Transmission of a D/D Reciprocal Translocation in a Family with High Incidence of Mental Retardation

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In 1960, Lejeune, Turpin, and Decourt reported the first case of translocation between chromosomes of the 13–15(D) group. Their patient also had XXY chromosomal constitution and clinical features of Klinefelter syndrome. Until the present time, D/D translocation has been described in two or more generations of seven families (Walker and Harris, 1962; Grouchy *et al.*, 1963; Jagiello, 1963; Hamerton, Giannelli, and Carter, 1963; Yunis *et al.*, 1964; Zergollern *et al.*, 1964; Engel *et al.*, 1965). In addition, several reports appeared on the sporadic occurrence of this translocation (Cooper and Hirschhorn, 1961; Bühler *et al.*, 1963; Kjessler, 1964). Although a vast majority of the family members with D/D translocation were phenotypically normal, most of the index cases had a variety of abnormalities, the most notable being hypogonadism, mongolism, and various congenital malformations. The present family with D/D translocation is characterized by a high incidence of an undifferentiated type of mental retardation as the sole phenotypic abnormality. The initial chromosome examination was performed as a part of comprehensive clinical and laboratory studies of familial mental subnormality.

MATERIAL AND METHODS

Clinical examination and chromosome analysis were carried out in all members of the family available for the study (Fig. 1). Chromosome studies were conducted in short term blood cultures according to the modified technique of Moorhead *et al.* (1960). Complete blood grouping and finger and palmar prints also were performed. DNA replication studies were carried out by means of autoradiography using tritiated thymidine in final concentration of 1 μC/ml as a marker and a continuous labeling process. Tritiated thymidine was added six hours before harvesting the cells. The autoradiographic method was a slight modification of that employed by Schmid (1963), using air drying techniques and not squash preparation. After initial photographs were taken, the cover slip was removed and the spreads were covered with AR-10 Kodak stripping film.

DESCRIPTION OF FINDINGS

Clinical Findings

The propositus, III-2 (Fig. 1), was a 16 year old male. The pregnancy and delivery were normal. His development was retarded since birth, and early in

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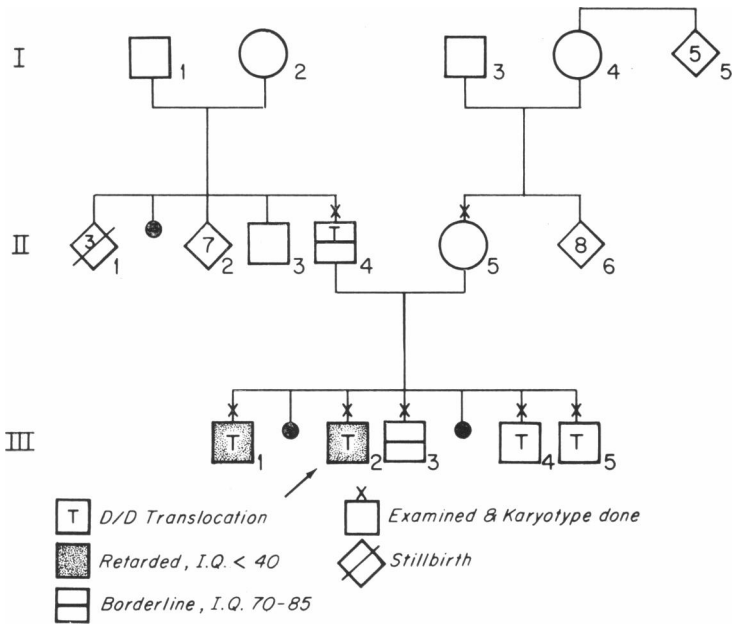

FIG. 1. Pedigree of the family.

life an operation was performed for left club foot and metatarsus varus on the right. Because of his backwardness, he was excluded even from a special class. His I.Q., tested on several occasions, ranged between 36 and 38 (Stanford-Binet). His physique was strong (Fig. 2A), and physical and neurological examinations were normal. Routine laboratory tests were negative, and sex chromatin bodies were absent in the cells from buccal smears. X-ray studies, glucose tolerance test, plasma lipids, and urinary amino acids were all within normal limits. The electroencephalogram showed diffuse slow background activity but no other abnormality. Clinical diagnosis: Mental deficiency at an imbecile level of undifferentiated type.

Chromosome studies in short term blood cultures consistently revealed a modal number of 45 chromosomes (Table 1). Karyotypes of metaphases showed only four large acrocentric chromosomes and one additional element resembling chromosome 3 in size and appearance (Fig. 3, left).

III-1 (Fig. 1), 17 years of age, is the older brother of the propositus. His development was retarded since birth. He began to walk at about three years of age and eventually was placed in an institution for the mentally retarded. Examination disclosed a restless male of a good general physique but with a "stigmatized" face (Fig. 2B). The neurological examination was not remarkable except for a deficiency of skill in fine movements. He had flat feet and knock-knee deformities. His most recent I.Q. was 29 (Stanford-Binet Form L). Routine laboratory tests, including protein-bound iodine, were all within normal limits. Sex chromatin positive cells were not found in buccal scrapings. He had 45 chromosomes in blood cultures (Table 1), and the karyotypes showed the presence of a translocation in the 13-15 group (Fig. 4).

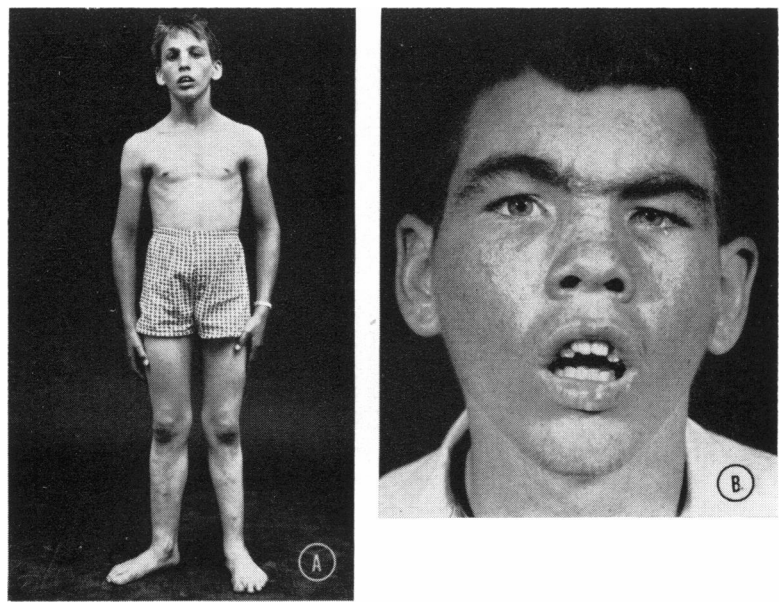

FIG. 2. Two retarded sibs with D/D chromosome translocation. A. The propositus (III-2). B. The older brother (III-1).

III-3 (Fig. 1), 23 years of age, is the next older brother of the propositus; he is mildly retarded. He attended special classes in public school and is now employed as a baker's helper. Results of physical and neurological examinations were within normal limits. He was well developed physically but was generally dull. His vocabulary was restricted and he was apprehensive while meeting new situations. His I.Q. on the Wechsler-Bellevue scale was 70. Chromosome studies in cultures from blood showed a modal number of 46 chromosomes and normal karyotypes (Table 1).

III-4 (Fig. 1), 21 years of age, and III-5, 20 years of age, are the two remaining brothers of the propositus. Development was normal for both; they completed high school and are gainfully employed. Results of physical and neurological examinations were normal. Chromosome studies (Table 1) showed a modal number of 45 chromosomes and the presence of D/D translocation in both.

II-4 (Fig. 1), 51 years of age, is the father of generation III. He attended elementary school and now works as a watchman. Examination showed a moderately obese, asthmatic man who functions satisfactorily in the family setting, where his wife assumes a supervisory role. His interests were narrow; he was apprehensive and displayed uninhibited laughter. No formal psychological examination was possible, but he appeared to function at best in the borderline normal range. Chromosome studies in a lymphocyte culture disclosed a modal number of 45 chromosomes and D/D translocation (Fig. 5). His parents are deceased; three of his sibs (Fig. 1, II-1) were stillborn; and seven sibs (II-2) have died either of accident, disease, or of old age. He

TABLE 1. SUMMARY OF KARYOTYPE ANALYSIS OF LYMPHOCYTE CULTURES IN THE SEVEN MEMBERS OF THE FAMILY

Subject	Culture number	Chromosome count					Total number of cells	
		43	44	45	46	47	Counted	Karyotyped
III-2	1		2	84	1		87	11
	2			20			20	5
III-1	1			20			20	4
	2			10			10	7
III-3	1			1	28		29	4
	2				19		19	8
III-4	1		1	26	1		28	10
III-5	1	1		54	1		56	20
II-4	1		1	28			29	9
II-5	1			1	45	1	47	9

thought that they had been mentally normal. His older brother (II-3), married but childless, was described as peculiar; he made himself unavailable for examination.

II-5 (Fig. 1), 48 years of age, is the mother of generation III. She has been always in good health. Examination revealed a female of normal physique and intelligence. Chromosome studies in cultured lymphocytes showed a modal number of 46 chromosomes and normal karyotypes. Eight of her siblings (all living in Europe) and her deceased parents were described by her as being normal in all respects.

Studies of DNA Replication

In an attempt to identify more closely which of the group D chromosomes are involved in the translocation in this family, a DNA replication study using tritiated thymidine was carried out. A total of 23 labeled karyotypes in a satisfactory phase of DNA replication was analyzed. From the examination of the unlabeled karyotypes, the D/D translocation chromosome corresponded in size and location of the centromere to chromosome 3 (Fig. 5). It is known from the studies on labeling of chromosomes in normal subjects that the two number 3 chromosomes label synchronously (Schmid, 1963; German, 1964) and that their grains are fairly uniformly distributed with slight preponderance for the central portion during the intermediate late stage (Schmid, 1963). On this basis, it is possible to identify the translocated chromosome because the labeling patterns were different from that of chromosome 3 (Figs. 3, 4). Of 23 labeled karyotypes analyzed, 14 showed the following: Two of the D chromosomes either were not labeled or had only a few grains. Of the remaining two chromosomes of group D, one revealed labeling over the short arm and near the centromere, the other in the middle and distal portion of the long arm. Two arms of the translocated chromosomes were predominantly labeled in the middle and distal portions, whereas the other two arms showed most grains near the centromere (Figs. 3, 4). Thus, the translocated chromosome is not derived from the two early labeling chromosomes of the 13-15 group.

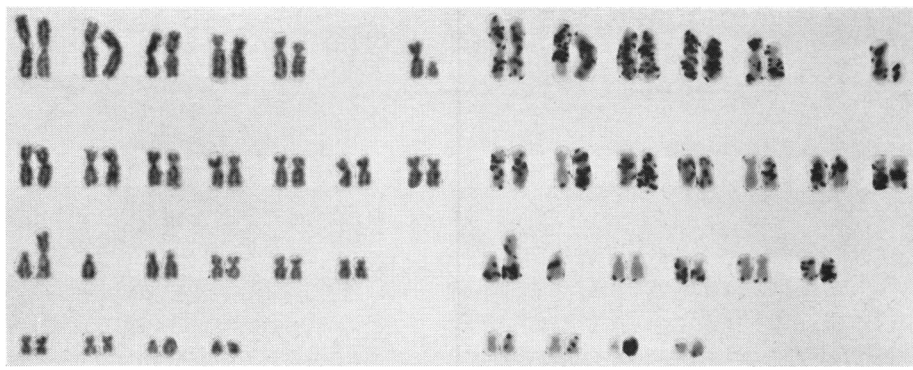

FIG. 3. Metaphase karyotype of intermediate–late labeled cell in III-1. Note that the pair of number 3 chromosomes is labeled quite heavily and about equally, whereas the translocated chromosome is labeled lightly. Two of the Group D chromosomes are unlabeled or show only minimal labeling.

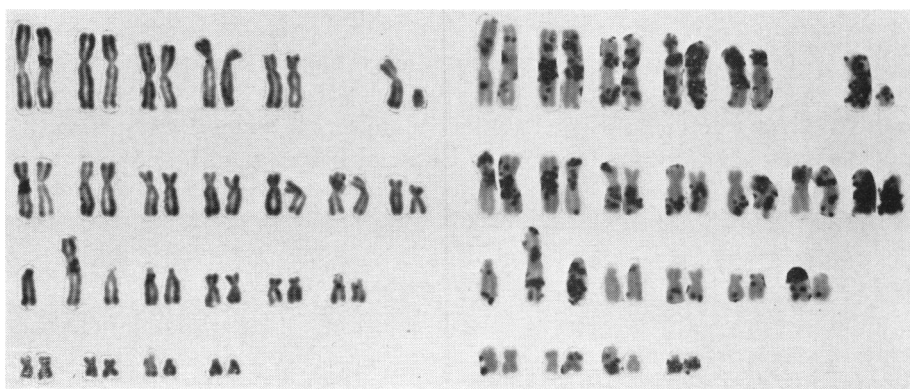

FIG. 4. Metaphase karyotype of intermediate–late labeled cells in III-2. Two of the Group D chromosomes are unlabeled or show only minimal labeling. The translocated chromosomes show labeling patterns resembling those of the remaining two chromosomes.

Linkage Studies and Dermatoglyphics

Studies of blood groups ABO, Rh, MNS, P, Kell, Duffy, Kidd, Lewis, Lutheran, Gm, and Inv were carried out in all examined members of the family (Table 2). There was no evidence of linkage between any of the markers tested and the presence of the translocated chromosome or the presence of retardation.

We are indebted to Dr. D. C. Rife for examination of dermatoglyphics. The following is a summary of his findings: "The analysis of pattern formulations, main line indices, and ATD angles on the palms as well as of the patterns and ridge counts on finger tips were conducted in seven members of the family. In no instance were outstanding or unusual features encountered."

DISCUSSION

The clinical and cytogenetic findings in seven index subjects and in the 30 carriers of the D/D translocation who were found in the seven families re-

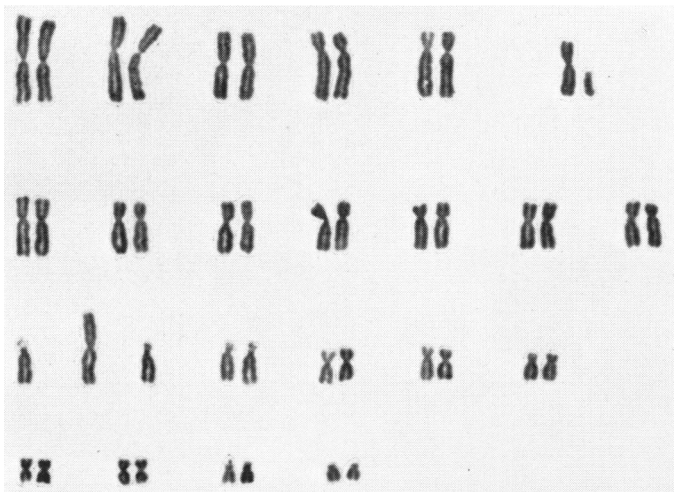

FIG. 5. Metaphase karyotype showing D/D translocation in the father, II-4.

ported in the literature can be summarized as follows: Only four of the 30 carriers had a phenotypic abnormality (two had clinical hypogonadism, one a malformation of the spine, and one an abnormality of the central nervous system); the 26 remaining carriers were considered normal. One of the seven index subjects was phenotypically normal, although he had D/D translocation. Chromosomes of this individual and his wife were examined because one of their offspring was anencephalic. Of the remaining six index subjects, one had hypogonadism, three were mongoloids (two had regular trisomy G and 47 chromosomes, one had trisomy G and D/D translocation), one had a malformation of the spine, and one had a malformation of the kidneys. Mental retardation was present in five of the seven index subjects, but it was considered to be related to coexisting conditions such as mongolism or malformation. In contradistinction, mental retardation present in four of the seven members of the family described by us differed since it was of undifferentiated type, that is, not related to other conditions known to be associated with low intellectual level. Comprehensive biochemical studies performed on two retarded subjects failed to reveal any abnormality.

The ratio of males to females among the members of the reported seven families with D/D translocation was 17 to 18; thus, sex is not significant in the segregation of translocated chromosomes during meiotic division. In a few large families reported (Walker and Harris, 1962; Hamerton, Giannelli, and Carter, 1963), the ratio of offspring with heterozygous D/D translocation to chromosomally normal offspring is close to the expected 1:1 ratio.

To most investigators, the appearance of the translocated chromosomes suggested centromeric fusion. Because the translocation was balanced and there was generally lack of monosomy and trisomy in the group D chromosomes in these families, there is agreement that the chromosomes involved must be heterologous. From the appearance and measurements of the group D chromosomes, Walker and Harris (1962), Hamerton, Giannelli, and Carter (1963), and Kjessler (1964) suggested that the translocated chromosomes could be 13

TABLE 2. BLOOD GROUPS AND Gm TYPES IN FAMILY MEMBERS EXAMINED

Subject	ABO	Rh Factors						MNS					P$_1$	Kell			
		C	C^w	D	E	c	e	M	N	S	s	U		K	k	Kp^a	Kp^b
II-4	O	−	−	+	+	+	+	+	−	+	+	+	+	+	+	−	+
II-5	A$_1$	+	−	+	+	+	+	+	+	+	+	+	+	−	+	−	+
III-2	A$_1$	+	−	+	−	+	+	+	−	+	+	+	+	+	+	−	+
III-1	O	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+
III-3	A$_1$	+	−	+	+	+	+	+	+	−	+	+	+	+	+	−	+
III-4	O	+	−	+	+	+	+	+	−	+	−	+	+	−	+	−	+
III-5	O	−	−	+	+	+	+	+	+	−	+	+	+	−	+	−	+

Subject	Duffy		Kidd		Lewis		Lutheran		Sutter		Gm				Inv
	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	Lu^a	Lu^b	Js^b	Xg^a	a	b^1	x	c	a
II-4	+	+	+	−	−	−	−	+	+	+	−	+	−	−	−
II-5	+	+	−	+	−	+	−			+	+	+	−	−	−
III-2	−	+	+	+	−	+	−			+	−	+	−	−	−
III-1	−	+	+	+	−	+	−	+	+	+	−	+	−	−	−
III-3	+	+	+	+	−	+	−			+	+	+	−	−	−
III-4	−	+	+	+	−	+	−	+	+	+	+	+	−	−	−
III-5	+	+	+	+	−	+	−	+	+	+	+	+	−	−	−

and 14, whereas Lejeune, Turpin, and Decourt (1960), Grouchy *et al.* (1963), and Zergollern *et al.* (1964) thought that the translocation might have occurred between chromosomes 14 and 15. On the basis of DNA replication analysis, Yunis *et al.* (1964) and also we believe that the translocated chromosomes are intermediate late replicators, possibly 13 and 14, since the two early replicating chromosomes are the shortest of the group D. However, it must be admitted that it is not definitely known which two of the six chromosomes of group D are involved in the translocation and whether they are the same in various families described.

There were no obvious chromosomal differences in the present family between phenotypically normal D/D carriers and carriers who are mentally retarded. It is possible that the presence of the translocation predisposes to other invisible chromosomal aberrations which are responsible for retardation. That these families are particularly susceptible to nondisjunction is demonstrated by the finding of three mongoloids among index cases of the seven families reported in the literature. However, in the present family, other interpretations are also possible. Thus, translocation and retardation might have been inherited independently, especially since one of the sibs in generation III is mildly retarded although his chromosomes are normal.

SUMMARY

A family is described in which five members of two generations have a reciprocal translocation in the 13–15 group of chromosomes. DNA replication study using tritium labeled thymidine and autoradiography demonstrated that the chromosomes involved in the translocation are the intermediate late replicators (possibly 13 and 14). The present family differs from others reported in the literature by the presence of a high incidence of mental retardation among its members.

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