A Case of XYY Down's Syndrome Confirmed by Autoradiography

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Double aneuploidy in Down's syndrome was first described by Ford *et al* (1959) in a patient showing both Down's and Klinefelter's syndromes. Since then, at least 33 further cases of Down's syndrome have been described with additional aneuploidy (see Table). Approximately half of these are associated with autosomal aneuploidy, the remainder with abnormalities of the sex chromosomes among which are three definite examples of Down's syndrome with an additional Y chromosome. The first, a 9-year-old boy, was reported by Verresen and van den Berghe (1965); the second, a newborn infant, who died aged 7 weeks as a result of severe cardiac malformation, was reported by Uchida, Ray, and Duncan (1966). The third was men-

tioned in a personal communication by D. S. Borgaonkar, S. P. Borkowf, V. A. McKusick, and E. Mules (1969). Moreover, the small acrocentrics, reported by Hall (1963), in two unrelated males with Down's syndrome and in their phenotypically normal fathers, may have been Y chromosomes rather than Ph₁ chromosomes.

The present report records an example of an extra Y chromosome in a case of Down's syndrome in which it was possible to confirm the identity of the additional chromosome by autoradiography.

Case History

The patient, a male, born in April 1969 was the result of a first, uneventful pregnancy and vertex delivery; the ages of the mother and father at his birth were 24 years and 27 years, respectively. Birthweight was 3034 g but the length was not determined. The family history was

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(a)

(b)

FIG. 1. Patient at 3 months of age.

unremarkable; a paternal second cousin is retarded but not a mongol. At birth the propositus was slightly jaundiced but not cyanosed. On the fourth day the parents were told of the diagnosis of Down's syndrome and, later, referred to the Kennedy-Galton Centre for advice.

The baby was seen in July at the age of 3 months. There was no record of illness and, apart from slight feeding difficulties, he was gaining weight satisfactorily. At 2 months he had been admitted to a near-by hospital for permanent care.

At the time of examination, the baby was well nourished, eutrophic, and readily recognizable as a typical case of Down's syndrome (Fig. 1). His weight was 5580 g, length 59.5 cm, head length, breadth, and circumference were 134, 110, and 386 mm respectively, with a cephalic index of 0.82. A third fontanelle was present in a wide sagittal suture, the anterior fontanelle measured 3 × 3 cm. Further features of Down's syndrome included oblique palpebral fissures, epicanthic folds, Brushfield's spots, a high arched palate, protruding tongue, small asymmetrical ear lobes with angular overlapping helices, incurved fifth fingers, visible spaces between first and second toes, hypotonic musculature, dry marmorated skin. There was no heart defect and no apparent abnormality of the external genitalia: both testes were descended. Head control was absent; the baby did not smile but was able to follow objects with his eyes.

He was seen again at 12 months, during a period of convalescence after a severe intercurrent infection (bronchopneumonia sin.). His weight was 7031 g (hav-

ing been as low as 5220 g at 11 months), the length was 68.5 cm, head length, breadth, and circumference were 136, 117, and 407 mm respectively, cephalic index 0.86, the chest circumference 381 mm. He had acquired head control, could smile and laugh aloud, grasp and play with toys. He could not sit up unaided and could

TABLE
EXAMPLES OF DOWN'S SYNDROME WITH
ADDITIONAL ANEUPLOIDY

Additional Aneuploidy	No. of Cases	Authors	Symptoms of Down's Syndrome Prevailing
Translocation (13-15):(13-15)	7	T. W. J. Hustinx (1963, personal communication) Zergollern <i>et al</i> (1964) Richards, Stewart, and Sylvester (1965) Marsden <i>et al</i> (1966) Orye and Delire (1967) Ridler <i>et al</i> (1969) Ridler <i>et al</i> (1969)	+ + + + ? + +
Translocation (13-15):(19-20)	1	Gripenberg and Airaksinen (1964)	+
Trisomy 13-15	1	Becker, Burke, and Albert (1963)	+
Mosaic trisomy 13-15	2	Smith, Lips, and Howard (1965) Porter, Petersen, and Browne (1969)	+ -
Trisomy 18	1	Gagnon <i>et al</i> (1961)	-
Mosaic trisomy 18	4	Hsu <i>et al</i> (1965) Marks, Wiggins, and Spector (1967) Zellweger and Abbo (1967) Glogowska (1969)	- + + +
Mosaic trisomy 19-20	1	Gustavson and Ek (1961)	+
Tetrasomy 21-22	1	Townes (1968)	+
Klinefelter's syndrome	7	Ford <i>et al</i> (1959) Lanman <i>et al</i> (1960) Forssman and Lehmann (1962) Hustinx <i>et al</i> (1961) van Gelderen and Hustinx (1961) Hamerton, Jagiello, and Kirman (1962) Milcou and Maicanesco (1963)	+ + + + + + ?
Mosaic Klinefelter	1	Punnett and Di George (1967)	+
Mosaic Turner's syndrome	2	van Wijck, Blakenborg, and Stolte (1964) Zergollern and Hoefnagel (1964)	+ +
Triple X	2	Day <i>et al</i> (1963) Yunis <i>et al</i> (1964)	+ +
Double Y	4 (? + 2)	Verresen and van den Berghe (1965) Uchida <i>et al</i> (1966) D. S. Borgaonkar and others (1969, personal communication) present case (1970) Hall (1963) (? 2 cases)	+ + + + +

FIG. 2. Main dermatoglyphic lines on palms and soles of the patient.

FIG. 3. Karyotype of leucocyte culture from the patient showing 48 chromosomes with trisomy G and XYY.

not turn over. His general physical appearance was unchanged and was characteristic of a patient with Down's syndrome.

The dermatoglyphic main lines of the patient's hands and feet are illustrated in Fig. 2. There is no four-finger crease on either palm, but the radial loop on the right fourth finger, bilateral distal palmar triradii (ie, wide maximal *atd* angles, right 82°, left 87°) and absence of pattern in both hallucal areas are all features characteristic of Down's syndrome (Penrose and Smith, 1966). The total ridge count, which is usually low in both Down's syndrome and in patients with supernumerary sex chromosomes (Penrose, 1967; Penrose and Loesch, 1967), is 165 (6 ulnar loops, 3 whorls, 1 radial loop) in this case, which is above that of the male average (145). The father's total ridge count is 180 and the mother's 77.

The chromosomes of the patient were analysed in preparations from leucocyte and fibroblast cultures. From leucocyte preparations only the parents were both found to have normal karyotypes. In the propositus, a consistent diploid number of 48 chromosomes was found in both tissues. In all cells examined, there appeared to be G-trisomy, together with an additional small acrocentric chromosome showing the characteristic morphology of a Y. Autoradiographically, this chromosome showed a labelling pattern consistent with that of a late replicating Y. There was no suggestion of mosaicism (see Figs. 3 and 4).

Discussion

Autoradiography seems to be an adequate way of confirming the identity of the extra chromosome as a Y because there are two very similar, late replicating chromosomes. Thus, any ambiguity which may have arisen in previous cases (Hall, 1963) is ruled out.

However, the significance of the additional Y chromosome is, as yet, insufficiently understood. An XYY sex chromosome complement, without any abnormal phenotypical effect, may be found in the general population (Forssman, Akesson, and Wallin, 1968). It may, on the other hand, be associated with the typical combination of tall stature and psychopathic behaviour (Price and Whatmore, 1967; Welch, Borgaonkar, and Herr, 1967). Alternatively, YY aneuploidy may be discovered because cytogenetical studies are prompted by the presence of a specific pathological condition, such as in the present case. The Table shows that the stigmata of Down's syndrome dominate the other symptoms.

The patient investigated by D. S. Borgaonkar and others (1969, personal communication) was found to be above the 90th centile for length at 6

FIG. 4. Karyotype with tritiated thymidine autoradiography.

months of age. This finding cannot be confirmed by the present observation: the patient's length was in the 25th centile at 3 months and below the 3rd centile at 12 months of age. This seems more in accordance with the prevailing symptoms of Down's syndrome than those caused by the additional Y chromosome which seem clinically unobtrusive, though they may be difficult to assess at the present age of the patient.

The chance that a patient with G-trisomy has additional aneuploidy is the product of the fre-

quencies of each of these events in the population. If the incidence of Down's syndrome in this country is 1 in 700 (Penrose and Smith, 1966) and that of a male with an additional Y chromosome is approximately 1 in 700 males (Court Brown, 1968; Ratcliffe *et al*, 1970), then the incidence of YY males with Down's syndrome* is roughly the product of 1 in 700 and 1 in 700, ie, 1 in about 500,000 male births.

* The fact that the sex ratio of Down's syndrome births sometimes indicates a predominance of males (Penrose and Smith, 1966) is negligible in a rough estimate such as the present one.

If maternal age is taken into consideration, then the chance of this event occurring is more remote. A mother in the age-group 25–29 (as in the present case) has an absolute risk of 1 in 1200 (Penrose and Smith, 1966) of having a child with Down's syndrome. Thus, the risk among all births of a YY male mongol would be 1 in 840,000.

The question naturally arises as to why so few patients with similar chromosomal complements have hitherto been reported. A plausible answer may be found if the chance of this event's occurring (1 in 700 males) is applied to the approximate number of mongols karyotyped in Britain. Ridler *et al* (1969), when estimating the incidence of D/D translocations in British series of mongols, found a total of 2209 karyotyped mongols in 13 reported series. One would thus expect to find 1.5 YY cases in such a series.

Summary

An extra Y chromosome is reported in a case of a male infant with Down's syndrome. The identity of the Y chromosomes is confirmed by autoradiography.

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