An XY/XYY Mosaic Cynomolgus Monkey (*Macaca fascicularis*)

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Chromosomal abnormalities have not often been reported in primate species other than man, possibly due to the relatively small number of individuals studied. The overall frequency of chromosome abnormalities in the human newborn population is estimated to be approximately 0.6% (Nielsen and Sillesen 1975). Among such chromosome abnormalities in humans, an XYY sex-chromosome condition is comparatively common. The frequency of the XYY condition among the newborn male population is 0.1%, with a further 0.02% showing mosaicism involving an XYY cell line (Nielsen and Sillesen 1975, Hook and Hamerton 1975, Jacobs 1979). The XYY condition has also been described in laboratory mice and rats (Cattanach and Pollard 1969, Rathenberg and Muller 1973, Evans *et al.* 1978, Das and Kar 1981, Yoshida 1984). A mosaic condition involving the Y chromosome has occasionally been observed in laboratory mice (Evans *et al.* 1969, Evans 1982, Das and Behera 1984), bulls (Dobryanov and Konstantinov 1970, Hanada and Muramatsu 1981, Miyake *et al.* 1984), the horse (Höhn *et al.* 1980) and a wild common shrew (Searle and Wilkinson 1986). Therefore, the frequency of identification of chromosome abnormalities in nonhuman primates can be expected to increase as more individuals are investigated.

To our knowledge, there have been no reports on the XYY condition in nonhuman primates. During a routine cytogenetic survey of the breeding colony of cynomolgus monkeys (*Macaca fascicularis*) at TPC (Tsukuba Primate Center for Medical Science, National Institute of Health) using blood specimens, we found an adult male that showed two distinct cell lines of differing chromosome constitution: 42, XY and 43, XYY. The present report summarizes cytogenetic findings of this case.

Materials and methods

Animal

The animal examined (ref. no. YY-11) was born in March, 1976 at the laboratory primate facility of NIH in Tokyo and moved to the breeding colony of TPC in 1978. The physical status at birth was normal, and the weight was 340 g. The pedigree of the propositus is presented in Fig. 1. The parents had the same father (ref. no. 5825, a wild-originating male) but different mothers (half-brother-sister inbreeding). YY-11 grew well physically, showing normal behavioral and sexual maturation. However, this individual was euthanized under anesthesia in December, 1984, because he had been severely emaciated exhibiting weight and total hair losses. At autopsy, no pronounced pathological changes were observed in any of the internal organs. The kidney tissue and the left testicle were removed for chromosome studies immediately after death.

Somatic cells

- Peripheral blood lymphocytes were cultured in RPMI 1640 medium supplemented with

20% fetal calf serum (FCS) and 3% phytohemagglutinin (PHA). After 46 hr of culture, chromosome preparations were made. Approximately 1 g of the kidney tissue was minced with a pair of scissors and cultured in Eagle's minimum essential medium supplemented with 10% FCS. After 7 days of culture in a CO₂ incubator, the proliferating cells were used for chromosome preparations.

Germ cells

Chromosome preparations were made according to the method of Meredith (1969) with slight modification. Spermatogonial cells, primary spermatocytes at stages between late diplotene and metaphase I (MI), and metaphase II (MII) spreads were scored with respect to sex-chromosome complement and pairing configurations.

Fig. 1. Pedigree of the XY/XYX mosaic cynomolgus monkey (*Macaca fascicularis*).

Table 1. Distributions of chromosome counts in cultured lymphocytes, kidney cells and spermatogonia of the XY/XYX mosaic cynomolgus monkey

	Number of cells	Chromosome counts						
		<40	40	41	42 ^a	43 ^b	44 ^c	44<
Lymphocytes	300	2	1	7 ^d	247	42	1	—
Kidney cells	92	1	—	1	85	5	—	—
Spermatogonia	23	—	—	—	22	1	—	—

^a 42, XY

^b 43, XYX

^c 44, XYYY

^d One cell with an additional Y chromosome is included.

Results and discussion

Cytogenetic findings are summarized in Table 1. Of 300 lymphocyte metaphases analyzed, 42 cells (14%) showed an extra chromosome having an identical size and shape to the Y chromosome (Fig. 2). The additional chromosome was confirmed to be the Y chromosome by both C-banding and high resolution G-banding analyses. No structural abnormalities were found in either the autosomes or the X chromosome. One cell was found to possess two extra Y chromosomes (44, XYYY). Since the culture time was 46 hr, it is unlikely that the cells had passed two cell cycles after culture initiation. Thus, the cell with an XYYY sex-chromosome constitution was considered not to be the product of non-disjunction *in vitro*. It is, however, unclear whether there was another cell line with an XYYY condition *in vivo*.

Examination of the kidney chromosomes indicated that the frequency of cells with the

XYY sex-chromosome condition (5.4%) was significantly lower than in lymphocytes ($\chi^2=4.12$, $P<0.05$). In spermatogonial cells, however, the incidence of such XYY cells (1/23) was not significantly different from those in lymphocytes ($\chi^2=0.99$, $P>0.25$) and kidney cells ($\chi^2=0.10$, $P>0.75$). It is not known whether these results indicate tissue differences in the rate of occurrence of XYY cells *in vivo* because the number of cells scored was small. Hypodiploid cells observed in both lymphocyte cultures and kidney cells were considered to be due to cell breakage during chromosome preparation. There was no evidence to suggest the presence of an XO cell line.

Fig. 2. Mitotic spreads of cultured lymphocytes from the XY/XYY mosaic cynomolgus monkey. (a) Normal karyotype showing one Y chromosome. (b) Abnormal karyotype showing two Y chromosomes. Arrows indicate Y chromosomes.

Fig. 3. (a) Normal primary spermatocyte spread showing an X-Y pairing configuration (arrow). (b) Normal meiotic MII spread ($n=21$) showing a Y chromosome (arrow).

Good numbers of late diplotene/diakinesis/MI and MII spreads were obtained (Fig. 3). Among the meiotic spreads analyzable (64 primary spermatocytes and 16 MII), however, the YY condition was not detected. Difficulties were encountered in scoring meiotic chromosomes because they often looked fuzzy. Moreover, the size of the Y chromosome was very small. This may sometimes have led to an underestimate of the number of Y chromosomes. The

discrepancy in the incidence of YY cells between spermatogonia and spermatocytes may be interpreted as being due to either the above-mentioned underestimation because of difficulties in scoring, or a mechanism resulting in selection against cells with the YY complement.

The presence of the XY and XYY cell lines in the three different systems suggests that the mosaicism arose by nondisjunction of the Y chromosome during an early mitotic division of an XY embryo with loss of the XO line. The results of pedigree studies indicated that no other members showed chromosomal abnormalities. The consanguinity of this pedigree did not seem to be associated with the occurrence of the mosaicism, although no evidence for this was available.

The physical characteristics associated with the XYY genotype in humans have been described in detail (for review, see Welch 1985), although such associations are sometimes controversial (Stewart 1982). The physical findings include above-average height, increased tooth size, psychological and hormonal deviations, and impairment of spermatogenesis. As for an XY/XYY mosaic condition in humans, however, no marked phenotypic abnormalities have been described so far. In the microscopic preparations of the germ cells from our XY/XYY cynomolgus monkey, sufficient numbers of cells at every spermatogenetic stage including spermatozoa were observed. Therefore, the spermatogenetic activity of this individual was considered to be normal.

In platyrrhine monkeys, Y-autosome translocations are common (Ma *et al.* 1975, 1976, Armada *et al.* 1987). Several cases of numerical chromosome abnormalities have been described in catarrhine monkeys and apes (McClure *et al.* 1969, Weiss *et al.* 1973, De Grauchy *et al.* 1973, Andrie *et al.* 1979). These results, although derived from a small number of individuals, suggest that the number of cases of chromosome abnormality might increase as more population surveys are performed.

Summary

In the course of a cytogenetic population survey of the cynomolgus monkeys in the breeding colony of the Tsukuba Primate Center for Medical Science, we found a phenotypically normal male with an XY/XYY mosaic sex-chromosome condition. The mosaic sex-chromosome complement was observed in cultured lymphocytes, kidney cells and spermatogenic cells. However, no such mosaicism was detected in spermatocytes.

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