

# Case reports

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## Prenatal diagnosis of a de novo non-fluorescent Y chromosome

**SUMMARY** We report a case with non-mosaic Yq-, missing the fluorescent segment, and detected as a fetus studied for advanced maternal age. The father had a Y chromosome of average size and paternity was established with a plausibility of 97.7% by HLA and erythrocyte antigen typing. The child had a normal male phenotype at delivery and developmental milestones were normal through the first year of life. The Yq- showed no mitotic instability since it was retained in foreskin culture for its in vitro lifetime of 60 population doublings.

De novo non-fluorescent Y chromosomes, often with mosaicism for an XO cell line, are reported to be associated with phenotypes ranging from normal males to females with Turner's syndrome.<sup>1-3</sup> Ascertainment bias favours phenotypic defects in reported cases. However, the incidence of Yq-, defined as Y/F ratio of less than 0.7, varies between 1.1 and 3.9 per 1000 in surveys of newborns.<sup>4</sup> The incidence of de novo non-fluorescent Y chromosomes at birth is not known. Macintyre *et al*<sup>5</sup> found a Yq- during prenatal cytogenetic analysis, but the father had a similar short Y chromosome. In the case reported here the Yq- in the fetus was not present in the father and interpretation of the fetal karyotype presented difficulties for both counsellor and parents.

### Case report

The proband had chromosome studies on cells cultured from amniotic fluid obtained at the 17th postmenstrual week. Indication for the study was the maternal age of 40 years at delivery. The father was 44 years old. Both parents were Caucasian, in good health, and had no physical defects. This was the couple's second pregnancy; the first ended 3 years earlier in a first trimester spontaneous abortion. The father had no children by a previous marriage. A four generation pedigree showed no genetic or birth defects on either side of the family.

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The fetal karyotype was interpreted as 46,XYq- and parental chromosomes were normal. During the postamniocentesis counselling, interview of parents suggested paternity. They were told that based on previously reported cases of 46,XYq- karyotypes, the fetus could fit into a spectrum of phenotypic development from a normal male to a Turner's syndrome female. They were also informed of the possibility of XO mosaicism as well as the unlikely chance of congenital defects if a reciprocal unbalanced translocation were involved. The testosterone concentration assayed from a stored aliquot of the amniotic fluid was 170 pg/ml, within the range for a male fetus (University of Pennsylvania, Dr M. Mennutti). However, this result was not known at the time of counselling. The parents elected to continue the pregnancy.

At 41 weeks' gestation, a phenotypically normal male, weighing 3380 g was delivered by caesarian section. At 5 months of age his developmental milestones and physical findings were normal, except for a single transverse palmar line and a distal axial triradius on the right hand. These two findings were not present in either parent. The infant's length was between the 25th and 50th centiles, weight was at the 25th centile, and head circumference at the 50th. His testicular size of 13 × 19 mm and stretched penis length of 38 mm (from suprapubic bone to tip of glans) were in the normal range for a 5 month old. At the age of 12 months developmental milestones were still on schedule but weight had fallen to the 5th centile.

### CHROMOSOME STUDIES

From amniotic fluid culture 50 metaphases were examined.<sup>6</sup> In all colonies and cultures a 46,XYq- karyotype was found (figure). On QFQ banding there was no fluorescent region on the presumed Y chromosome. No translocation between the Y and another chromosome was detected by QFQ, GTG or RHG banding. There was no evidence for satellite association of the deleted chromosome with D or G chromosomes. CBG banding did not show measurable C band in any region. Chromosomes of the mother and father were 46,XX and 46,XY respectively. The paternal Yq had a Q band and a C band of intermediate size. Alleged paternity was not excluded by fluorescent heteromorphism analysis. Measurement of photographs from ten Q banded

metaphases gave a ratio of  $0.96 \pm 0.04$  for the paternal Y compared to chromosome 20 in the same cell, and a ratio of  $0.61 \pm 0.03$  for the fetal Yq-. Similar measurements of the non-fluorescent region of the paternal Y chromosome and chromosome 20 gave a ratio of  $0.56 \pm 0.05$ , indicating that non-fluorescent material was not lost in this deletion. The Yq- was as long as the paternal Y non-fluorescent region and, furthermore, a measurable translocation to the Yq- could be ruled out. Compared to the Y measurements reported by Verma *et al.*,<sup>7</sup> the paternal Y reported here is of average size and occurred in 67% of the 60 phenotypically normal Caucasian males in their study. However, the fetal Yq-/20 ratio of 0.6 reported here is classified as very small and did not occur in their series.

The same Yq- morphology was seen in all metaphases from cord blood obtained at delivery (Yq-/20 ratio =  $0.59 \pm 0.05$ ) and in a primary culture of foreskin fibroblasts. Studies at 10, 20, 30, 40, 50, and 60 population doublings from the first subculture of fibroblasts continued to show the Yq- in every metaphase examined. Thus the deleted Y was stable through successive somatic divisions in vitro and did not produce a 45,X cell line.

A buccal smear from the child was negative for X and Y bodies. The father's buccal smear was positive for Y bodies of average size and frequency.

**HLA AND ERYTHROCYTE ANTIGEN TYPING**

Studies for plausibility of paternity are summarised in the table. These tests did not exclude the alleged father from paternity. Moreover, the plausibility of paternity  $\left[ W = \left( \frac{X}{X + Y} \right) 100 \right]$  was 97.7% (see

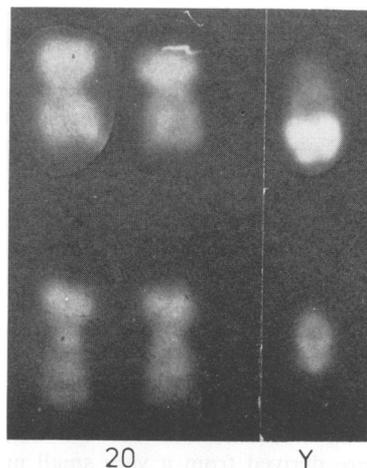


FIGURE Partial karyotypes showing chromosomes 20 and Y from the father's lymphocytes (top) and amniotic fluid cells (bottom).

footnote to the table). Only six in 10 000 random Caucasian males carry the combination of obligatory genes needed by the biological father (the value for Y being 0.0006; see footnote to the table).

**Discussion**

It has been postulated that 45,X/46,XYq- results from mitotic loss of the deleted Y and emergence of a 45,X cell line.<sup>2</sup> We found no evidence for mitotic instability of the Yq- in the foreskin culture established from our case and maintained through 60

TABLE Studies for plausibility of paternity

System	Alleged father	Mother	Child	Obligatory genes*	Gene frequencies of sperm	
					Alleged father (x)	Random male (y)
ABO	O	A	O	O	1	0.6604
MNS	MNSs	MNs	Ns	Ns or M <sup>g</sup> s or M <sup>k</sup>	0.4250	0.3878
Rh	D+,C+,E+, c+,e+	D-,C-,E-, c+,e+	D+,C+,E-, c+,e+	D + C + e +	0.4900	0.3905
Kell	K-	K-	K-	k	1	0.9600
Duffy	Fya+b+	Fya+b+	Fya+b+	Fy <sup>a</sup> or Fy <sup>b</sup>	0.5000	0.4910
Kidd	Jka+b+	Jka+b-	Jka+b+	Jk	0.5000	0.4899
HLA	A2,A10, B7,B15	A11,A29 B8,B12	A2,A29, B12,B15	A2,B15	0.5000	0.0260

\*Genes which must be carried by fertilising sperm.

x = individual probabilities that the alleged father carries certain tested obligatory genes.

y = individual probabilities that a random male carries the same tested obligatory genes. Probabilities for random male are from Albert *et al.*<sup>9</sup> and Walker.<sup>10</sup>

X = (x<sub>ABO</sub>) (x<sub>MNS</sub>) (x<sub>Rh</sub>) ... = probability that alleged father carries all the tested obligatory genes needed by the biological father = 0.026.

Y = (y<sub>ABO</sub>) (y<sub>MNS</sub>) (y<sub>Rh</sub>) ... = probability that a random male carries all the tested obligatory genes needed by the biological father = 0.0006.

Plausibility of paternity  $W = \left( \frac{X}{X + Y} \right) 100 = \left( \frac{0.026}{0.0266} \right) 100 = 97.7\%$

population doublings. However, this in vitro test may or may not duplicate in vivo conditions producing loss of the Yq-. The degree of deletion may also be a factor in its instability.

When the fetus has a Y chromosome without the fluorescent segment, since the phenotype is unknown, it is important to quantify the size of the fetal and paternal Y chromosomes and compare them to standards for variation in the size of normal Y chromosomes. The availability of testing for HLA and H-Y associated antigen on amniotic fluid cell cultures would have helped to establish paternity and the presence of the Y chromosome, respectively, in the case of the de novo Yq- reported here. However, the possibility of a small translocation or mosaicism for 45,X would have remained. Existing methods do not rule out this possibility. The cultures are derived from a very small number of cells which proliferate in vitro. Mosaicism can be missed because these few cells may not be representative of the fetus. Furthermore, evidence indicates that the major cell type in second trimester amniotic fluid cell cultures is derived from trophoblastic tissue and, as such, represents fetal membranes but not the fetus proper.<sup>8</sup>

Since they lacked complete knowledge of the consequences of the Yq- chromosome, the parents' decisions in this case were influenced in a major way by their fear of aborting a child that could be normal, their concern that another pregnancy would not be possible, and their willingness to raise a child who might have clinical abnormalities.

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## 13q-/r(13) mosaicism

**SUMMARY** A 2-month-old female infant with typical features of the 13q- syndrome was found to be a hitherto unreported mosaic consisting of 46,XX,del(13)(q22)/46,XX,r(13)(p13q22). Both of the 13q- and r(13) chromosomes were AgN banding positive. Therefore, it was assumed that they had retained the satellite stalks. Two possible mechanisms were proposed for the genesis of the mosaicism. Firstly, the patient started with the 13q- chromosome, which then underwent breakage and reunion at both ends to form the r(13) chromosome. Secondly, the patient started with the r(13) chromosome, which reopened at or close to the joining point to form the 13q- chromosome.

More than 70 cases of 13q- syndrome have been reported. They include both those with a chromosome 13 with a partial deletion of the long arm (13q-), and those with a ring chromosome 13[r(13)].<sup>1,2</sup> However, there has been no instance

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