Pediat. Res. *1:* 104–109 (1967)

Chromosomes
chromosome abnormalities
(translocations, satellites)
genetics
convulsions
micrognathism

Familial Transmission of a Presumptive D/E (13–15/17–18) Short Arm Translocation

M. M. COHEN and MARILYN A. LOCKWOOD

Division of Human Genetics, Department of Pediatrics, State University of New York at Buffalo, School of Medicine, and Children's Hospital of Buffalo, N.Y., USA

Extract

This paper reports a family possessing a presumptive D/E translocation in which only the short arm of each chromosome is involved. Karyotypes of the propositus, his mother and sister were abnormal, evidencing an obvious satellited member among the chromosomes of pairs No. 17–18. This marker chromosome was often found at the periphery of the metaphase plate and entered into satellite associations with the other satellited acrocentrics. In addition to the E group marker, one D group element in these individuals appeared to possess a 'knobby' short arm and could be identified in almost all cells. This chromosome did not show satellite association with the other acrocentric chromosomes. The most likely interpretation of the karyotypic finding in this case is that of a balanced reciprocal translocation involving the short arm of a D and E group chromosome.

Speculation

Single cases such as this illustrate the problem of a relation between karyotypic abnormality and phenotypic deviation. That the chromosomal anomaly is etiologically related to the physical condition of the propositus is a moot question. Normal individuals in the same family with an identical karyotypic anomaly emphasize the need for future studies of the general population and additional cases with similar conditions before postulating direct causality.

Introduction

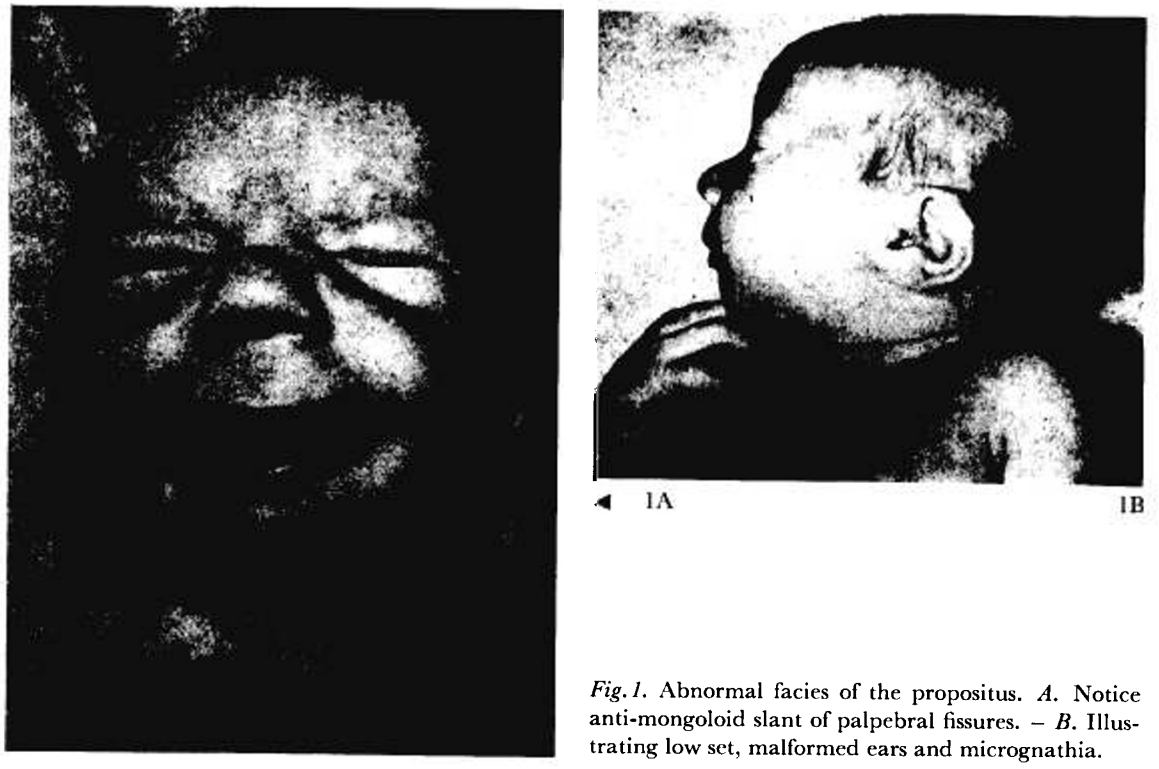
Reciprocal translocations frequently include a satellited acrocentric chromosome of either group D (13–15) or group G (21–22). Translocations of group E (16–18) chromosomes have also been observed, and in many instances the second translocation chromosome was acrocentric (VISLIE *et al.* [1962]; DE LOZZIO and VALENCIA [1963]; BRIEBART *et al.* [1964]; MIGEON and YOUNG [1964]; TOWNES and ZIEGLER [1965]). Such translocations often involve the long arm of each chromosome so that the normal morphology of both chromosomes has been sufficiently altered to allow detection. On the other hand, translocations of the short arm would be more difficult to discern. Through the use of satellites as morphological landmarks in identifying abnormally satellited 'marker' chromosomes (ELLIS *et al.* [1962]; DILL and MILLER [1964]; ROHDE [1965]), such aberrations may be detected. We wish to report a family with a satellited E chromosome (? No. 18), and a D group element with a 'knobby' short arm, which is best explained by a presumptive D/E translocation involving only the short arm of each chromosome.

Case History

The propositus was born (birthweight was 2506 g) to a 28-year-old father and a 22-year-old mother following a 37-week gestation. Prenatally, on three occasions, the mother had experienced mild 'flu-like' illnesses. Drug ingestion during pregnancy included hydrochlorothiazide, methamphetamine hydrochloride, sodium pentobarbital, and chlordiazepoxide hydrochloride. Total weight gain was 14 pounds.

At 17 days of age, the propositus was admitted to the Children's Hospital with a history of frequent unilateral seizures involving either side of the body. On admission, intermittent convulsions of the left side were noted. Physical examination revealed a small, pale infant with unusual facies (fig. 1 A). Weight was 2580 g, length 49.5 cm and head circumference 33 cm. Pulse rate was 152/min, respirations 52/min. Blood pressure was 85 mm Hg in the right arm and 75 mm Hg in the right leg (flush method). The anterior and posterior fontanels were open, small and flat. Transillumination of the cranium appeared normal. Ears were low set with poor formation of the left superior helix and the eyes showed anti-mongol palpebral fissures (fig. 1 B). The mandible was small, simulating micrognathia. Bilateral Chvostek signs were demonstrable. A grade IV/VI harsh pansystolic murmur was heard along the left sternal border. The penis was normally formed and both testes were palpable just above the scrotum.

Laboratory studies showed hemoglobin-11.2 gm %; blood sugar-69 mg %; BUN-7.7 mg %; and serum calcium-5.9 mg %. Intravenous and oral therapy with calcium were instituted and only one further seizure, eight hours after admission, was noted. Levels of calcium in serum returned to normal. At 21 days of age the EEG, as well as skull and roentgenograms of the skull and chest were normal. EKG was compatible with a ventricular septal defect. At 26 days of age bloody diarrhea due to pathogenic *E. coli* 026 occurred and subsequently hemoglobin values fell to 8.7 gm %. Neomycin and colistin sulfate eradicated the pathogenic strain of *E. coli*.



◀ 1A 1B

Fig. 1. Abnormal facies of the propositus. *A.* Notice anti-mongoloid slant of palpebral fissures. – *B.* Illustrating low set, malformed ears and micrognathia.

The infant was seen again at five months of age and during this interim had remained free of seizures. At three months of age he had begun to smile and became active and responsive. The heart murmur and relative cardiac size were unchanged. Head control was poor and muscle tone was slightly hypotonic. Both parents were in good health; the only sibling was a three-year-old girl who appeared to be normal.

Cytogenetic Studies

Chromosome preparations using the method of MOORHEAD *et al.* [1960] were made from peripheral leukocyte cultures employing a commercially available microculture chromosome kit (Grand Island Biological Co., Grand Island, N.Y.). Numerous cultures were obtained from each family member and four separate studies were made on the propositus. In addition, fibroblast cultures, derived from a skin biopsy of the propositus, were also investigated.

In all family members the modal chromosomal count was 46 (table I); however, the karyotypes of the propositus, his sister and mother were abnormal. In these three individuals there was an obviously satellited member among the chromosomes of pairs No. 17–18 (fig. 2). This abnormal chromosome was often found at the periphery of the metaphase plate and frequently entered into association with the other satellited acrocentrics. Although the abnormal marker was visible in variable frequencies in the different individuals and tissues (table I), it was thought to be present in all cells. In many of those cells which did not obviously show the marker, karyotypic analysis revealed three apparent No. 16 chromosomes and only three No. 17–18 elements (fig. 3). It is quite possible that the 'extra No. 16' was in reality the satellited E chromosome but due to the addition of colcemide, excessive contraction of the satellite stalks occurred, simulating elongation of the short arm. In those few cells which appeared normal, breakage of the satellite stalks with the loss of the satellites through technical manipulation could not be ruled out. In addition to the E group marker, one member of group D in the propositus, his mother and sister had an abnormal 'knobby' short arm; this could be identified in many cells (table I, figs. 2–4).

A detailed investigation of 110 cells of the propositus with extremely prominent satellites yielded the following results. Ninety-three cells (84.5 %) contained the satellited E chromosome. The 17 cells in this sample which did not show this marker were distributed as follows. Ten cells (9.1 %) had three 'No. 16' elements, with one of these presumably representing the contracted satellited E. Three of these cells showed a satellite association of the 'third No. 16' with an acrocentric chromosome. The remaining 7 cells (6.4 %) had a normal male karyotype with no evidence of the satellited marker and most probably reflected breakage and loss of the satellites during technical preparation.

In no cells were all six chromosomes of group D satellited; however, in 76.4 % of the cells, five of the six large acrocentrics bore satellites. In 66% of the cells, one D chromosome had the obvious 'knobby' short arm. This marker participated in satellite associations in only 3.5 % of the cells, while the satellited E marker was 'associated' in 18.2 %. The abnormal D chromosome was also apparent in many cells which did not clearly show the satellited E. The remaining 23.6 % of the cells had satellites on less than five large acrocentrics.

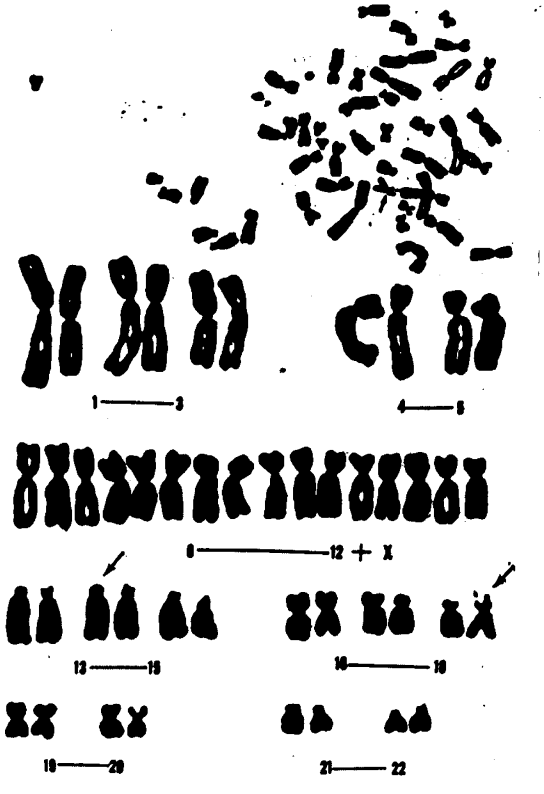
In many of these cells (68.3 %) all four of the No. 21–22 chromosomes either participated in an acrocentric association or bore obvious satellites. Figure 4 demonstrates partial karyotypes of three cells with ten satellited chromosomes, including the satellited E marker and the non-satellited D chromosome. Karyotypes of the family members showed no obvious abnormality of the long arms of either the D and E group chromosomes. These observations are consistant with the proposal that a reciprocal translocation had occurred in the centromeric regions of a D and E group chromosome, involving little or no long arm material. The karyotype of the father was normal. Sex chromatin determinations were concordant with phenotypic sex in all cases.

Table I. Distribution of chromosome counts and marker chromosomes in the family

Family member	Number of chromosomes				Total	Visible satellites on E group chromosome	'Knobby' D group chromosome
	< 44	44	45	46			
Father	1	2	2 (1)	20 (9)	25 (10)	0	0
Mother		1	4 (1)	45 (9)	50 (10)	33 (66 %)	41 (82 %)
Sister	1	3	7 (2)	39 (8)	50 (10)	32 (64 %)	37 (74 %)
Propositus							
Blood	9 (2)	7 (3)	22 (5)	112 (12)	150 (22)	132 (88 %)	118 (79 %)
Skin		3 (1)	6 (2)	41 (7)	50 (10)	24 (48 %)	13 (26 %)
Total	9 (2)	10 (4)	28 (7)	153 (19)	200 (32)	156 (78 %)	131 (66 %)

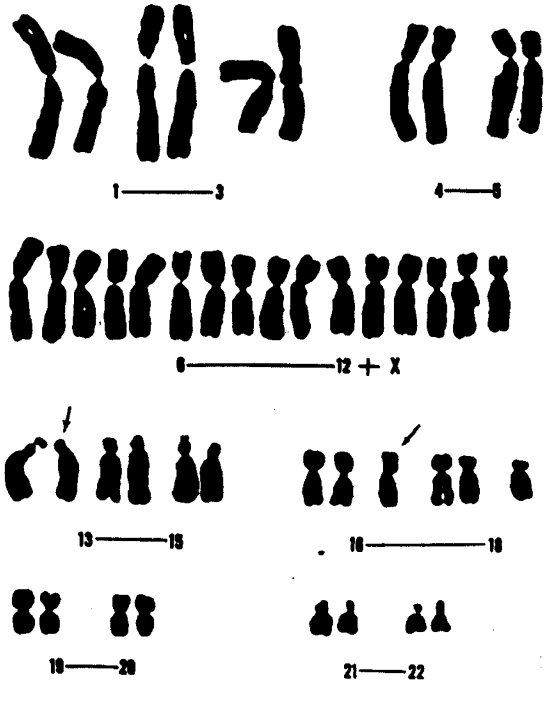
Figures in parenthesis refer to numbers of cells photographically and/or microscopically analyzed.

2A



2B

3



4

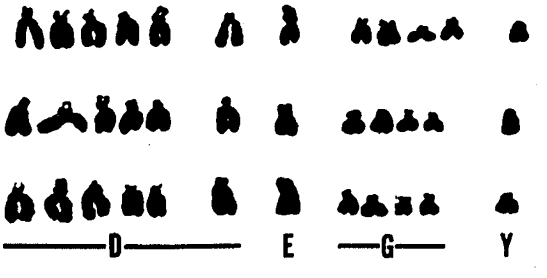


Fig. 2. A. Karyotype of the propositus. – *B.* Karyotype of the propositus' mother. Notice satellited member in Group E (? No. 18). Arrows indicate 'knobby' short arms on a D group chromosome.

Fig. 3. Karyotype of the sister showing three apparent No. 16 chromosomes. Arrows indicate satellited E which simulates a No. 16 due to contraction of satellite stalks and 'knobby' short arms on a D group chromosome.

Fig. 4. Partial karyotype of three cells from the propositus illustrating five satellited D chromosomes, the sixth D group member showing 'knobby' short arm; the satellited E; and four satellited members of Group G.

Discussion

It is generally accepted that all ten of the acrocentric chromosomes of man are satellited; however, variation exists in the number of chromosomes in a given cell which bear satellites (FERGUSON-SMITH and HANDMAKER [1961]; MILLER and MUKHERJEE [1962]). Satellites on the acrocentric chromosomes have been shown to follow Mendelian transmission in families and in this regard are valuable 'markers' in identifying individual chromosomes. Such enlarged satellites on the chromosomes of groups D and G have been observed in individuals with various clinical disorders, as well as in phenotypically normal persons (DE LA CHAPELLE *et al.* [1963]; FERRIER *et al.* [1964]; BISHUN *et al.* [1964]). Normal acrocentric chromosomes with duplicated or 'tandem' satellites have been described (BOVER *et al.* [1965]). On the other hand, morphologically aberrant chromosomes have also shown satellites such as doubly satellited elements bearing satellites on both the long and short arms (ELLIS *et al.* [1962]; DILL and MILLER [1964]; ROHDE [1965]).

The appearance of satellites on a group E chromosome was first reported by EDWARDS [1961] who suggested that chromosome No. 18 may always be satellited. However, the rarity of this observation in normal individuals, in contrast to the frequency of satellited acrocentrics, suggests that if there is a normal satellite on No. 18, it is extremely small and at the limit of resolution of the light microscope. Observations of an occasional association of an E group member (No. 17–18) with chromosomes of the D and E groups have been made in this and other laboratories. However, FERGUSON-SMITH *et al.* [1962] found only eight satellited E chromosomes (No. 17) in 1303 cells derived from a number of patients with various chromosomal abnormalities as well as from normal controls. SMITH *et al.* [1965] described a mentally retarded female with bilateral equinocavus who possessed satellites on a No. 18 in 65% of her cells. FERGUSON-SMITH [1966] has investigated a family, ascertained through a propositus with the 'cri-du-chat' syndrome, in which a satellited No. 17 was segregating. In addition, JACOBS [1964] described a family in which an apparent D/E short arm translocation, manifesting a satellited No. 18, was present. The family described by JACOBS differs from that in the present report in that the involved D group chromosome is abnormal, appearing in some individuals as a 'telocentric' deleted element due to loss of chromosomal material in the translocation process.

Whether the chromosomal aberration in the present case is etiologically related to the physical condition of the propositus is a moot question. Since both the mother and the sister manifest the same cytogenetic abnormality but are phenotypically normal, a causal relationship seems weakened and suggest that the dysplastic features of the propositus may be entirely coincidental. Reports such as this one, involving phenotype-karoytype correlations, must consider the inherent problem of ascertainment bias. Since cytogenetic investigation is usually undertaken only *after* noting somatic abnormalities, the probability of such anomalies is assured and their rarity is negated. Therefore, the probability of observing these anomalies in association with a chromosomal aberration is not the product of the two individual probabilities; but that of the chromosomal defect alone. The true frequency and importance of such minor chromosomal anomalies (variants?) can only be assessed through 'double-blind' surveys in the general population of normal individuals. The most likely interpretation of the karyotypic findings in the present family is that of a balanced reciprocal translocation involving the short arm of a D and an E group chromosome.

References and Notes

1. BISHUN, N.P.; RASHAD, M.N. and MORTON, W.R. M.: Enlarged satellites in father and mongol child. Lancet *i:* 988 (1964).
2. BOVER, G.F.; CANDELA, R.B.; AGUIRRE, E.A. and CERCOS, C.L.: Un chromosoma marcador familiar: Autosoma G con dobles satelites. Med. esp. *54:* 1 (1965).
3. BRIEBART, S.; MELLMAN, W.J. and EBERLEIN, W.R.: Developmental retardation associated with an unbalanced 13–15/18 translocation. Cytogenetics *3:* 252 (1964).
4. DE LA CHAPELLE, A.; AULA, P. and KIVALO, E.: Enlarged short arm or satellite region. A heritable trait unassociated with developmental disorder. Cytogenetics *2:* 129 (1963).
5. DILL, F.J. and MILLER, J.R.: Personal communication (1964).
6. EDWARDS, J.H.: Chromosomal association in man. Lancet *ii:* 317 (1961).
7. ELLIS, J.R.; MARSHAL, R. and PENROSE, L.S.: An aberrant small acrocentric chromosome. Ann. hum. Genet. *26:* 77 (1962).
8. FERGUSON-SMITH, M.A. and HANDMAKER, S.D.: Observations on the satellited human chromosomes. Lancet *i:* 638 (1961).
9. FERGUSON-SMITH, M.A.; FERGUSON-SMITH, M.E.; ELLIS, P.M. and DICKSON, M.: The sites and relative frequencies of secondary constrictions in human somatic chromosomes. Cytogenetics *1:* 325 (1962).
10. FERGUSON-SMITH, M.A.: Personal communication (1966).

11. Ferrier, P.; Ferrier, S.; Stalder, G.; Buhler, E.; Bamatter, F. and Klein, D.: Congenital asymmetry associated with diploid-triploid mosaicism and large satellites. Lancet *ii:* 80 (1964).
12. Jacobs, P.A.: Chromosome studies in the general population; in Cytogenetics of cells in culture, pp. 111–121 Ed. R.J.C. Harris (Academic Press; New York, 1964).
13. de Lozzio, C.B. and Valencia, J.I.: A case of translocation 21–22/17–18. Lancet *i:* 1106 (1963).
14. Migeon, B.R. and Young, W.J.: Reciprocal (D/E) translocation: Euploid transmission in three generations. Bull. Johns Hopk. Hosp. *115:* 379 (1964).
15. Miller, O.J. and Mukherjee, B.B.: Normal variations in the human karyotypes. Trans. N.Y. Acad. Sci. *24:* 372 (1962).
16. Moorhead, P.S.; Nowell, P.C.; Mellman, W.J.; Battips, D.M. and Hungerford, D.A.: Chromosome preparations of leukocytes cultured from human peripheral blood. Exp. Cell Res. *20:* 613 (1960).
17. Rohde, R.A.: A masculinizing syndrome associated with a doubly-satellited extra chromosome. J. med. Gen. *2:* 243 (1965).
18. Smith, W.S.; Welter, D.A. and Littlefield, L.G.: Personal communication [1965).
19. Townes, P.L. and Ziegler, N.A.: D/E (13–15/17–18) translocation: Occurrence in an infant with 45 chromosomes. Amer. J. Dis. Child. *110:* 686 (1965).
20. Vislie, H.; Wehn, M.; Brogger, A. and Mohr, J.: Chromosome abnormalities in a mother and two mentally retarded children. Lancet *ii:* 76 (1962).
21. The authors wish to express their appreciation to Dr. Margaret H. MacGillivray for helpful suggestions and critical reading of the manuscript. We are indebted to Miss Maryann Zimmerman and Mrs. Michelle Marinello for their excellent technical assistance.
22. Supported by Project No. 417 from the United States Children's Bureau.