Maternal uniparental heterodisomy of chromosome 14: chromosomal mechanism and clinical follow up

D Sanlaville, M C Aubry, Y Dumez, M C Nolen, J Amiel, M P Pinson, S Lyonnet, A Munnich, M Vekemans, N Morichon-Delvallez

Abstract
To our knowledge, 22 cases of chromosome 14 maternal uniparental disomy (UPD(14)mat) have been reported so far. The majority of cases were ascertained because of an abnormal phenotype associated with a Robertsonian translocation involving chromosome 14. We report here on a child with UPD(14)mat detected prenatally and resulting from trisomy rescue in a maternal meiosis I non-disjunction trisomic zygote. After four years of clinical follow up, in addition to intrauterine growth retardation (IUGR), only short stature and small hands and feet were observed. These clinical data as well as the ascertainment and mechanism of origin of UPD(14)mat were compared with those observed in previously reported cases. It appears that the clinical spectrum of UPD(14)mat is milder in our patient than in patients with UPD(14)mat resulting from other chromosomal mechanisms. In addition, a hypothesis based on abnormal imprinting is proposed to explain the variability of the UPD(14)mat.

Keywords: maternal UPD; chromosome 14; MCP; imprinting

Case report
A transabdominal chorionic villus sampling (CVS) was performed at 11 weeks of gestation in a 41 year old woman. Chromosome analysis of cytotrophoblastic cells showed a 47,XX,+14 karyotype in all 28 cells examined. Conversely, cells obtained after culture of the mesenchymal stroma showed a 47,XX,+14 karyotype in 11 of the 52 cells examined (21%). After counselling, an amniocentesis was performed at 16 weeks and a normal 46,XX karyotype was found in all 76 cells examined. However, molecular study of amniotic fluid cells showed the presence of chromosome 14 maternal heterodisomy (see below). An ultrasound examination performed at 20 weeks did not show any malformation. After genetic counselling, the parents decided to continue the pregnancy.

Fetal sonographic follow up showed intrauterine growth retardation (IUGR) at 25 and 33 weeks.
weeks (<3rd centile). A female infant was delivered by caesarean section at 35 weeks of gestation, weighing 1640 g with a height of 41 cm and a head circumference of 30 cm (all parameters below the 3rd centile). Clinical examination was normal except for the presence of median angiomas on the face and the nuchal area. A chromosomal analysis performed on cord blood showed a 46,XX karyotype in all 97 cells examined.

At 1 month of age, the child’s weight was 2230 g (−2 SD) and height 44 cm (−4 SD). Her head circumference was 33 cm (−1 SD) and she was developing well. At 15 months of age, her weight was 7.9 kg (−2 SD) and height was 71.2 cm (−2 SD). Both clinical examination and psychomotor development were normal. She was able to sit at 8 months and walked at 14 months and began to say several simple words. X-ray examination showed normal bone structure, and renal ultrasound and echocardiogram were normal. At 35 months of age, the child was still developing well. Fine motor skills and organised speech were acquired. No behavioural disorder was observed. At 4 years 4 months, the child’s height was 96 cm (−2 SD), her weight was 15 kg (−2 SD), and her head circumference was 48.5 cm (−1.5 SD). She had short hands and feet (−3 SD). Clinical examination was normal. Bone age was 3 years. Psychological examination showed that she was a pleasant child with good social contact. Testing with the Borel Maisonny Scale showed a developmental age of 3 years 9 months with a mild delay in drawing and spatial orientation. Therefore the child’s development was considered within normal limits (IQ=87).

### Methods

#### CYTOGENETIC STUDIES

Chromosomal studies of CVS (both direct and long term culture), amniotic fluid, and peripheral blood lymphocytes were performed using standard RHG banding.

#### MOLECULAR STUDIES

DNA was extracted from the parents’ leucocytes, amniotic fluid cells, and eight different sites of the placenta according to standard protocols. Nine evenly distributed microsatellite DNA markers were used to determine the parental origin of chromosomes 14, namely AFM 199 zF4, AFM 242 xa9, AFM 214 yg5, AFM 058 yh2, AFM 210 zh4, AFM 260 xb1, AFM 093 yg5, and AFM 234 we5 at loci D14S72, D14S80, D14S75, D14S63, D14S74, D14S67, D14S81, D14S65, and D14S78 and were obtained from the French Association against Myopathies. Paternity was tested using highly informative microsatellite DNA markers located on chromosome 5.

### Results

#### CYTOGENETIC RESULTS

The chorionic villus sampling showed the presence of confined placental mosaicism for trisomy 14 since all amniotic cells were 46,XX and no trisomic cell was observed in peripheral blood lymphocytes.

#### MOLECULAR RESULTS

Two chromosome 14 polymorphic loci were fully informative. For both loci, the proband’s DNA isolated from amniotic fluid cells showed heterozygosity and two alleles derived from the mother. Informative marker D14S63 is shown in fig 1. These findings are consistent with maternal uniparental heterodisomy of chromosome 14. In addition, multiple site analysis of term placenta showed a trisomic genotype with two maternal haplotypes and one paternal haplotype (fig 2).

Both non-paternity and maternal cell contamination of the amniotic fluid were excluded by studying additional polymorphic markers on chromosome 5 (data not shown).

### Discussion

Here we report on four years’ clinical follow up of a case of chromosome 14 maternal uniparental heterodisomy owing to trisomy rescue. To our knowledge, a total of 22 cases of

### Table 1

<table>
<thead>
<tr>
<th>Ascertainment</th>
<th>Hetero</th>
<th>Iso</th>
<th>Hetero/Iso</th>
<th>Total</th>
<th>Ref</th>
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<td>De novo rob and abnormal phenotype</td>
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<td>3</td>
<td>3</td>
<td>8</td>
<td>5,6,7,9,12,13,17,19 case 2</td>
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<td>1</td>
<td>4</td>
<td>3,14,15,19 case 1</td>
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<tr>
<td>Normal karyotype and abnormal phenotype</td>
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<td>1</td>
<td>1</td>
<td>3</td>
<td>16,21,22</td>
</tr>
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<td>Recurrent miscarriages</td>
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<td></td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>CPD/maternal age</td>
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<td></td>
<td>1</td>
<td>1</td>
<td>Our case</td>
</tr>
<tr>
<td>Mechanism of origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Maternal rob(14)(q10) or rob(14q14q) formation and complementation or aneuploidy correction</td>
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<td></td>
<td>1</td>
<td>6</td>
<td>4,6,12,13,17,19 case 2</td>
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<td>3,5,7,9,14,15</td>
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<tr>
<td>Aneuploidy and correction of a trisomic 14 zygote</td>
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<td></td>
<td>1</td>
<td>4</td>
<td>16,21,22, our case</td>
</tr>
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<td>1</td>
<td>1</td>
<td>19 case 1</td>
</tr>
</tbody>
</table>
Maternal uniparental heterodisomy of chromosome 14

Table 2  Clinical data of patients with UPD(14)mat

| Reference | UPD | MF/F | Iso/Hetero* | Hetero | Iso/Hetero | Hetero | Iso | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | Iso/Hetero | Hetero | ISO = isodisomy, Hetero = heterodisomy.

UPD(14)mat, including the present case, have been reported to date. Five cases were excluded because all the clinical or molecular data were not available.

Of the remaining 17 cases, six were associated with a rob(13q14q), six with an i(14)(q10) or a rob(14q14q), and one with a rob(14q21q). Only in four cases (including the present case) was UPD(14)mat not related to a Robertsonian translocation. With respect to UPD(14), seven cases resulted in heterodisomy, six in isodisomy, and four in both hetero- and isodisomy for chromosome 14 (table 1).

The different modes of ascertainment and the presumed mechanism of origin of the UPD(14)mat are listed in table 1. In the present case, the diagnosis was made prenatally through the detection of confined placental mosaicism and UPD(14)mat arose through loss of the paternal homologue in a maternal meiosis I non-disjunction trisomic zygote.

The clinical features associated with patients with UPD(14)mat are summarised in table 2. The most characteristic features are IUGR, hypotonia, short stature, short hands and feet, precocious puberty, and motor development delay. Among these, only precocious puberty appears to be constant. No specific dysmorphic features were described. Mental development was considered normal in 10 cases (10/15) and mildly to moderately delayed in five cases. In previous publications, hydrocephalus was noted in three instances but has not been reported since.

In the present case, in addition to IUGR, only short stature and short hands and feet were observed after four years of clinical follow up. This suggests that the clinical spectrum observed in our patient might be milder than in patients with UPD(14)mat resulting from other chromosomal mechanisms. However, one could argue that some of the features of UPD(14)mat may appear only during late childhood.

Low birth weight and small hands and feet are observed in both UPD(14)mat and distal maternal trisomy 14.23 This suggests that the molecular basis of these findings might result from a double dose of genes submitted to paternal imprinting and active on the maternal chromosome rather than from the absence of expression of maternally imprinted genes and active on the paternal chromosome, or a triple dose of genes not submitted to imprinting. Indeed, previous studies of UPD(14) suggested the presence of imprinted genes on this chromosome since similar clinical findings were observed in both maternal iso- and heterodisomy of chromosome 14.24 In addition, cases of paternal UPD(14) are more severely affected.25 So far, however, no imprinted genes have been identified on human chromosome 14 or on a conserved syntenic region on mouse chromosome 12, which is known also to be associated with imprinting effects.25 26 Also mosaicism for trisomy 14 in the connective tissue cannot be excluded.

Finally, an overlap with Prader-Willi syndrome (PWS) has been suggested recently.14 19 22 However, obesity does not seem to be as severe and hypogonadism and behavioural disorders are not constant features in UPD(14)mat. Therefore, the need to test for UPD(14)mat in patients with a Prader-Willi-like phenotype and a normal DNA analysis remains questionable.

In conclusion, our observation suggests that the UPD(14)mat phenotype might be related to the presence of a double dose of genes submitted to paternal imprinting and active on the maternal chromosome. In addition, the chromosomal mechanism of the trisomic rescue might be a modulating factor of the UPD(14)mat phenotype. Future clinical and molecular analysis of similar cases of UPD(14) need to be carried out in order to assess the relative frequency of this phenomenon and to derive risk figures for genetic counselling.

We thank Professor Marc Dommergues for his comments about this case and Fatima Fernandes for manuscript preparation.

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J Med Genet 2000 37: 525-528
doi: 10.1136/jmg.37.7.525

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