

## Case reports

TRC in their XXXXY patients (Zaleski *et al.*, 1966; Korten *et al.*, 1975), while others have documented a decreased TRC, ranging from 28 to 118 ridges. In our patients, the TRCs were 64 and 58 ridges, in good agreement with Penrose's observed mean for 9 patients with an XXXXY chromosome complement.

Before this paper, leucocyte culture autoradiographic techniques with tritiated thymidine have shown the XXXXY chromosome pattern in several studies, but only de la Chapelle and Schroder (1973) and Korten *et al.* (1975) reported the use of trypsin-Giemsa banding techniques.

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## References

- Chopra, I. J., Ho, R. S., and Lam, R. (1972). An improved radioimmunoassay of triiodothyronine in serum: its application to clinical and physiological studies. *Journal of Laboratory and Clinical Medicine*, **80**, 729-739.
- Chopra, I. J. (1972). A radioimmunoassay for measurement of thyroxine in unextracted serum. *Journal of Clinical Endocrinology and Metabolism*, **34**, 938-947.
- de la Chapelle, A., and Schroder, J. (1973). Autoradiographically identified karyotype 49, XXXXY, t(4;11)(q 35; q 23) confirmed by banding. *Hereditas*, **74**, 291-292.
- Fraccaro, M., Kaijser, K., and Lindsten, J. (1960). A child with 49 chromosomes. *Lancet*, **2**, 899-902.
- Gardner, R. J. M., Sands, U. E., Veale, A. M. O., Howarth, D. A., and Parslow, M. I. (1972). XXXXY syndrome with mosaicism: case report. *New Zealand Medical Journal*, **74**, 22-27.
- Gorlin, R. J. (1974). Clinical manifestations of chromosome disorders. In *Human Chromosome Methodology*, p. 220. Ed. by J. J. Yunis. Academic Press, New York.
- Houston, C. S. (1967). Roentgen findings in XXXXY chromosome anomaly. *Canadian Radiologists Association Journal*, **18**, 258-267.
- Korten, J. J., Van Dorp, A., Hustinx, Th. W. J., Scheres, J. M. J., and Rutten, F. J. (1975). Self-mutilation in a case of 49, XXXXY chromosomal constitution. *Journal of Mental Deficiency Research*, **19**, 63-71.
- Pekary, A. E., Hershman, J. M., and Parlow, A. F. (1976). A sensitive and precise radioimmunoassay for human thyroid stimulating hormone. *Journal of Clinical Endocrinology and Metabolism*, **41**, 676-684.
- Penrose, L. S. (1967). Fingerprint pattern and the sex chromosomes. *Lancet*, **1**, 298-300.

Schalch, D. S., and Parker, M. L. (1964). A sensitive double antibody immunoassay for human growth hormone in plasma. *Nature*, **203**, 1141-1142.

Sinha, Y. N., Selby, F. W., Lewis, U. J., and Vanderlaan, W. P., (1974). A homologous radioimmunoassay for human prolactin. *Journal of Clinical Endocrinology and Metabolism*, **36**, 509-516.

Tenbrinck, M. S., Boyd, J. H., and Buchin, S. Y. (1976). The chromosome 49, XXXXY syndrome. Report of a case in an adult. *Arizona Medicine*, **33**, 546-551.

Zaleski, W. A., Houston, C. S., and Pozsonyi, J. (1966). The XXXXY chromosome anomaly: report of 3 new cases and review of 30 cases from the literature. *Canadian Medical Association Journal*, **94**, 1143-1154.

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## Dissociation as probable origin of mosaic 45,XY,t(15;21)/46,XY,i(21q)

**SUMMARY** A patient is described with some features of Down's syndrome and a 45,XY,t(15;21)(15qter → 15p13::21p11 → 21qter)/46,XY,i(21)(qter → cen → qter) karyotype. Two mechanisms are proposed for the origin of the mosaicism, one assuming the dissociation of a translocation (15;21) chromosome already present in the zygote, and the other involving a chromatid translocation in a 46,XY zygote. The possible independent origin of the two cell lines is also considered.

## Case report

The propositus (GB 260674) was born at term after an uneventful pregnancy and normal delivery; birth-weight was 3400 g. The parents were in good health and both were 32 years of age. The only sister, born in 1972, was normal. There was no history of abortions or other cases of congenital abnormalities in the family.

Examination at 2 years of age showed a healthy boy with normal neuropsychomotor development. His height was 86 cm, and his head circumference 47 cm. He had a flat face with depressed supraorbital ridges, discrete mongoloid slanting of the palpebral fissures, and bluish sclera. There was partial syndactyly between the 3rd and 4th digits on the right hand. The rest of the physical examination was normal.

Table Dermatoglyphic patterns

	Digits					TRC	Aid angle	Palmar formula	Hallucal areas
	I	II	III	IV	V				
Right	W	W	W	U	U	135	79°	11.9.7.5'.13t''-W*.O.O.L <sup>d</sup> .0	L <sup>d</sup>
Left	U	W	U	U	U		45°	11.9.7.5'.13t-O.O.O.L <sup>d</sup> .O	L <sup>d</sup>

Dermatoglyphs are summarised in the Table. The Walker index (Walker, 1957) was +0.34.

#### CYTOGENETIC STUDIES

Chromosome analyses were performed on peripheral blood lymphocytes. Chromosomes were identified through G-banding (Seabright, 1971) and Q-banding (Caspersson *et al.*, 1971). C-bands were obtained according to the method of Sumner (1972). Nucleolar organisers were stained using the Ag-As staining procedure of Goodpasture and Bloom (1975).

The patient had 45 chromosomes in 34 (68%) of the 50 cells analysed in routine Giemsa-stained preparations. A chromosome was missing in groups D and G, and an extra C chromosome was observed;

a C chromosome always showed a conspicuous secondary constriction in the short arm (Fig. 1a). Trypsin G-banding allowed the identification of the missing chromosomes as a 15 and a 21; the extra C was formed by the long arms of chromosomes 15 and 21. The centromere appeared to belong to chromosome 15 and the secondary constriction of its short arm seemed also to be present (Fig. 2a). These findings indicate a balanced translocation involving chromosomes 15 and 21. The remaining 16 cells (32%) analysed had 46 chromosomes. A chromosome 21 was missing and it was replaced by an isochromosome of the long arm of a chromosome 21 (Fig. 1b and 2b). Therefore, this line was trisomic for chromosome 21. No chromosome in the C group had a secondary constriction in the short

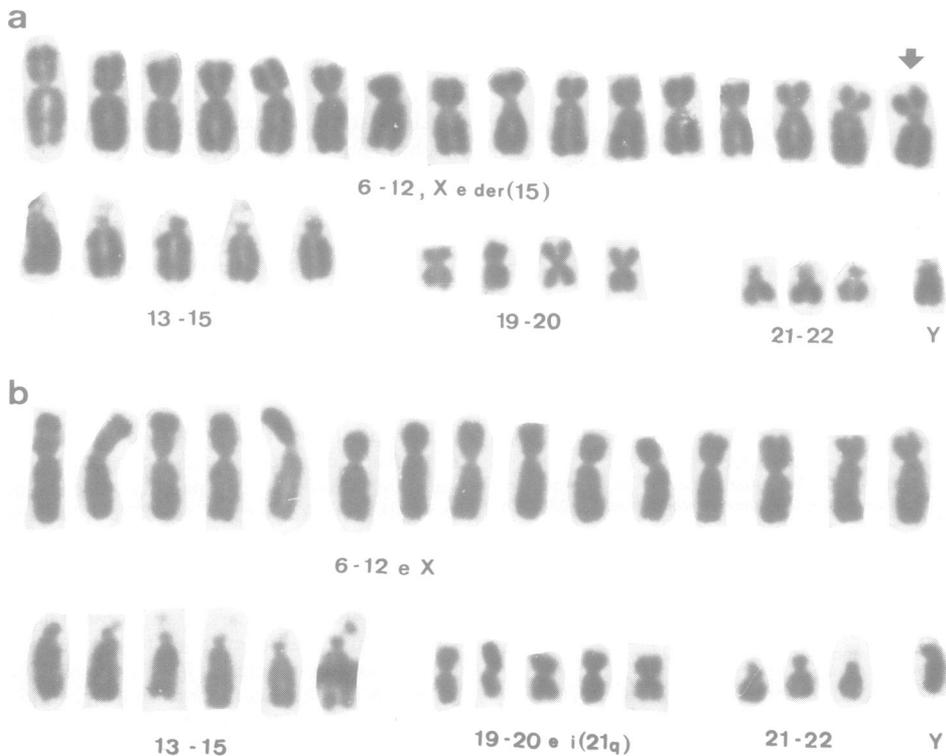


Fig. 1 Routine Giemsa partial karyotypes of (a) the translocation (15;21) line, and (b) the *i*(21q) line. Arrow points to the C with a constriction in the short arm.

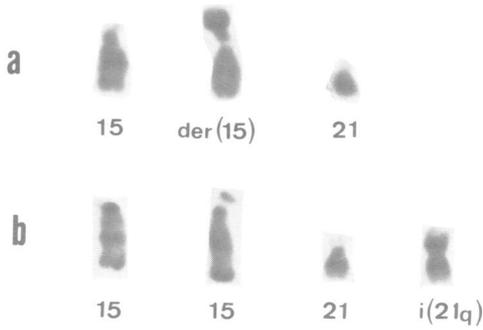


Fig. 2 G-bands of chromosomes 15 and 21 in (a) the translocation (15;21) line, and (b) the i(21q) line.

arm. In the normal D group a chromosome 15 had a very prominent satellite, not observed in the cells with the translocation t(15;21).

Q-banding showed the translocated 15/21 chromosome to possess a brightly fluorescent band on its short arm near the centromere. In the cells with 46 chromosomes, one of the 15 chromosomes had intensely fluorescent satellites.

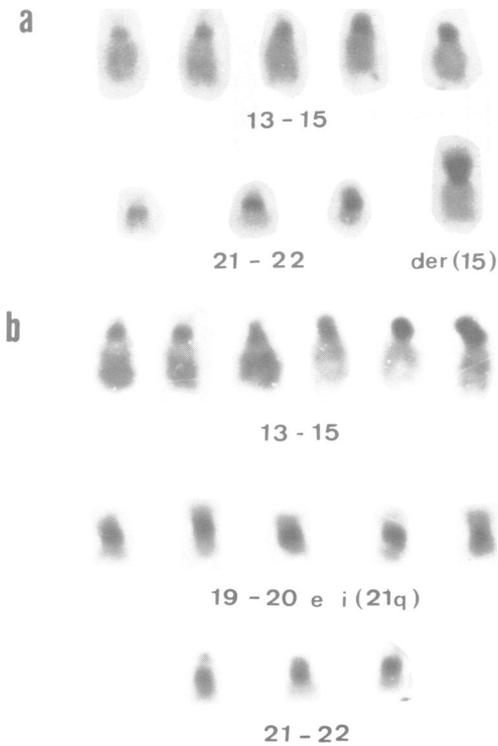


Fig. 3 C-banded partial karyotypes of (a) the translocation (15;21) line, and (b) the i(21q) line.

After C-banding, the cells with the t(15;21) showed a C chromosome with a heterochromatic block in the short arm, a little distance from the centromeric block (Fig. 3a). This was not seen in the 46,i(21q) cells, which had a D chromosome with a very prominent heterochromatic satellite. The isochromosome could not be picked out from the F-group (Fig. 3b).

The NOR-staining technique enhanced a region not far from the centromere on the short arm of a C chromosome in the cells with the t(15;21). In 1 out of 10 cells of this type that were studied, this region was associated with the Ag-stained segment of a G chromosome. In neither cell line did a D chromosome show a specially heavy staining (Fig. 4).

The translocation (15;21) chromosome may be interpreted as being formed by the long arm, centromere, secondary constriction, and satellite of a chromosome 15 plus the long arm and probably the centromere of a 21. The fluorescence pattern indicates the presence of the satellite of the 15. The hypothesis that the heterochromatic block on the short arm of the translocation (15;21) chromosome represents only the centromeric heterochromatin of chromosome 21 does not seem plausible, since that block is bigger than the pericentromeric one in the 21, and is more similar in size to the large heterochromatic satellite seen in one of the 15s in the 46,XY,i(21q) line. We may infer that

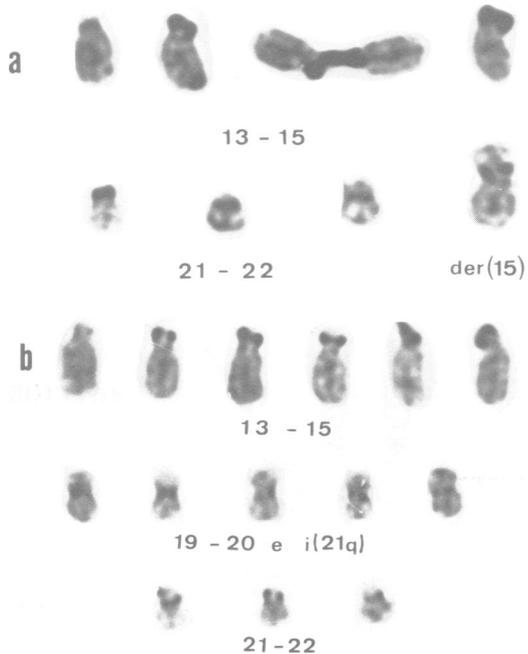


Fig. 4 Ag-As-stained partial karyotypes of (a) the translocation (15;21) line, and (b) the i(21q) line.

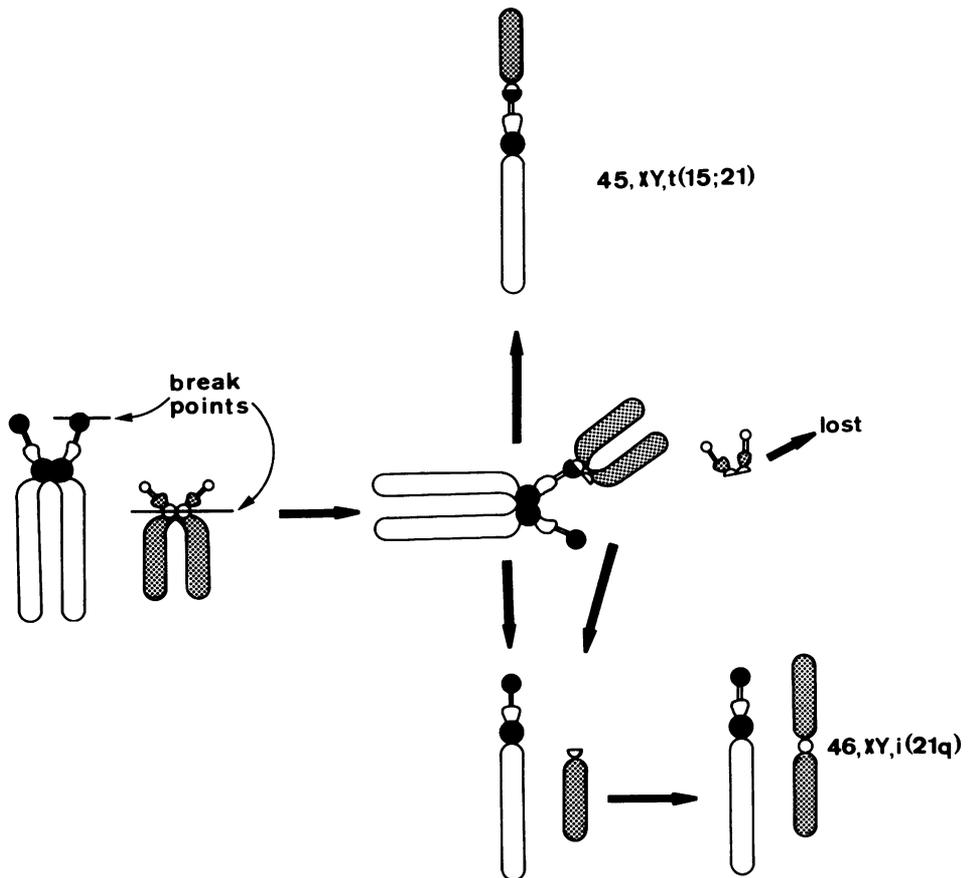


Fig. 5 Diagram showing the origin of the mosaicism  $45,t(15;21)/46,i(21q)$  from a normal zygote through a chromatid translocation (see text).

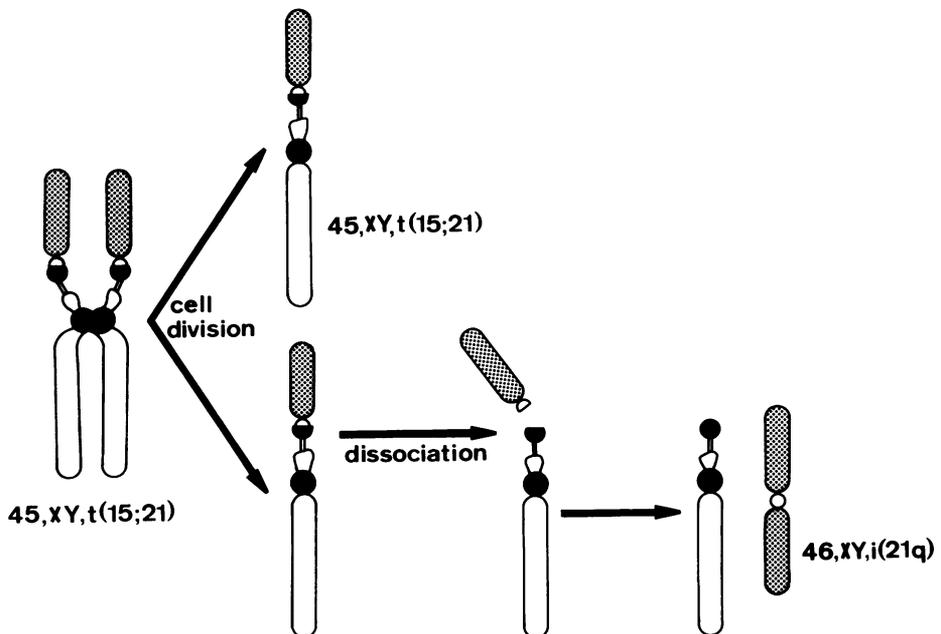


Fig. 6 Diagram showing the origin of the mosaicism  $45,t(15;21)/46,i(21q)$  from a  $45,t(15;21)$  zygote through the dissociation of the dicentric translocation chromosome (see text).

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the 15 involved in the translocation is the one with a big satellite in the other line.

Both parents and the normal sister of the patient have normal karyotypes. The father has one 15 with a large satellite.

## Discussion

The two cell lines may have arisen independently from the two first chromosomally normal blastomeres, as already suggested by Atkins and Bartsocas (1974) who described a similar mosaicism in a female infant with Down's syndrome.

On the other hand, a single event may produce both lines from a normal zygote with breaks occurring after DNA replication at the very tip of the satellite in one chromatid of chromosome 15 and at the centromere, or very near it, in the short arm of both chromatids of 21. One 21 chromatid would be translocated to the satellite of chromosome 15. At anaphase, this translocation chromatid and the normal 15 would have segregated, the latter going to the same pole as the remaining 21. The isochromosome would then be formed after DNA replication (Fig. 5).

Another alternative would be that the t(15;21) was already present in the zygote. The dissociation of the translocation chromosome would give rise to a 15 with 'healed' satellite, and an unstable telocentric 21 that would form the isochromosome (Fig. 6).

The two latter mechanisms imply the presence of the centromere of chromosome 21 in the translocation chromosome. This centromere would be latent in the sense that it would be nonfunctional to the extent of not competing with the 15 chromosome centromere.

Dissociation of dicentric into monocentric chromosomes have been described in humans. Angell *et al.* (1970) observed a few cells with dissociated chromosomes in two cases of dicentric Y chromosomes. Niebuhr (1972a) found a dicentric translocation 5/13, with loss of material from the short arm of chromosome 5 in a case of 'cri du chat' syndrome; in 4% of the cells, the dicentric appeared dissociated and the karyotype was 45,XX,5p-. Niebuhr (1972b) reported the dissociation of Robertsonian chromosomes 13/13 and 15/21 with two centromeres in some cells of two carriers. These chromosomes appeared otherwise to be very stable and the 15/21 translocation was familial. The dicentric D/D chromosome described by Jacobs *et al.* (1974) was found to be dissociated into two acrocentrics in 5 out of 60 cells.

These dissociations could be the result of occasional criss-cross separation of the dicentric chromatids. Breakage in the intercentromeric region and failure of reunion would lead to the formation of monocentric chromosomes. Sears and Câmara (1952) observed this behaviour

occasionally in a dicentric wheat chromosome during mitosis. Also, the point of reunion in the translocation chromosomes could be a structurally fragile site as noted by Pallister *et al.* (1974); the translocation involved the entire chromosomes 6 and 19, the latter contributing to the functional centromere. The translocation chromosome tended to separate spontaneously at the point of reunion, giving rise to a monocentric 19 and an acentric 6.

It is an interesting fact that in the instances where dissociation into stable chromosomes has occurred, the translocation usually involved the short arm of acrocentrics, and the breakpoints were located at or very near the telomere. It is possible that these regions have a high capacity for 'healing'. In the case of Niebuhr (1972a) the break was in a chromosome region (5p) not infrequently involved in terminal deletion and where an interstitial telomere (Hsu, 1963) could be present.

It is reasonable to suppose that the clinical signs of the patient are caused by the trisomic cell line. It is perhaps significant that in the case described by Atkins and Bartsocas (1974), in which the trisomic was the major line, Down's syndrome features were more striking than in our case.

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## References

- Angell, R., Giannelli, F., and Polani, P. E. (1970). Three dicentric Y chromosomes. *Annals of Human Genetics*, **34**, 39-50.
- Atkins, L., and Bartsocas, C. S. (1974). Down's syndrome associated with two Robertsonian translocations, 45,XX,-15,-21,+t(15q21q) and 46,XX,-21,+t(21q21q). *Journal of Medical Genetics*, **11**, 306-309.
- Caspersson, T., Lomakka, G., and Zech, L. (1971). The 24 fluorescence patterns of the human metaphase chromosomes-distinguishing characters and variability. *Hereditas, Genetiskt Arkiv*, **67**, 89-102.
- Goodpasture, C., and Bloom, S. E. (1975). Visualization of nucleolar organizer regions in mammalian chromosomes using silver staining. *Chromosoma*, **53**, 37-50.
- Hsu, T. C. (1963). Longitudinal differentiation of chromosomes and the possibility of interstitial telomeres. *Experimental Cell Research*, **9**, Suppl., 73-85.
- Jacobs, P. A., Melville, M., Ratcliffe, S., Keay, A. J., and Syme, J. (1974). A cytogenetic survey of 11,680 newborn infants. *Annals of Human Genetics*, **37**, 359-376.

- Niebuhr, E. (1972a). A 45,XX,5,-13,-dic+ karyotype in a case of cri-du-chat syndrome. *Cytogenetics*, **11**, 165–177.
- Niebuhr, E. (1972b). Dicentric and monocentric Robertsonian translocations in man. *Humangenetik*, **16**, 217–226.
- Pallister, P. D., Patau, K., Inhorn, S. L., and Opitz, J. M. (1974). A woman with multiple congenital anomalies, mental retardation and mosaicism for an unusual translocation chromosome t(6;19). *Clinical Genetics*, **5**, 188–195.
- Seabright, M. (1971). A rapid banding technique for human chromosomes. *Lancet*, **2**, 971–972.
- Sears, E. R., and Câmara, A. (1952). A transmissible dicentric chromosome. *Genetics*, **37**, 125–135.
- Sumner, A. T. (1972). A simple technique for demonstrating centromeric heterochromatin. *Experimental Cell Research*, **75**, 304–306.
- Walker, N. F. (1957). The use of dermal configurations in the diagnosis of mongolism. *Journal of Pediatrics*, **50**, 19–26.

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## Translocation of chromosome 4 and 9 with ring formation of chromosome 4 short arm

**SUMMARY** Cytogenetic investigation of a 3-year-old mentally retarded boy revealed a translocation of the long arm of chromosome 4 onto the short arm of chromosome 9, with ring formation of the remaining short arm of chromosome 4. The clinical features are described and correlated with the cytogenetic findings. The behaviour of the ring derived from a deleted chromosome 4 is discussed.

Structural abnormalities of chromosome 4 have been reported on many previous occasions. Borgaonkar and Dolling (1977) list over 40 translocations involving this chromosome, and the recipient has been found to include all chromosome groups except group F. In the C-group chromosomes, there is no report of chromosome 9 being involved in a translocation with chromosome 4. Deletion of the short arm of chromosome 4 has been sufficiently well documented to present a clinically identifiable syndrome, Wolf's syndrome (Guthrie *et al.*, 1971), but no distinct phenotype has yet been delineated for long arm deletions of this chromosome (Van Kempen, 1975). Ring formation of chromosome 4, however, has been reported very rarely, only 8 cases being quoted by McDermott *et al.* (1977), one of these showing a complex

rearrangement of chromosome 4 with ring formation (Bobrow *et al.*, 1971). We wish to report a complex abnormality, involving a translocation of chromosomes 4 and 9, with ring formation of the remaining portion of chromosome 4.

### Case report

A 3-year-old boy was referred for investigation of mental retardation of unknown aetiology. He was born 3 weeks prematurely, after an uneventful pregnancy and a prolonged labour, to young unrelated parents of normal intelligence. The father was 25 years old and the mother 27 years old. There was no history of miscarriages or stillbirths. His birthweight was 2200 g and he was placed in an incubator for 2 weeks postnatally because of respiratory problems (hyaline membrane disease?). At 2 months he had a severe attack of gastroenteritis necessitating intravenous fluid replacement, and he developed an ear infection at 6 months. He has had no serious infections since then. At 9 months of age his parents became concerned about his slow development. He sat

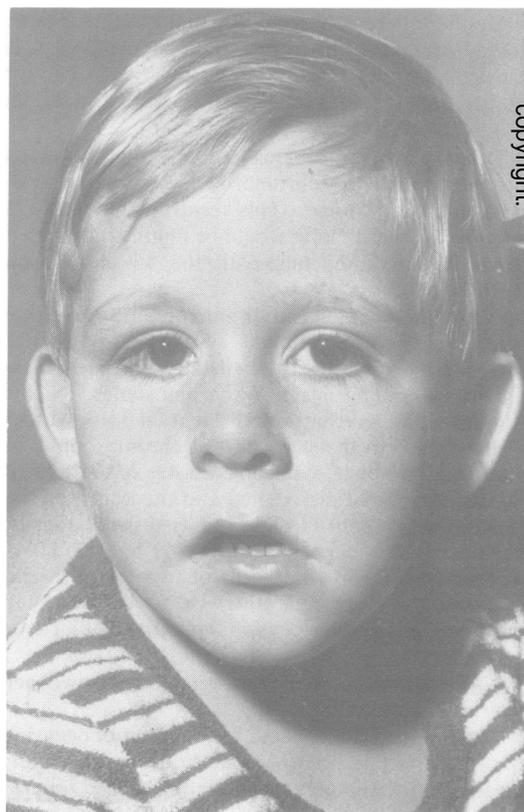


Fig. 1 Facial appearance of proband at 3 years of age.