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

Chih-Ping Chen, Schu-Rern Chen, Chen-Chi Lee, Wen-Lin Chen, Ming-Hong Chen, Kuo-Ming Chang

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 D14S252 (absent) and between loci D14S64 (present) and D14S394 (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.

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

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.
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, haemangiomata 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, 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

<table>
<thead>
<tr>
<th>Locus</th>
<th>Father</th>
<th>Proband</th>
<th>Mother</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>D14S72</td>
<td>a,b</td>
<td>a</td>
<td>a,c</td>
<td>Non-informative</td>
</tr>
<tr>
<td>MYH7</td>
<td>b,c</td>
<td>c</td>
<td>a,b</td>
<td>Paternal</td>
</tr>
<tr>
<td>D14S64</td>
<td>a,b</td>
<td>a</td>
<td>a,b,c</td>
<td>Paternal</td>
</tr>
<tr>
<td>D14S252</td>
<td>a,c</td>
<td>a</td>
<td>a,b,c</td>
<td>Biparental</td>
</tr>
<tr>
<td>D14S80</td>
<td>a,c</td>
<td>b</td>
<td>b,c</td>
<td>Biparental</td>
</tr>
<tr>
<td>D14S70</td>
<td>a,b</td>
<td>a</td>
<td>a,b</td>
<td>Biparental</td>
</tr>
<tr>
<td>D4S125</td>
<td>a,b</td>
<td>a</td>
<td>a,b</td>
<td>Non-informative</td>
</tr>
<tr>
<td>D4S412</td>
<td>a,b</td>
<td>a</td>
<td>c,d</td>
<td>Paternal</td>
</tr>
<tr>
<td>D4S43</td>
<td>a,c</td>
<td>c</td>
<td>a,b</td>
<td>Paternal</td>
</tr>
<tr>
<td>D4S394</td>
<td>a,b</td>
<td>b</td>
<td>a,b</td>
<td>Non-informative</td>
</tr>
<tr>
<td>D4S403</td>
<td>a,b</td>
<td>a</td>
<td>a,c</td>
<td>Biparental</td>
</tr>
<tr>
<td>D4S2960</td>
<td>a,c</td>
<td>c,d</td>
<td>b,d</td>
<td>Biparental</td>
</tr>
</tbody>
</table>

The critical region of this WHS was delineated and whether the particular parental origin of the deletion in certain regions of proximal 14q causes differences in phenotype remains unclear. 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. 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 neonatal isodisomy 14, 45,XX, idic(14)(p11), as well as the fetus we describe here. More cases are needed to elucidate the possible role of imprinting in this phenomenon.

The peculiarities of this case are the absence of holoproencephaly (HPE), and the association...
with partial hemihypoplasia and unilateral short limb. An HPE gene locus has been tentatively located on 14q11.1-q13.7 Levin and Surana10 reported a case of HPE with del(14)(q11.1q13), and Bruyere et al11 described another case of HPE with del(14)(q11.1q13) or (q11.2q12). Chen et al12 presented a case of HPE with del(14)(q13q21.1) or (q13q21.2) 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 14q13. Short limbs have been reported in cases of paternal and maternal uniparental disomy for chromosome 14.813-18 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.151019 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.

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