RESEARCH LETTER

Prenatal diagnosis of a ring chromosome 14 in a fetus with a severe skeletal dysplasia

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Ring chromosome 14 syndrome [r(14)] is a rare cytogenic disorder associated with growth retardation, facial dysmorphism, hypotonia, seizures and retinitis pigmentosa (Van Karnebeek et al., 2002). Here we report on a new case of r(14) in a fetus with severe skeletal dysplasia and clinical features reminiscent of the phenotype described in paternal uniparental disomy of chromosome 14 [upd(14)pat] (Curtis et al., 2006). The clinical features observed in the present case are compared to those reported in previously published cases of r(14) and upd(14)pat (Jean et al., 1997; Van Karnebeek et al., 2002; McGowan et al., 2002; Sutton et al., 2003; Kagami et al., 2005; Curtis et al., 2006).

A 34-year old G4P2 woman was referred at 19 weeks’ gestation because of a cystic hygroma and intrauterine growth retardation (IUGR) were observed on ultrasound examination. No known drugs, radiation or teratogenic exposure were reported. The couple was not consanguineous. The woman’s past obstetrical history revealed two early miscarriages and the birth of a healthy baby girl. Maternal serum screening performed at 16.4 week’s gestation showed elevated human chorionic gonadotrophin (hCG) (3.45 MoM) and alpha fetoprotein (AFP) (3.30 MoM) levels.

Detailed ultrasound examination performed at 18 weeks revealed the presence of multiple abnormalities: ascites, cystic posterior cerebral edema, narrow thorax with hyperechogenic lungs, short ribs, hepatomegaly. The biparietal diameter was 37 mm (10 percentile), the abdominal diameter was 43 mm (90 percentile) and the femoral length was 17 mm (<2.5 percentile). All feet, tibia, humeri and radii measurements were below the 2.5 percentile.

The association of short and long bones, large extremities, femoral curvuration was suggestive of a severe fetal skeletal dysplasia.

After genetic counseling the parents elected to terminate the pregnancy. Amniotic fluid was sampled for karyotyping at termination of pregnancy (20 weeks’ gestation). A female fetus was delivered and a necropsy was performed.

The fetus weighed 310 g and was 23 cm long. It showed generalized micromelia, cervical hygroma, a small bell-shaped thorax and a protruding abdomen. Facial features included a long prominent philtrum and retrognathism.

Autopsy revealed the presence of ascites, bilateral renal hypotrophy (combined weight : 1.12 g; expected weight : 2.4 ± 1.0 g) and cardiomegaly with right heart dilatation. The presence of tubular microcysts was noted in the cortical and medullar layers. Neuropathology examination revealed a small brain (<5th percentile) with abnormal organization of the cortical plate and of the subplate filled with heterotopic nodules. Longitudinal tracts were disorganized at the mesencephalic level.

X-ray examination confirmed the presence of short ribs and femora. The pelvis showed hypoplastic iliac bones. Mild platyspondyly was noted. Hands showed hypoplasia of distal phalanges. An absence of ossification of mid and distal phalanges of the 5th fingers was noted. (Figure 1(a) and (b))

Histological examination of the kidneys showed a normal cortico-medullar organization. Histological study of the epiphysal plate showed a regular cartilage-bone junction but poorly ossified cartilage columns (data not shown).

Cytogenetic analysis of 14 amniotic cells (RHG and GTG) showed a female karyotype. A ring chromosome 14 was observed in 50% of cells examined (Figure 1(c)). Seven metaphases showed 45 chromosomes with a missing ring 14 chromosome. The karyotype was interpreted as 45.XX,-14(7)/46,XX,r(14)(7). Parental karyotypes were normal.

FISH analysis was performed using BAC RP11-123M6 and BAC RP11-158A2 clones spanning respectively the MEG3 locus and the subtelomeric region.
In all metaphases, BAC RP11-158A2 and BAC RP11-123M6 were present on the normal chromosome 14. On the ring chromosome 14, BAC RP11-158A2 was deleted and the fluorescent signal of BAC RP11-123-M6 corresponding to the MEG3 locus was present but weak. (Figure 1(d) and (e)).

We concluded that the breakpoint was located in BAC RP11-123M6 between the MEG3 gene and the DLK1 gene located proximally (UCSC genome browser database).

Therefore the karyotype of the fetus can be described as 45,XX,-14/46,XX,r(14)(p11q32.2).

DNA was obtained from cultured amniotic fluid cells and from each of the parents. The methylation pattern of the MEG3 gene was studied (Murphy et al., 2003). PCR products were obtained using only paternally derived methylated allele specific primers. This result suggests that the maternal allele was absent (Figure 1(f)). Molecular analysis of eight polymorphic markers spanning the proximal part of chromosome 14 clearly indicated a biparental contribution (data not shown). We concluded that the ring chromosome 14 was maternal in origin and that the terminal deletion encompassed the MEG3 gene.

Here we report on a case of mosaic ring chromosome 14 diagnosed prenatally. Molecular and FISH studies of the ring chromosome showed a distal deletion of the 14q32.2-14qter region of maternal origin.

As shown in Table 1, the clinical features reported in the present case of ring chromosome 14 are unusual. The dysmorphic facial features classically described in patients presenting a ring chromosome 14 are absent. This can be explained by the early term of the pregnancy.
since precise dysmorphic description is difficult at this term. In the unique case of prenatally diagnosed ring chromosome 14, revealed by a 8 mm cystic hygroma, the pregnancy was terminated at 14 weeks of gestation (Jean et al., 1997). The features described in this case cannot be attributed to the monosomic cell line since we do not know its distribution in the fetus. Nevertheless, in all cases of ring chromosome, whatever the chromosome implicated is, the presence of a monosomic cell line never affects the phenotype.

The narrow thorax with abnormally curved ribs and generalized skeletal dysplasia observed here have never been reported in cases of ring chromosome 14 or linear terminal deletion of chromosome 14. They are rather suggestive of paternal upd(14), which is associated with a severe musculoskeletal phenotype radiologically characterized by a bell-shaped thorax and ‘coat-hanger’ appearance of the ribs (Table 1). A cluster of reciprocally imprinted genes has been identified at 14q32.2. MEG3, also referred as GTL2, encodes for a nontranslated RNA and shows a maternal monolelactic expression and DLKI mapping 90 kb proximal to MEG3, which encodes for a transmembrane protein that contains epidermal growth factor (EGF)-like repeat motifs and shows a paternal monolelactic expression. This domain presents spatial, structural and epigenetic similarities with the well characterized IGF2/H19 domain on chromosome 11 (Wylie et al., 2000). In the present case, the maternal allele of MEG3 has been deleted and the maternal allele of DLKI being preserved. We therefore postulate that the phenotype, particularly the radiological features observed in pat upd(14) and in the present case, results from a lack of expression of MEG3. Therefore, we can presumably explain the presence of features suggestive of pat upd(14) in this case of ring chromosome 14 by the extent of the deletion. It has been shown in effect that in cases of ring chromosome 14 or telomeric 14q32 deletions studied by FISH-mapping the breakpoints were always more telomeric than in the present case. The deletions never encompassed MEG3/DLKI region (Schlade-Bartusiak et al., 2005). We cannot explain why such extended deletions are not more often described, probably the severity of the phenotype impairs embryogenesis and fetal development and leads to early miscarriages.

In summary, a case of mosaic ring chromosome 14 was diagnosed prenatally in a fetus with a phenotype reminiscent of upd(14)pat. Molecular and FISH studies detected a maternal deletion of the 14q32.2–14qter region encompassing the MEG3 gene. This suggests that some of the phenotypic features observed in upd(14)pat might result from absence of expression of the MEG3 gene rather than over-expression of the paternally expressed DLKI gene.

REFERENCES