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SHORT COMMUNICATION

PRENATAL DIAGNOSIS OF *DE NOVO* INTERSTITIAL 16q DELETION IN A FETUS ASSOCIATED WITH SONOGRAPHIC FINDINGS OF PROMINENT CORONAL SUTURES, A PROMINENT FRONTAL BONE, AND SHORTENING OF THE LONG BONES

CHIH-PING CHEN[1,2]*, SCHU-RERN CHERN[2], CHEN-CHI LEE[3], LI-FENG CHEN[3] AND CHUN-YU CHUANG[2]

[1]*Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan, Republic of China*
[2]*Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan, Republic of China*
[3]*Cytogenetic Laboratory, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan, Republic of China*

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SUMMARY

De novo interstitial 16q deletion diagnosed *in utero* has not previously been reported. We present a case of fetal *de novo* interstitial 16q deletion associated with the sonographic findings of prominent coronal sutures, a prominent frontal bone, and shortening of the long bones. Genetic amniocentesis at 23 weeks' gestation revealed a *de novo* deletion of 16q13–q22. At birth, the fetus manifested a dysmorphic phenotype correlated with monosomy 16q syndrome. Linkage analysis of the family confirmed the maternal origin and the extent of the deletion. We suggest that prenatal detection of a prominent frontal bone with prominent cranial sutures and shortening of the long bones should prompt cytogenetic analysis looking for a deletion in the long arm of chromosome 16. © 1998 John Wiley & Sons, Ltd.

KEY WORDS: interstitial 16q deletion; ultrasound; prenatal diagnosis

INTRODUCTION

Deletions of the long arm of chromosome 16 are uncommon. The majority of affected cases have been reported in infancy and childhood. To our knowledge, *in utero* diagnosis of *de novo* interstitial 16q deletion has not been previously described. In this report, prenatal ultrasonography and the diagnostic amniocentesis helped to detect a *de novo* deletion of 16q13–q22 in a fetus.

CASE REPORT

A 33-year-old Chinese woman, gravida 2, para 1, was referred to our hospital for genetic counselling during the second trimester because of prenatal sonographic findings of an abnormally shaped fetal head and short limbs. The parents

*Correspondence to: Dr Chih-Ping Chen, Department of Obstetrics and Gynecology, and Department of Medical Research, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan, Republic of China.

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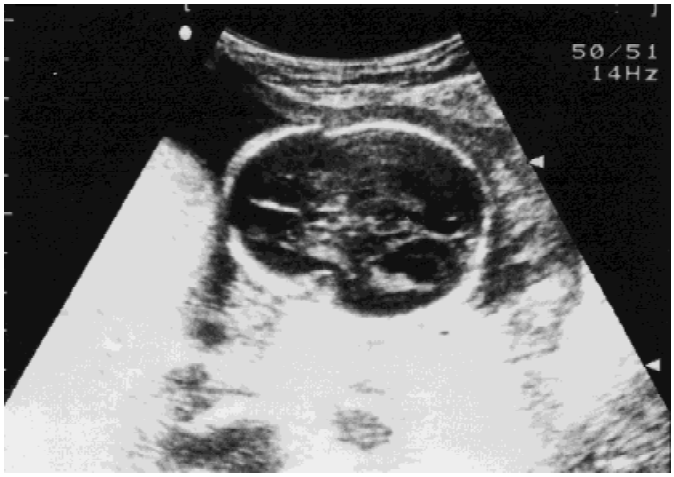

Fig. 1—An abnormally shaped fetal head caused by a prominent frontal bone and prominent coronal sutures was noted on the axial scan at 23 weeks' gestation

involved in this pregnancy were unrelated and there was no history of congenital malformations, skeletal dysplasia, mental retardation, or diabetes mellitus. The paternal age was 36 years. The mother had a 2-year-old healthy son. She did not undergo any maternal serum screening test for Down syndrome during this pregnancy.

A sonographic examination at 23 weeks' gestation revealed a normal amount of amniotic fluid, a single fetus with a biparietal diameter of 5·4 cm equal to 21 weeks, an occipitofrontal diameter of 7·29 cm, a cephalic index of 74·1 per cent, a femur length of 3·2 cm equal to 19 weeks, and an abdominal circumference of 17·5 cm equal to 22 weeks. An abnormally shaped fetal head caused by a prominent frontal bone and prominent coronal sutures was noted (Fig. 1). Genetic amniocentesis revealed an interstitial deletion of the long arm of one chromosome 16, 46,XX,del(16)(q13q22) (Fig. 2). The parental karyotypes were normal. A further sonographic examination during termination at 25 weeks' gestation showed persistently prominent frontal bone and coronal sutures, and shortening of the long bones with the femur length measuring 3·4 cm, tibia 2·9 cm, fibula 2·8 cm, humerus 3·3 cm, radius 3·2 cm, and ulna 2·8 cm. The lengths of the long bones were below the tenth centile of Chinese fetal biometry. The shape of the long bones was normal. The abdominal circumference measured 21·1 cm, equal to 26 weeks. The biparietal diameter measured 6·3 cm, equal to 24 weeks. The occipitofrontal diameter measured 7·56 cm. The cephalic index was 83·3 per cent. The cerebral ventricles were normal. No abnormalities of the cardiovascular, urinary, central nervous, and gastrointestinal systems or spine could be identified. At birth, the proband weighed 560 g and measured 30 cm in length. She manifested specific craniofacial features of 16q deletion syndrome, i.e., a high prominent forehead, a large anterior fontanelle with prominent cranial sutures, hypertelorism, a broad and flat nose, upward slanting palpebral fissures, low-set malformed dysmorphic ears, a high-arched palate, micrognathia,

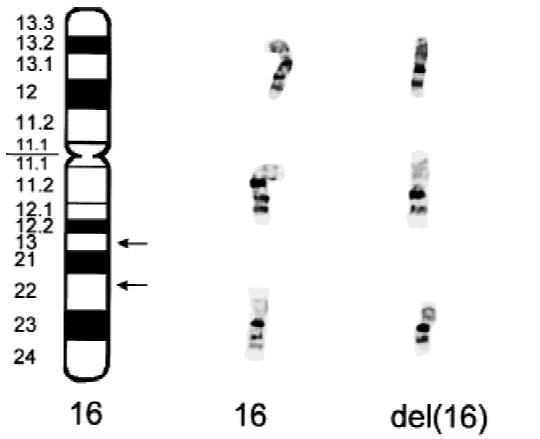

Fig. 2—Partial karyotype of the proband showing the abnormal chromosome 16, which is indicated by del(16). Arrows point to the diagram of a normal chromosome 16 indicating the breakpoints

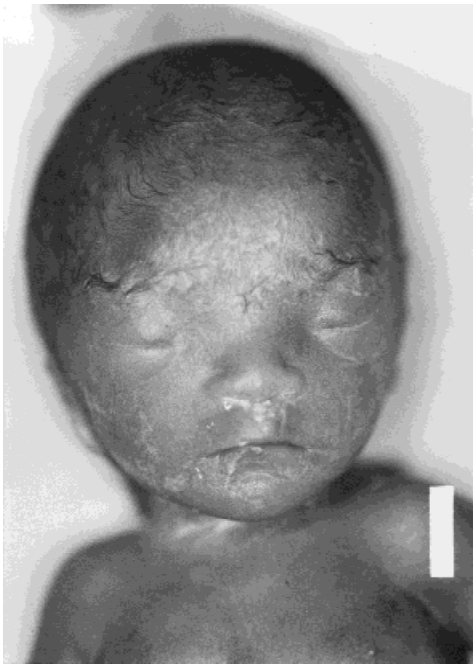

Fig. 3—Craniofacial appearance of the proband

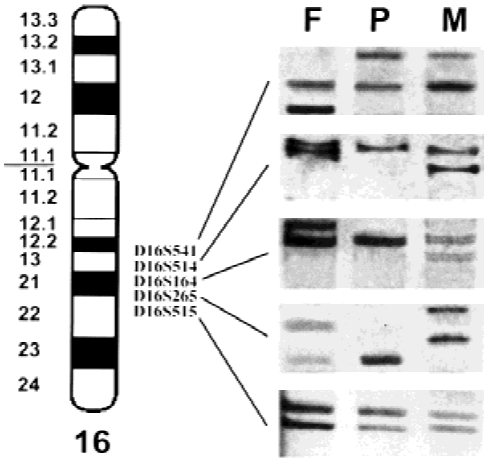

Fig. 4—Linkage analysis of the family showing maternal deletion of the marker D16S265 in the proband (P). The deletion breakpoints are found to map between the markers D16S541 and D16S514, and D16S265 and D16S515, respectively. M: mother, F: father.

and a short neck (Fig. 3). The neonate had additional findings of a narrow thorax, bilateral palmar creases, absence of distal creases of the fifth fingers, rhizomelic shortening of the arms and legs, overriding toes, broad big toes, and an imperforate anus. The gross appearance of the extremities was normal. The parents refused the suggestion of necropsy. Gross examination of the placenta was normal. The umbilical cord contained two arteries and one vein.

Genetic marker analysis

We investigated the extent and parental origin of the deletion by the use of genetic markers mapping to 16q. Genomic DNA was obtained from buffy coat cells of the parental blood and from the tissue of the proband. Approximately 200 ng of genomic DNA was amplified in a 50 μl polymerase chain reaction (PCR) mixture. Five sets of primers were used to amplify microsatellite DNA markers, i.e., D16S541, D16S514, D16S164, D16S265, and D16S515 (NIH/CEPH Collaborative Mapping Group, 1992; Murray *et al.*, 1994; Dib *et al.*, 1996). Amplification was carried out on a DNA Thermal Cycler (Perkin Elmer, U.S.A.) with 35 cycles at 95°C for 30 s and 55–62°C for 40 s. A 12 μl aliquot of each of the PCR products was analysed on 8 per cent sequencing gels. Visualization of bands was done by silver staining of the gels. Following drying of the gels, the bands were analysed by densitometry (UVP, U.S.A.). For the microsatellite markers D16S541 and D16S515, two alleles were seen in the proband, but for D16S514, D16S164, and D16S265, only one allele was present, D16S265 was informative with only one allele inherited from the father (Fig. 4). Genetic marker analysis showed that the deletion was of maternal origin. The deletion breakpoints were found to map between D16S541 and D16S514, and between D16S265 and D16S515, respectively.

DISCUSSION

Fryns *et al.* (1977, 1979, 1981, 1990a, 1990b) described malformed newborns with deletions in the long arm of chromosome 16 and proposed a clinical entity of monosomy 16q syndrome. About 25 cases of deletions of the long arm of chromosome 16 have been reported (Crawford *et al.*, 1967; Fryns *et al.*, 1977, 1981; Ferguson-Smith and Aitken, 1978; Taysi *et al.*, 1978; Duca *et al.*, 1981; Brenholz *et al.*, 1982; Lin *et al.*, 1983; Elder *et al.*, 1984; Hoo *et al.*, 1985; Rivera *et al.*, 1985; Cooke *et al.*, 1987; Krauss *et al.*, 1987; Natt *et al.*, 1987, 1989; Naritomi *et al.*, 1988; Witt *et al.*, 1988;

Casamassima *et al.*, 1990; Edelhoff *et al.*, 1991; Carter *et al.*, 1992; Fujiwara *et al.*, 1992; Schuffenhauer *et al.*, 1992; Trautmann *et al.*, 1993; Doco-Fenzy *et al.*, 1994). In addition, there are two reports with a phenotype of monosomy 16q syndrome but without demonstrable 16q deletion (Fryns *et al.*, 1979; Côté *et al.*, 1980). The common features of monosomy 16q syndrome include a low birth weight, feeding disturbances, hypotonia, a feeble suck, delayed growth and psychomotor development, mental retardation, a high forehead, a prominent metopic suture, a large anterior fontanelle with diastasis of the cranial sutures, hypertelorism, a broad nasal bridge, narrow palpebral fissures, low-set dysmorphic ears, micrognathia, a short neck, a narrow thorax, diverse skeletal anomalies of the head and trunk (i.e., microcephaly), large big toes, malpositioning of the toes, and a short stature with rhizomelic shortening of the limbs. Associated findings are congenital heart defects, an ectopic anus, hydrocephalus, intestinal malrotation, neural deafness, and renal hypoplasia. To our knowledge, five cases (Fryns *et al.*, 1981; Fryns, 1990a; Lin *et al.*, 1983; Naritomi *et al.*, 1988; Casamassima *et al.*, 1990; Edelhoff *et al.*, 1991) with an interstitial 16q deletion encompassing 16q21 and extending into both 16q13 and 16q22 have been reported. All had parts of the clinical craniofacial and skeletal features consistent with the syndrome. A comparison of our proband with the five previous patients is shown in Table I. The novel aspect of our case is the sonographic identification of fetal abnormalities which led to the prenatal diagnosis of del(16)(q13q22).

Table I—Craniofacial and skeletal features of our proband compared with five previous cases with a deletion of 16q13–q22

	Previous cases*	Present case
Craniofacial features		
Ventriculomegaly	2/5	No
Microcephaly	3/5	No
High forehead	5/5	Yes
Large anterior fontanelle	4/4	Yes
Diastasis of cranial sutures	3/4	Yes
Prominent metopic suture	4/4	Yes
Hypertelorism	4/4	Yes
Short palpebral fissures	3/5	Yes
Upslanting palpebral fissures	1/4	Yes
Downslanting palpebral fissues	2/4	No
Broad nasal bridge	3/5	Yes
Low-set dysmorphic ears	3/5	Yes
Cleft palate	1/4	No
High arched palate	3/4	Yes
Micrognathia	4/5	Yes
Skeletal features		
Short stature	3/5	Yes
Short neck	5/5	Yes
Narrow thorax	3/5	Yes
Flex fingers	2/3	No
Simian creases	4/4	Yes
Talipes equinovarus	2/5	No
Broad halluces	5/5	Yes
Malpositioning of toes	3/5	Yes
Scoliosis	1/1	No

*Adapted from Schuffenhauer *et al.* (1992) according to the clinical reports of Fryns *et al.* (1981), Fryns (1990a), Lin *et al.* (1983), Naritomi *et al.* (1988), Casamassima *et al.* (1990), and Edelhoff *et al.* (1991).

The critical region responsible for monosomy 16q syndrome has been proposed to be various locations including 16q21 (Fryns *et al.*, 1981; Fryns, 1990b; Lin *et al.*, 1983; Naritomi *et al.*, 1988; Edelhoff *et al.*, 1991), 16q12.2–q13 (Elder *et al.*, 1984), 16q22 (Fujiwara *et al.*, 1992), 16q11.2–q12.2 (Doco-Fenzy *et al.*, 1994), 16q21–q22 (Rivera *et al.*, 1985) and 16q13 (Schuffenhauer *et al.*, 1992). The deletions involving 16q21 and regions either proximal, i.e., 16q13, or distal, i.e., 16q22.1 (or both), apparently produce identical 16q deletion phenotypes (Schuffenhauer *et al.*, 1992). In this report, we have documented the first case of *in utero* manifestations of a fetus with a deletion of 16q13 to q22. Linkage analysis of the family confirmed the extent and maternal origin of the deletion. This deletion appears to include the chromosomal regions that are thought to be involved in the appearance of the clinical features associated with monosomy 16q syndrome.

The prominent forehead or high forehead can be a peculiar feature in many skeletal disorders, syndromes, and chromosomal aberrations (Schinzel, 1983; Buyse, 1990; Jones, 1997). Ultrasonography permits prenatal diagnosis of deformities of the fetal head and alterations in long bone growth. On the basis of our experience, we would recommend that prenatal detection of a prominent frontal bone with prominent cranial sutures and shortening of the long bones should prompt cytogenetic analysis looking for a deletion in the long arm of chromosome 16.

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