GROUP B/D TRANSLOCATION CHROMOSOME IN A CASE WITH STIGMATA OF THE D TRISOMY

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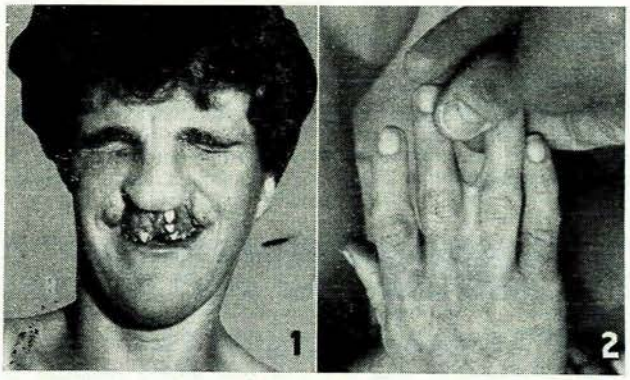
Several autosomal chromosome translocations have been reported. These generally involve 2 acrocentric chromosomes. Translocations have been described between group 13 - 15 and 21 - 22 as well as translocations between individual members of these 2 groups. It is less common to find translocations involving an acrocentric and a non-acrocentric chromosome.

The subject of this report presents with some of the physical stigmata of the D trisomy and with a large B/D translocation chromosome.

CLINICAL SUMMARY

The patient, a 35-year-old female, has been an inmate of the Witrand Mental Institution since 1937. The mother had been in poor health during her fourth pregnancy. Quinine tablets were taken in the first trimester for suspected malaria, and a threatened abortion, at that time, was treated by her medical practitioner. A baby, weighing 6 lb., was delivered normally. Several anomalies of the baby were noted at birth: a cleft palate, a hare-lip, with part of the upper lip attached to the nose, and eyeless orbits. The attachment of the lip to the nose was surgically corrected. Five other siblings, 2 of whom were born after the patient, were outwardly normal. There were no abortions or stillbirths. It was not possible to obtain blood for chromosome analysis from either the mother or any of the siblings.

Physical examination revealed a deaf and severely mentally retarded adult female, who was difficult to examine. Her height was 57 inches, span 56 inches and head circumference 20 inches. The physiognomy was striking: the vault of the skull was somewhat flattened, the orbits were eyeless, the nose broad and flat, and the ears malformed and a little low-set. A complete bilaterally cleft lip and cleft palate were present (Fig. 1). There were normal secondary sex characters and no cardiac anomaly could be detected clinically. There was webbing between phalanges 3 and 4, running up to the proximal interphalangeal joints (Fig. 2) and between toes 2 and 3.



Figs. 1 and 2. See text.

'Rockerbottom' feet were not present. The palmar creases tended to be horizontal. The muscle tone was normal and there was no hyperextensibility of joints. Angiomata were not observed. The blood count was normal and buccal smears showed a chromatin-positive status.

CYTOLOGICAL STUDIES

Peripheral blood leukocyte cultures were prepared on 3 separate occasions, using a modification of the technique of Moorhead *et al.*[1] Fifty cells were counted and the great majority contained 45 chromosomes.

	Chromosome counts					
Number of chromosomes	<43	43	44	45	46	47
Number of cells	2	1	2	45	—	—

Each cell counted exhibited a large abnormal chromosome. Detailed analyses of 5 cells were carried out and karyotypes prepared. In each case a chromosome of the B group was missing, as was a chromosome of the D group.

The abnormal chromosome was the largest in any individual cell examined and demonstrated a submedian centromere. The upper arms of this chromosome resembled the upper arms of the chromosomes in the B group, and the length of the abnormal chromosome was approximately that of the combined lengths of the missing chromosomes. Occasionally the chromosomes showed a secondary constriction slightly more than half-way down the length of the long arm. The features are well demonstrated in the metaphase plate and karyotype (Figs. 3 and 4). The characteristics of this large chromosome are explicable on the basis of a translocation, probably between chromosomes 4 and 15. The cells analyzed showed no other abnormality.

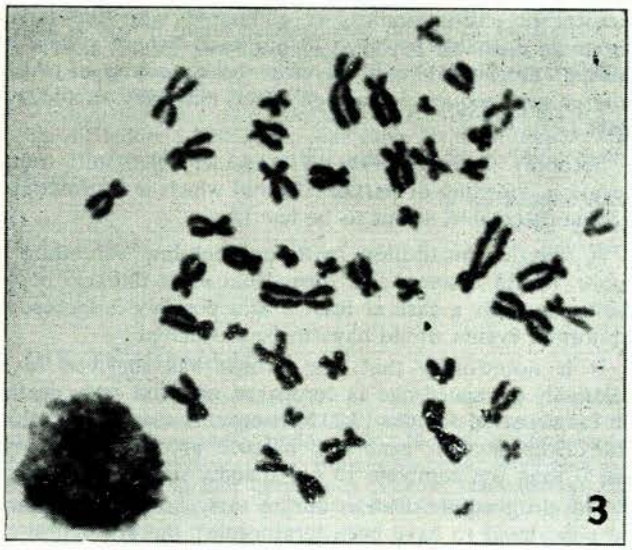


Fig. 3. Chromosomes as seen at metaphase.

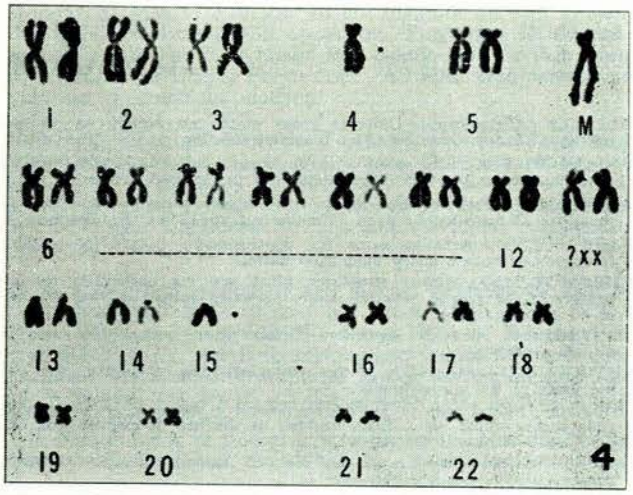


Fig. 4. Karyotype of metaphase seen in Fig. 3. Missing chromosomes no. 4 and no. 15 are represented by dots.

DISCUSSION

Essentially our patient exhibits many of the congenital stigmata of the 13 - 15 trisomy syndrome, as summarized by Lubs *et al.*[2] Cytologically, there is a modal chromosome count of 45 and a large B/D translocation chromosome. These findings pose several problems of interpretation, and a number of possibilities suggest themselves in attempting to link the clinical features with the cytological findings.

The first, and most likely, explanation is that the physical abnormalities are due to a reciprocal translocation, with loss of the terminal section of the B, as well as the centric region of the D chromosome. Despite the rule of conservation of telomeres, it is possible that simple

translocation has occurred. However, phenotypically normal translocation carriers are well documented. It may be that this is due to the fact that smaller amounts of genetic material are usually lost in such translocations between acrocentric chromosomes, as compared with the larger amounts probably involved in our case—where a state of 'partial monosomy' can therefore be conceived of. Also, altered gene sequence (position effect) may play an additive part.

Secondly, a three-break rearrangement (i.e. shift translocation, insertion or partial trisomy) which is microscopically undetectable, seems to be less likely.

A mosaic constitution (with one cell-line exhibiting a 'pure' 13 - 15 trisomy) is a formal but more unlikely possibility. In such a case at least 2 and possibly 3 successive abnormal events would have to be postulated.

It is noteworthy that our patient has survived to a relatively advanced age as compared with the early deaths so far reported for the 13 - 15 trisomy. It seems likely that the disturbance of genotypic balance in our case is less lethal than the complete 13 - 15 trisomy status.

The drug administration during early pregnancy cannot be considered to have been teratogenic: the aberration of reciprocal translocation having arisen during gametogenesis.

SUMMARY

A mentally defective adult female with physical signs of the 13 - 15 trisomy syndrome and in whom peripheral blood cultures revealed a modal count of 45 and a hitherto undescribed translocation chromosome, is presented. Consideration is given to the possible correlation between the clinical and the cytological findings. We incline to the view that *reciprocal translocation* with *loss of genetic material* is responsible for the picture in this patient.

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REFERENCES

1. Moorhead, P. S., Nowell, P. C., Mellman, N. J., Battips, D. M. and Hungerford, D. A. (1960): Exp. Cell Res., **20**, 613.
2. Lubs, H. A., Koenig, E. U. and Brandt, I. K. (1961): Lancet, **2**, 1001.