Trisomy 9 mosaicism in two girls with multiple congenital malformations and mental retardation

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Abstract
Two girls with mosaicism for an extra chromosome 9 are reported. Clinical findings included growth and mental retardation, facial dysmorphism, delayed ossification, single flexion crease, gastroesophageal reflux in one girl, and ventricular and atrial septal defects in the other patient. These findings are compared to the other previously reported cases of trisomy 9 mosaicism.  
(J Med Genet 1993;30:433-5)

Chromosomal aberrations are one of the most frequent causes of multiple congenital malformations/mental retardation (MCA/MR) syndromes.12 Full trisomy 9 is usually not viable,7 but trisomy 9 mosaicism has been reported in a few cases with a similar phenotype consisting of mental and growth retardation, congenital heart defect, and urogenital, craniofacial, and skeletal anomalies.34 In this study two girls with mosaic trisomy 9 and MCA/MR syndrome are described.

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Received 21 July 1992.  
Revised version accepted 9 September 1992.

Case reports
CASE 1
A baby girl was born in 1991 3 weeks preterm to a white gravida 8, para 4 mother. Two brothers aged 28 and 24 years and one sister aged 18 years are normal. The mother's reproductive history included a spontaneous abortion at 21 months, a child born at term, a second spontaneous abortion at 24 months, the proband, and a third spontaneous abortion at 21 months. The father, born in 1943, the mother, born in 1945, and the sibs are healthy. For two years the mother had taken fluoxetine for depression and it was taken through the whole pregnancy. Prenatal chromosomal diagnosis was refused.

Delivery was normal, birth weight was 2440 g, length 44 cm, and head circumference (OFC) 32.5 cm. Apgar scores were 10 at one and five minutes. Multiple dysmorphic features were seen.

The patient was first seen at our genetic department at 8 months of age because of poor weight gain and developmental delay. Weight (5000 g), height (58.5 cm), and OFC (39 cm) were all below the 3rd centile. Developmental milestones were at a 3 month level. Multiple dysmorphic features were observed (fig 1) including a large forehead, hypertelorism with short, downward slanting palpebral fissures, bilateral epicanthic folds and broad nasal bridge, protruding, thin upper lip, high arched palate, micrognathia, and low set, posteriorly rotated ears. The neck was short with redundant skin folds posteriorly. The chest had normal contours with hypoplastic, widely spaced nipples.

A single flexion crease and fifth finger clinodactyly were present bilaterally. Stridor was present from birth. Bone age was retarded (6 months). Transfontanellar ultrasonography and CT scan of the brain showed cortical and subcortical atrophy. X rays showed gastroesophageal reflux. Laryngoscopy was normal. Visual and ocular evoked potentials were normal.

CASE 2
This girl was born at 37 weeks after an uneventful pregnancy to a normal, white, gravida 1, para 1 mother aged 30 years. The 30 year old father was also normal. The parents were non-consanguineous. Delivery was normal, birth weight was 2470 g, height 47 cm, and head circumference 32 cm. Apgar scores were 10. Multiple dysmorphic features were seen (fig 2) including narrow temples, small palpebral fissures, bulbous nose, high arched palate, long philtrum, micrognathia, and low set, posteriorly rotated ears. Skeletal abnormalities were present at birth including bilateral club hand with ulnar deformity, calcaneovalgus deformity, hypomineralisation of the bones, and delayed ossification. A cardiac murmur was present and stridor was present from birth. There was a single flexion crease on the right and subdigital triradius c was absent bilaterally.

Developmental milestones were delayed. At 6 months of age she could not hold up her head.

Figure 1 Case 1.
CYTOGENETIC FINDINGS
Peripheral blood cultures were set up and harvested after 72 hours using standard techniques. The lymphocyte karyotype showed two cell lines, one with a normal karyotype and another with 47 chromosomes with three chromosomes 9. Based on the analysis of 100 RHG and QFQ banded cells, the proportion of 46,XX and 47,XX,+9 was 72% and 28% respectively for case 1 and 86% and 14% respectively for case 2. The karyotypes of both parents of case 1 and case 2 were normal.

Fibroblast cultures were set up from both patients. The proportions of 46,XX and 47,XX,+9 was 88% and 12% respectively for case 1 and 82 and 18% respectively for case 2. Unfortunately cell lines from these patients are not available.

Clinical manifestations of trisomy 9 mosaicism.

| Reference | % trisomic cells, lymphocytes | % trisomic cells fibroblasts | Sex | Birth weight (g) | Birth length (cm) | Growth retardation | Psychomotor retardation | Craniofacial anomalies | Microcephaly | Narrow temples | Craniosynostosis | Small palpebral fissures | Exophthalmos | Bulbous nose | High arched palate | Thin, protruding upper lip | Low set, malformed ears | Micrognathia | Ocular abnormalities | Skeletal abnormalities | Dislocated hips | Calcaneovalgus deformity | Joint hyperextension | Punctate mineralisation | Scoliosis/kyphosis | Hands | Simian crease | Overlapping fingers | CNS abnormalities | Seizures | Spasticity | Gross abnormalities | Cardiopulmonary abnormalities | Gastrointestinal abnormalities | Genitourinary abnormalities | Death | Present report |
|-----------|-----------------------------|----------------------------|-----|-----------------|-------------------|------------------|---------------------|----------------------|-------------|----------------|------------------|----------------------|--------------|--------------|-------------------|---------------------|-------------------|-----------------|-----------------|------------------|-------------|----------------|----------------|------------------|------------------------|---------------------|------------------------|----------------|----------------|----------------|----------------|------------------|---------------------|------------------------|----------------|----------------|----------------|----------------|----------------|------------------|------------------------|------------------|----------------|----------------|----------------|
| 3         | 48                          | 51                          | 12  | 42              | 21/0              | 5/8              | 13                | 44                  | 14                | 14            | 32            | 9                | 99                  | 15           | 8             | 11                | 10                 | 12                | 2               | 15               | 11               | 1              | 9               | 10                 | 9                 | 10                | 11             | 10              | 11               | 11              | 10                | 11               | 10              | 10              | 11               |
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Trisomy 9 were absent and because a severe midfacial malformation (absence of the nose and nostrils) was seen.

Comparison of the findings in mosaic trisomy 9 with those reported in complete trisomy 9, reviewed by Kaminker et al.,\(^1\) shows that the two phenotypes are similar. The clinical variability could be the result of a variable degree of mosaicism and differences in the location of the tissues involved. Our case 2, who had fewer trisomic cells in lymphocytes than case 1, is more severely affected than case 1. In most cases where fibroblasts were studied the percentage of trisomic cells was lower in fibroblasts than in lymphocytes. This was not the case in our case 2 who had more trisomic cells in her fibroblasts (18\%) than in her lymphocytes (14\%).

Our two patients are alive at 1 year and 6 months of age, respectively. Seven out of the 15 patients listed in the table died, most of them in the weeks following birth.

The clinical features of our case 1 are not related to the intake of fluoxetine by the mother during pregnancy as it has been shown that fluoxetine is not a teratogen.\(^1\)

The phenotypic signs of trisomy 9 mosaicism, which are similar to those of full trisomy 9, can be detected on fetal ultrasound\(^7\) and the fetal karyotype can then be studied to confirm the diagnosis.