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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of an interstitial deletion of 18q12.1-q12.3 encompassing *DTNA*, *CELF4* and *SETBP1*

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ABSTRACT

Objective: We present prenatal diagnosis and molecular cytogenetic characterization of an interstitial deletion of 18q12.1-q12.3.

Case report: A 35-year-old woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 46,XX,del(18)(q12.1q12.3). The fetal ultrasound was unremarkable. The woman underwent repeat amniocentesis at 20 weeks of gestation. Array comparative genomic hybridization (aCGH) using uncultured amniocytes revealed a 10.76-Mb interstitial deletion 18q12.1-q12.3 or arr 18q12.1q12.3 (31,944,347–42,704,784) × 1.0 encompassing 19 Online Mendelian Inheritance of in Man (OMIM) genes including *DTNA*, *CELF4* and *SETBP1*. Metaphase fluorescence *in situ* hybridization analysis on cultured amniocytes confirmed an 18q proximal interstitial deletion. The parental karyotypes were normal. Polymorphic DNA marker analysis determined a paternal origin of the deletion. The pregnancy was subsequently terminated at 24 weeks of gestation, and a 650-g fetus was delivered with characteristic facial dysmorphism.

Conclusion: aCGH analysis and polymorphic DNA marker analysis at amniocentesis are useful for determination of the deleted genes and the parental origin of the *de novo* deletion, and the acquired information is helpful for genetic counseling.

Introduction

Amniocentesis because of advanced maternal age or abnormal ultrasound may incidentally detect a paternal origin *de novo* chromosome aberration [1–3]. We previously reported prenatal diagnosis of a case with 18q12.1-q12.3 interstitial deletion [1]. Here, we present an additional case with an 18q12.1-q12.3 interstitial deletion.

Case report

A 35-year-old, gravida 2, para 1, woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Her husband was 31 years old, and there was no family history of

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congenital malformations. During this pregnancy, amniocentesis revealed a karyotype of 46,XX,del(18)(q12.1q12.3). The fetal ultrasound was unremarkable. The parental karyotypes were normal. The parents consulted our department and requested for repeat amniocentesis. Repeat amniocentesis was performed at 20 weeks of gestation. aCGH analysis on uncultured amniocytes by SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K Array (Agilent Technologies, Santa Clara, CA, USA) revealed a 10.76-Mb interstitial deletion of 18q12.1-q12.3 or arr 18q12.1q12.3 (31,944,347–42,704,784) × 1.0 [GRCh37 (hg19)] encompassing 19 Online Mendelian Inheritance of in Man (OMIM) genes including *DTNA*, *CELF4* and *SETBP1* (Fig. 1). Conventional cytogenetic analysis on cultured amniocytes revealed a result of 46,XX,del(18)(q12.1q12.3) (Fig. 2). Polymorphic DNA marker analysis using the DNAs extracted from parental bloods and uncultured amniocytes determined a paternal origin of the deletion (Fig. 3). Metaphase fluorescence *in situ* hybridization analysis on cultured amniocytes confirmed an 18q proximal interstitial deletion (Fig. 4). The pregnancy was subsequently terminated at 24 weeks of gestation, and a 650-g fetus was delivered with characteristic facial features of telecanthus, frontal bossing, deep-set eyes and midface hypoplasia (Fig. 5).

Discussion

Proximal interstitial 18q deletions encompassing the bands 18q12→q21 define a rare del(18)(q12.1q12.3) syndrome with characteristic facial features of telecanthus, frontal bossing, deep-set eyes and midface hypoplasia, behavior problems, autism spectrum disorder, hyperactivity, aggressivity, moderate to severe mental retardation, hypotonia, seizures and language impairment but lack of major congenital defects [4–14]. The present case had a 10.76-Mb interstitial deletion 18q12.1-q12.3 encompassing *DTNA*, *CELF4* and *SETBP1*.

SETBP1 (OMIM 611060) encodes set-binding protein 1 and is located at 18q12.3. Mutations or deletions of *SETBP1* can be associated with autosomal dominant mental retardation-29 (OMIM

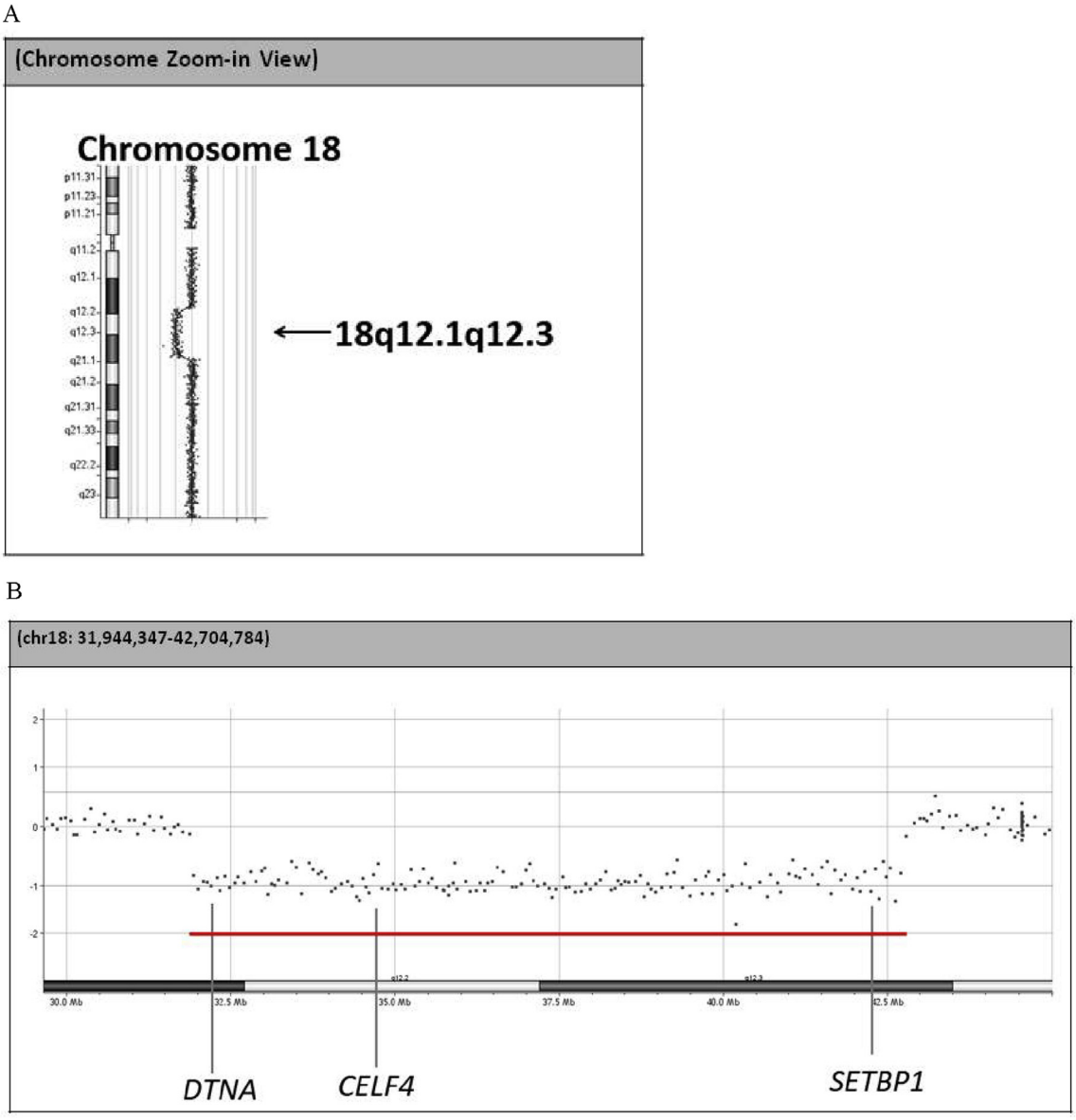

Fig. 1. Array comparative genomic hybridization on uncultured amniocytes shows a 10.76-Mb interstitial deletion of 18q12.1-q12.3 encompassing *DTNA*, *CELF4* and *SETBP1*. (A) and (B) Chromosome 18 zoom-in views.

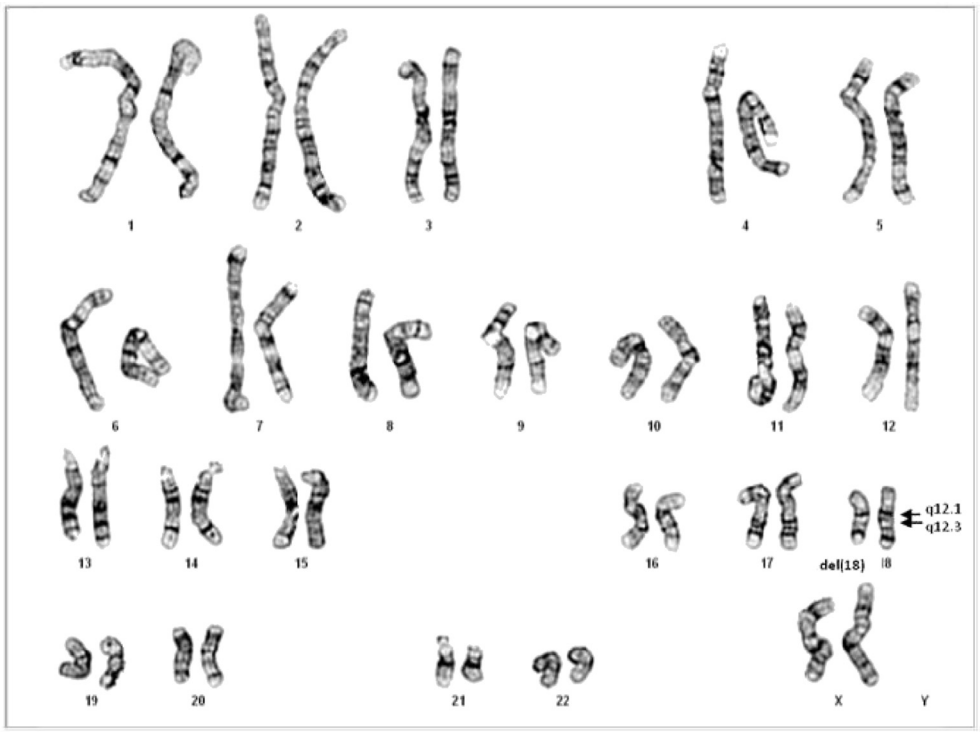

Fig. 2. A karyotype 46,XX,del(18)(q12.1q12.3).

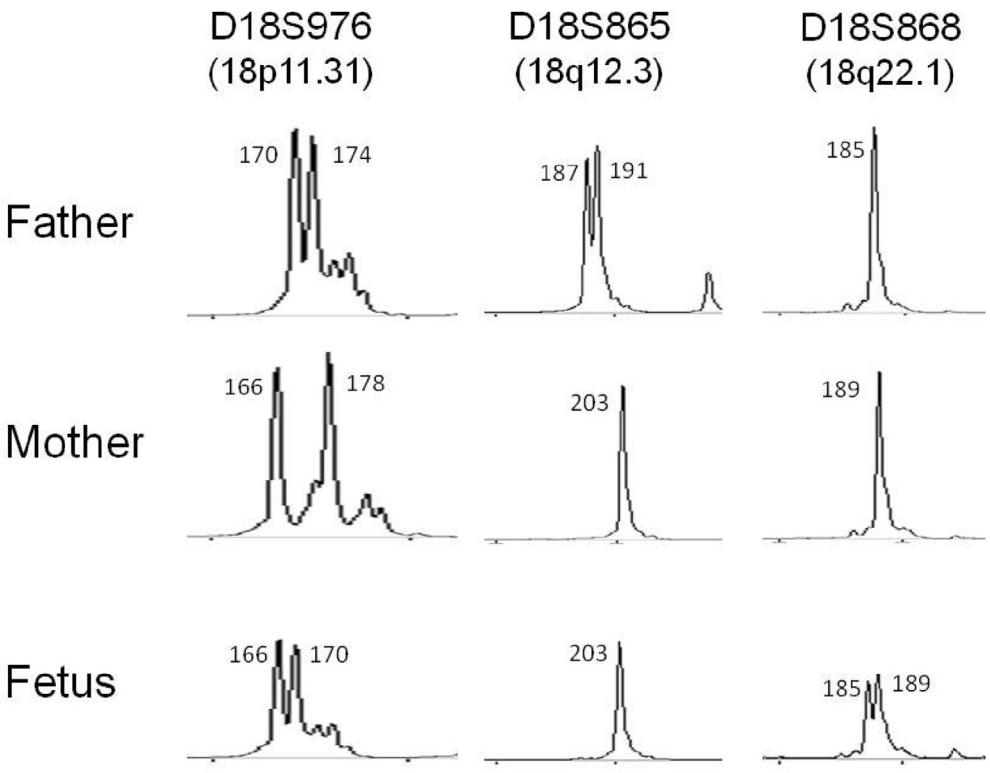

Fig. 3. Polymorphic DNA marker analysis using the DNAs extracted from parental bloods and uncultured amniocytes with the informative markers of D18S976 (18p11.31), D18S865 (18q12.3) and D18S868 (18q22.1) shows that the fetus has biparental inheritance in D18S976 and D18S868. However, in D18S865 at 18q12.3, the fetus inherits only one maternal allele, indicating a paternal origin of the deletion.

616078), and heterozygous *de novo* mutations in *SETBP1* cause autosomal dominant Schinzel-Giedion midface retraction syndrome (OMIM 269150). Bouquillon et al. [15] reported two patients with an 18q12.3 deletion, *SETBP1* haploinsufficiency and expressive speech delay. Filges et al. [16] reported *SETBP1* haploinsufficiency in two patients with an 18q12.3 microdeletion, global developmental and expressive language delay and minor facial anomalies. Marseglia et al. [17] reported a patient with an

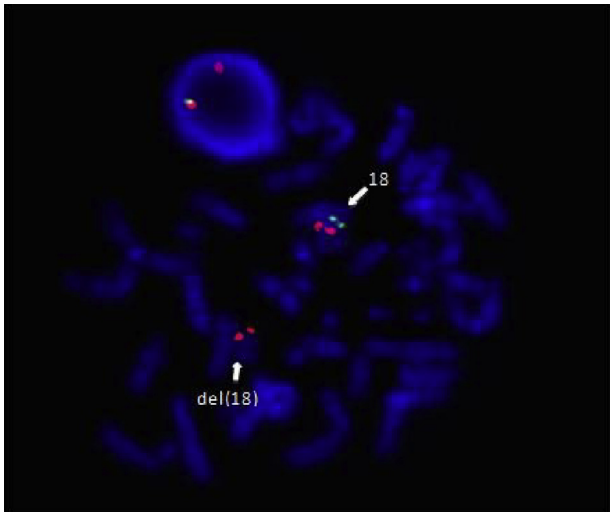

Fig. 4. Metaphase fluorescence *in situ* hybridization analysis on cultured amniocytes using the 18q12.2-specific probe of RP11-938M23 [fluorescein isothiocyanate (FITC), spectrum green] and the18p11.22-specific probe of RP11-918F20 (Texas red, spectrum red) shows both the green and red signals in a normal chromosome 18, and only the red signal in the chromosome of del(18), indicating an 18q proximal interstitial deletion in the del(18). del = deletion.

18q12.3 microdeletion causing *SETBP1* haploinsufficiency in association with mild mental retardation and expressive speech impairment. Rauch et al. [18] and Coe et al. [19] reported patients with loss-of-function frameshift or nonsense mutations in *SETBP1* causing speech and motor delays, mild dysmorphic features and behavioral difficulties. Heterozygous *de novo* mutations in *SETBP1* cause Schinzel-Giedion midface retraction syndrome which is characterized by severe mental retardation, distinctive facial features of midface retraction, skeletal abnormalities, genitourinary and renal malformations, cardiac defects and neuroepithelial neoplasia [20–28].

CELF4 (OMIM 612679) located at 18q12.2 is highly expressed in brain and gallbladder [29]. Halgren et al. [30] reported haploinsufficiency of *CELF4* at 18q12.2 in a patient with developmental and behavioral disorders, myopia, obesity and febrile seizures in childhood, and suggested that *CELF4* is important for human brain development. Barone et al. [31] reported familial 18q12.2 microdeletion involving *CELF4* in a child with syndromic intellectual disability and autism and her mother with minor dysmorphism, mild intellectual disability and autistic behavior, and suggested that *CELF4* plays a role in brain development and autism spectrum disorders. 18q12.2 deletion syndrome is a highly recognized condition characterized by the neuropsychiatric phenotype of developmental delay, intellectual disability, seizures, motor coordination disorder, behavioral disturbances and autism spectrum disorders, and other features of facial dysmorphism, myopia and obesity [8,13,30,32].

DTNA (OMIM 601239) located at 18q12.1 and encodes α-dystrobrevin which participates in the formation of sarcoglycan–sarcospan complex [33]. Wang et al. [34] identified a 4-Mb *de novo* duplication of 18q12.1 in a girl with autistic disorder, intellectual disability, focal epilepsy and idiopathic small stature and suggested that deletion or duplication of *DTNA* at 18q12.1 is associated with physical and neurological development including autism and intellectual disability.

Poissonnier et al. [35] reported two unrelated mentally retarded patients with del(18)(q12.1q12.3) that manifested facial dysmorphism, small midface, prominent forehead, epicanthic folds, full periorbital tissue, wide/flat nasal bridge, abnormal ears, behavioral disorders, autistic-like disorders, hypotonia and seizures. Our case is an additional case of del(18)(q12.1q12.3). Our case shows that array comparative genomic hybridization (aCGH) analysis and polymorphic DNA marker analysis at amniocentesis are useful for determination of the deleted genes and the parental origin of the *de novo* deletion, and the acquired information is helpful for genetic counseling.

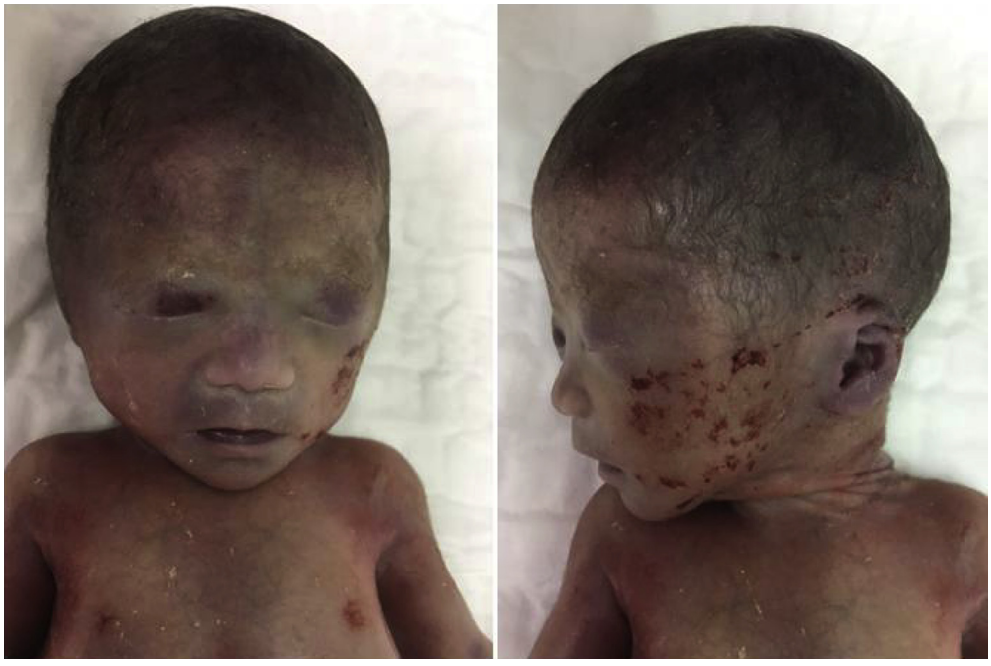

Fig. 5. Anterior and lateral views of the craniofacial appearance of the proband at birth.

Conflicts of interest

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

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