, *FGFR3* and *LETM1* can cause the most severe WHS facial appearance along with short long bones.

In summary, we present prenatal diagnosis of a 1.6-Mb 4p16.3 interstitial microdeletion encompassing *FGFRL1* and *TACC3* because of prenatal ultrasound findings of bilateral cleft lip and palate and short long bones. Our case shows that haploinsufficiency of *FGFRL1* and *TACC3* at 4p16.3 can be associated with bilateral cleft lip and palate of WHS facial dysmorphism and short long bones. We suggest that prenatal diagnosis of facial cleft with short long bones should raise a suspicion of chromosome microdeletion syndromes.

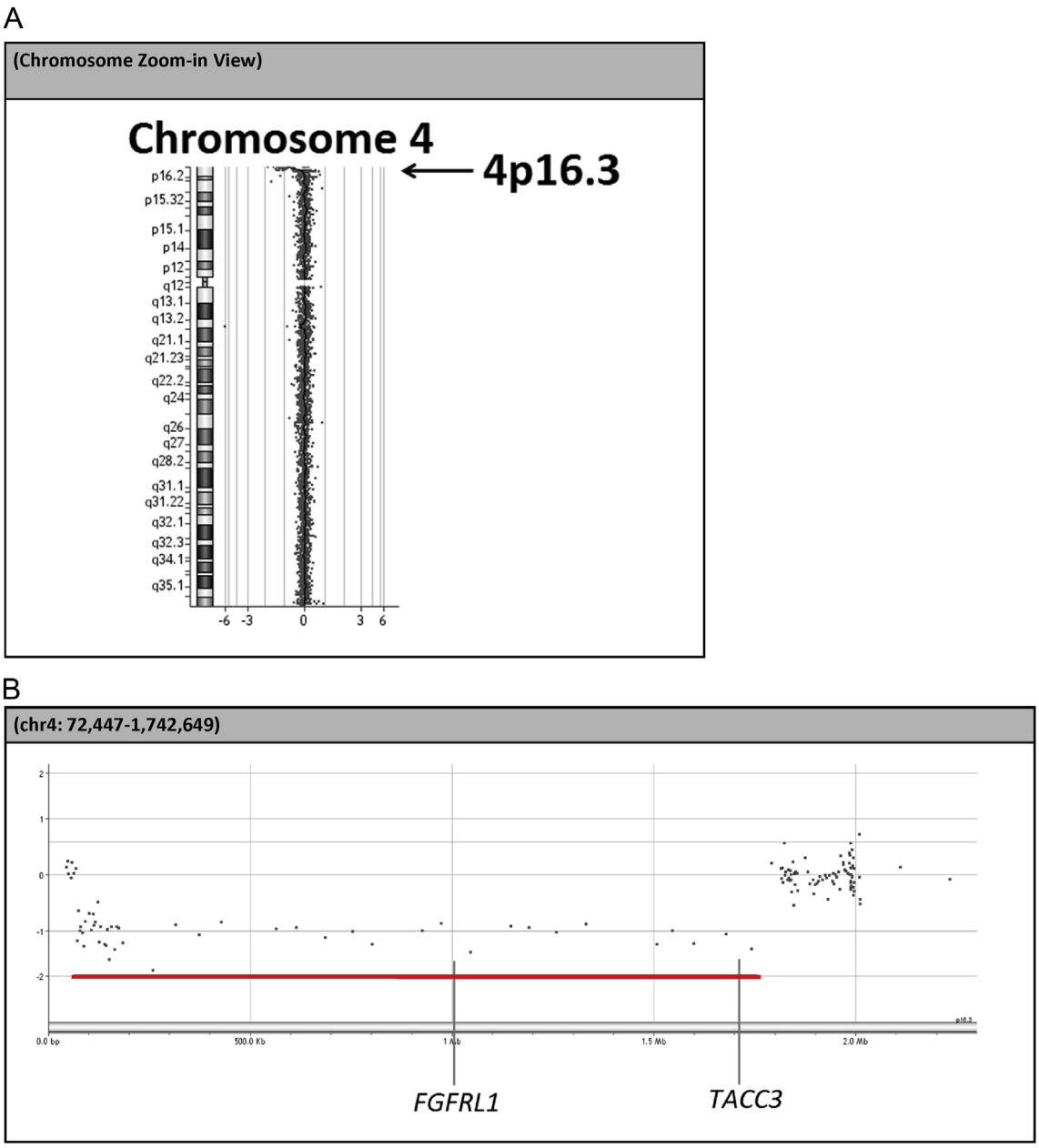

Fig. 5. Oligonucleotide array comparative genomic hybridization analysis on the DNA extracted from umbilical cord shows a 1.67-Mb interstitial 4p16.3 microdeletion or arr 4p16.3 (72,447–1,742,649) × 1.0 [GRCh37 (hg19)] encompassing *FGFRL1* and *TACC3* (A) and (B) Zoom-in views of the 4p16.3 microdeletion.

Conflicts of interest

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

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