De novo unbalanced translocation resulting in monosomy for proximal 14q and distal 4p in a fetus with intrauterine growth retardation, Wolf-Hirschhorn syndrome, hypertrophic cardiomyopathy, and partial hemihypoplasia

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Abstract

We present the perinatal findings of a fetus with a de novo unbalanced chromosome translocation that resulted in monosomy for proximal 14q and monosomy for distal 4p. Prenatal sonographic examination at 27 weeks of gestation showed intrauterine growth retardation, microcephaly, cardiomegaly with arrhythmia, and asymmetry of the upper limbs. Genetic amniocentesis showed an abnormal karyotype of 45,XX,der(4)t(4;14)(p16.3;q12),-14. Linkage analysis of the family confirmed the maternal origin of the deletions. Molecular refinement of the deletion breakpoints indicated that the breakpoints at 4p16.3 and 14q12 were located between loci D4S403 (present) and D4S394 (absent), and between loci D14S252 (present) and D14S64 (absent), respectively. Necropsy showed dysmorphic features compatible with Wolf-Hirschhorn syndrome, hypertrophic cardiomyopathy, partial hemihypoplasia, and a normal brain without evidence of holoprosencephaly. Our case

adds to the list of clinical phenotypes associated with the proximal regions of 14q.

(J Med Genet 1998;35:1050-1053)

Keywords: chromosome 14; chromosome 4; prenatal diagnosis; hypertrophic cardiomyopathy

Prenatal diagnosis of monosomy for proximal 14q has rarely been described. We report a fetus with prenatal sonographic findings of intrauterine growth retardation, microcephaly, congenital heart defects, and asymmetry of the upper limbs. Diagnostic amniocentesis led to detection of a de novo unbalanced chromosome translocation resulting in monosomy for proximal 14q and distal 4p.

Case report

A 28 year old gravida 2, para 0, woman was referred to our hospital for confirmation of multiple fetal malformations during the late second trimester. The woman had previously experienced pregnancy loss owing to a blighted ovum. Her husband was 32 years of age. She and her husband, both Chinese, were healthy

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Received 10 December 1997
Revised version accepted for publication 24 April 1998

Figure 1 Partial karyotype of the proband showing chromosomes 4, der(4), and 14. Large arrowheads pointing to the derivative chromosome 4 indicate the break-rejoin junctions. Small arrowheads pointing to normal chromosomes 4 and 14 indicate the breakpoints.

Figure 2 Anterior view of craniofacial dysmorphism.

Figure 3 Lateral view of craniofacial dysmorphism.

Figure 4 Whole body view of the proband.

and unrelated. There was no family history of cardiomyopathy, hemihypoplasia, or congenital malformations. Prenatal sonography at 27 weeks' gestation showed a biparietal diameter of 5 cm (20 weeks), a femur length of 4.1 cm (23 weeks), an abdominal circumference of 15.9 cm (22 weeks), microcephaly, scalp oedema, a thick nuchal fold, cardiomegaly with dilated ventricular and atrial chambers, congenital A-V block, atrioventricular valve regurgitation, ventricular septal defect, and asymmetry of the upper limbs. Genetic amniocentesis showed an abnormal karyotype of 45,XX,der(4)t(4;14)(p16.3;q12),-14 (fig 1). The parental karyotypes were normal. The pregnancy was terminated at 29 weeks' gestation. At birth, the proband weighed 746 g and measured 30 cm in length. She had some features of Wolf-Hirschhorn syndrome (WHS), including low birth weight, microcephaly, prominent glabella, hypertelorism, epicanthus, high arched eyebrows, a broad nose, low set ears, micrognathia, haemangioma of the forehead, and flexion/contracture deformities of the hand (figs 2, 3, and 4). She also had scalp oedema, a puffy face, a short neck, hemihypoplasia of the right upper limb, wrist,

Figure 5 Whole body radiograph shows asymmetry of the ribs, marked shortening of the right humerus, radius, and ulna, and ipsilateral hypoplasia of the scapula.

Figure 6 Posterior view of the lungs and heart shows an enlarged heart (H), hypoplasia of the right lung (RL), a normal left lung (LL), and trachea (T).

hand, and pectoral muscles, and right sided brachydactyly (fig 4). A whole body radiograph (fig 5) showed asymmetry of the ribs, marked shortening of the right humerus, radius, and ulna, and ipsilateral hypoplasia of the scapula. However, unilateral hypoplasia was not noted in the calvaria, mandible, pelvis, or lower limbs. Necropsy further showed hypertrophic cardiomyopathy (HCM), a ventricular septal defect, hypoplasia of the right lung (fig 6), and agenesis of the right kidney, adrenal gland, ureter, ovary, and fallopian tube. The brain, spinal cord, skin, and subcutaneous fat tissues were normal. There was no evidence of holoprosencephaly. Neither atrophy of subcutaneous fat tissue and overlying skin nor unilateral erythema, scaling, or pigmentation changes could be identified. Other internal organs seemed normal on gross appearance. Examination of the placenta showed no abnormality. The umbilical cord contained two arteries and one vein. A cytogenetic study performed on Giemsa banded chromosomes from cord blood lymphocytes confirmed the same aberrant

Table 1 Results of the microsatellite analysis

Locus	Father	Proband	Mother	Inheritance
D14S72	a,b	a	a,c	Non-informative
MYH7	b,c	c	a,b	Paternal
D14S64	a,b	a	b,c	Paternal
D14S252	a,c	a,c	b,c	Biparental
D14S80	a,c	b,c	b,c	Biparental
D14S70	a,b	a,b	a,b	Biparental
D4S125	a,b	a	a,b	Non-informative
D4S412	a,b	a	c,d	Paternal
D4S43	a,c	c	a,b	Paternal
D4S394	a,b	b	a,b	Non-informative
D4S403	a,b	a,c	a,c	Biparental
D4S2960	a,c	c,d	b,d	Biparental

chromosome as was found in the amniocytes. A cell line is not available.

Genetic marker analysis

DNA was extracted from tissue samples of the proband and blood samples of the parents using standard methodology. Six polymorphic dinucleotide repeat markers (D14S72, MYH7, D14S64, D14S252, D14S80, and D14S70) for chromosome 14 and six DNA markers (D4S125, D4S412, D4S43, D4S394, D4S403, and D4S2960) for chromosome 4 were used to determine the breakpoints and the parental origins of the rearrangement. The marker loci were based on microsatellite maps of chromosomes 4 and 14.¹ To perform polymerase chain reaction (PCR), 20 ng genomic DNA was amplified in a 20 µl reaction mixture. Amplifi-

cation was carried out in a DNA Thermal Cycler (Perkin Elmer, USA) with 35 cycles at 95°C for 30 seconds and at 60°C for 40 seconds. A 12 µl aliquot of the PCR products was analysed on 8% sequencing gels. After silver staining and drying of the gels, the DNA bands were analysed by densitometry (UVP, USA) to estimate their intensities. The parental origins were determined by comparing the allele dosages. With the microsatellite markers D14S252, D14S80, and D14S70, two alleles were seen in the proband, but with D14S72, MYH7, and D14S64, only one allele was present (fig 7). The informative 14q markers MYH7 and D14S64 showed only one allele inherited from the father. Similarly, the proband inherited only one allele for markers D4S125, D4S412, D4S43, and D4S394 and two alleles for markers D4S403 and D4S2960 (fig 8). The informative 4p markers D4S412 and D4S43 showed only one allele inherited from the father. Genetic marker analysis showed that the proband did not have an allele inherited from the mother, thus the deletion of 14q and 4p was of maternal origin (table 1). Molecular refinement of the deletion breakpoints showed that the breakpoints at 4p16.3 and 14q12 were located between loci D4S403 (present) and D4S394 (absent), and between loci D14S252 (present) and D14S64 (absent), respectively.

Discussion

The critical region for WHS within 4p16.3 has been located between loci D4S168/FGFR3 and D4S166/D4S43, encompassing an interval of less than 750 kilobase pairs.^{2,3} Our patient had maternal origin of a terminal deletion of 4p with the breakpoint proximal to D4S43 and showed dysmorphic features compatible with WHS. Previous studies have shown no difference in the WHS phenotype in relation to differing parental origin of the distal 4p deletion. However, a distinct proximal 14q deletion syndrome has not yet been delineated and whether the particular parental origin of the deletion in certain regions of proximal 14q causes differences in phenotype remains unclear.^{4,5} In this paper we report phenotypic findings of proximal 14q deletion and an unusual association of maternally derived haploinsufficiency of MYH7 on proximal 14q with in utero HCM. Missense mutations in the β -myosin heavy chain gene on chromosome 14q11 are the most common cause of hypertrophic cardiomyopathy.⁶ The abnormal protein produced by the mutant allele of the β -myosin heavy chain gene can be incorporated into the contractile apparatus and disturbs cardiac contractile function despite the presence of a normal protein encoded by the other normal allele.⁷ However, such a dominant negative mutation may not be able to explain all occurrences of HCM, for example, as in an infant reported to have paternal isodisomy 14, 45,XY,idic(14)(p11),⁸ as well as the fetus we describe here. More cases are needed to elucidate the possible role of imprinting in this phenomenon.

The peculiarity of this case is the absence of holoprosencephaly (HPE), and the association

Figure 7 Linkage analysis shows maternal deletion of markers MYH7 and D14S64. The breakpoint is found to map between markers D14S252 (present) and D14S64 (absent).

Figure 8 Linkage analysis shows maternal deletion of markers D4S412 and D4S43. The breakpoint is found to map between markers D4S403 (present) and D4S394 (absent).

with partial hemihypoplasia and unilateral short limb. An HPE gene locus has been tentatively located on 14q11.1-q13.⁹ Levin and Surana¹⁰ reported a case of HPE with $\text{del}(14)(\text{q}11.1\text{q}13)$, and Bruyere *et al*¹¹ described another case of HPE with $\text{del}(14)(\text{q}11.1\text{q}13)$ or $(\text{q}11.2\text{q}21)$. Chen *et al*¹² presented a case of HPE with $\text{del}(14)(\text{q}13\text{q}21.1)$ or $(\text{q}13\text{q}21.2)$ and suggested an HPE locus on 14q13. The absence of holoprosencephaly in our case adds to the list of clinical phenotypes associated with the segment of chromosome 14 proximal to 14q12. Short limbs have been reported in cases of paternal and maternal uniparental disomy for chromosome 14.^{8 13-18} Our patient had unilateral short limb and partial hemihypoplasia with proximal deletion of chromosome 14q. However, short limbs and asymmetry have not been described in the seven previous case reports of proximal 14q deletion.^{4 5 10 11 19} The cause of asymmetry and hemihypoplasia in our patient is unknown but is possibly the result of abnormal vasculature or disruption of embryonic and fetal vasculature associated with the complex congenital cardiac defects.

This work was supported by a Research Grant (NSC-86-2314-B-195-006) to Chih-Ping Chen for fetal cerebral malformations from the National Science Council, Taiwan, ROC.

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