The Inheritance of a Structural Anomaly of One Chromosome No. 16 in a Kindred (46,16-,C+)*

JUAN CHEMKE† and ARTHUR ROBINSON

From the Departments of Biophysics and Pediatrics, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver, Colorado 80220, USA

Variations in the human karyotype have been found in association with a variety of congenital anomalies and also in the normal population (Miller and Mukherjee, 1962; Court Brown, 1967). Court Brown's population studies (1967) have revealed that between 2 and 3% of the normal adult population has a karyotype with structural autosomal variations. Occasionally, homologous autosomes reveal differences in length and arm ratio between each other, variations in length being common in those chromosomes which have recognized secondary constrictions.

The present report concerns a family in which such a structural abnormality of one of the chromosomes no. 16 is segregating. Four generations of this family were studied, all of the members examined being phenotypically normal. Blood grouping, haptoglobins, gal-l-p uridyl transferase and galactokinase activities, immunoglobulins, phenylthiocarbamide tasting tests, and dermatoglyphic analyses were performed, in search of possible linkages between these genetic characteristics and the chromosomal structural anomaly.

Family History

Family History. The proband, a female infant of Mexican-American origin, was born on 20 May 1967 (case IV.3, Fig. 1). Ascertainment was due to the fact that the analysis of sex chromatin of the amniotic membrane showed 99% sex chromatin positive cells, with 14% double Barr bodies. Her buccal smear had 29% sex chromatin positive cells, without any double Barr bodies. Chromosome analyses on lymphocyte and fibroblast cultures were performed, and revealed no C-chromosomal

aneuploidy. Consequently, these findings were interpreted as probably being due to mosaicism, with aneuploidy being present in the extra-embryonic tissues only (Robinson and Puck, 1967).

This child is phenotypically normal, and had a normal pattern of psychomotor development at age 20 months. Her sister and 22 other members of the kindred were also studied. Examination of all these individuals revealed no significant abnormalities or disease (Fig. 1).

Laboratory Studies

1. Chromosomal analyses of peripheral lymphocytes, by modification of the technique of Moorehead *et al* (1960), were performed in 24 individuals (Fig. 1).

A fibroblast culture obtained from a skin biopsy of the proband was established by modification of a standard technique (Tjio and Puck, 1958), and 15 suitable cells were karyotyped.

The results of these studies are summarized in Table 1 and Fig. 2.

2. Blood groups and haptoglobins were studied in 27 members. Blood group analysis revealed a discrepancy between I.2 and his offspring II.8 and II.9 (Fig. 1). Consequently, it is a fair assumption that II.8 and II.9 were not conceived by I.2.

3. Gal-l-p uridyl transferase and galactokinase activities were performed in 23 individuals using the technique of Puck and Hill (1967). The results are listed in Table II, and reveal normal K_2/K_1 ratios for red blood cells. The relatively low K_2/K_1 ratios of IV.2 and IV.3 are normal for their respective ages.

4. Immunoglobulins were determined in 24 individuals and were all within the normal range (Fulginiti *et al*, 1966).

5. Phenylthiocarbamide tasting tests were performed in 19 individuals, by a modification of the technique described by Harris and Kalmus (1949). All tested individuals were 'tasters' on solution no. 6. Children under 5 years of age were not tested.

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† Present address: Kaplan Hospital, Rehovot, Israel.

FIG. 1. Kindred in which 7 members have an extra C group chromosome and a missing chromosome no. 16.

TABLE I
CYTOGENETIC STUDIES

Family Member	Age (yr.)	No. of Cells	-45	45	46	47	+47	Karyotype
I.1	75	25			25			46,XX
I.2	78	26	2	5	21			46,XY,16-,C+
II.2	50	15			15			46,XY
II.3	47	25		1	24			46,XX,16-,C+
II.4	38	26	3		23			46,XY
II.6	31	25		2	23			46,XY
II.8	22	26			25		1	46,XX
II.9	17	25		4	21			46,XX
III.1	28	25		1	24			46,XY
III.2	26	25			25			46,XY,16-,C+
III.3	24	15		1	14			46,XX
III.5	23	25		2	23			46,XX,16-,C+
III.6	21	25			25			46,XX
III.7	17	25		1	24			46,XX
III.8	13	26	1	2	23			46,XY
III.9	6	26		2	24			46,XX
III.10	5	25		2	23			46,XX
III.11	4	25	1		24			46,XY
IV.1	3	25		1	24			46,XY
IV.2	3	46		3	43			46,XX,16-,C+
IV.3	1½	64	1	3	60			46,XX,16-,C+
		15*		1	14			46,XX,16-,C+
IV.4	6	25		1	24			46,XX,16-,C+
IV.5	4	25		1	24			46,XX
IV.6	2½	26	1	2	23			46,XY

* Skin fibroblasts.

6. Dermatoglyphic analyses were performed in 24 members of this family. The finger patterns, total finger ridge counts, a-b ridge counts, palmar axial triradii (expressed as % and as *aid* angles; Table III) did not reveal a specific or different configuration in those individuals with a 46,16-,C+ karyotype. In summary, none of the genetic markers investigated showed abnormal segregation.

Discussion

In the present study, 24 phenotypically normal members of a family in 4 generations were investigated, a missing chromosome no. 16 with an addi-

tional chromosome in the C group being found in 7 individuals. In Court Brown *et al*'s studies of unselected adults (1966), chromosome no. 16 was among the commonest autosomes involved in structural anomalies (0.53% of the entire population). The presence of a secondary constriction is frequently associated with an exaggeration in chromosomal length, which, in the case of chromosome no. 16, should not exceed the length of the shortest chromosome in the C group, in order to permit its identification. Morphologically, these structural anomalies have a characteristic location, are inherited and are usually present in all cells

FIG. 2. C, D, and E group chromosomes of patients with the anomalous no. 16 and a normal control.

TABLE II
LINKAGE STUDIES

Family Member	Blood Group	D	C	C ^w	E	c	e	M	N	S	s	P	K	Fy ^a	Hapto-globins	Phenyl-thiocarbamide Tasting	K ₂ /K ₁ Ratio	Immunoglobulins		
																		γ-G	γ-A	γ-M
I.1	A ₁	+	+	-	+	+	+	+	+	-	+	+	-	+	1-1	+	7-94	1035	259	347
I.2	A ₁	+	+	-	+	+	+	+	+	-	+	+	-	+	2-1	+	9-69	900	242	82
I.3	A ₁	+	+	-	+	+	+	+	+	-	+	+	-	+	2-1	+				
II.2	O	+	-	-	+	+	-	+	+	+	+	-	-	-	2-1	+	6-98	900	389	173
II.3	O	+	-	-	+	+	-	+	+	+	+	-	-	+	2-1	+	7-79	855	264	210
II.4	O	+	-	-	+	+	-	+	+	+	+	-	-	+	1-1	+	7-23	1035	363	313
II.6	O	+	-	-	+	+	-	+	+	+	+	-	-	+	2-1	+	9-3	720	285	68
II.7	O	+	-	-	+	+	-	+	+	+	+	-	-	+	2-2	+				
II.8	A ₂ B	+	-	-	+	+	-	+	+	-	+	+	-	-	2-2	+				
II.9	B	+	-	-	+	+	-	+	+	-	+	+	-	-	1-1	+	7-8	900	281	82
III.1	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-1	+	10-24	1107	421	210
III.2	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-2	+	8-13	900	276	82
III.3	B	+	-	-	+	+	-	+	+	+	+	+	-	+	2-1	+	7-94	1107	421	90
III.4	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-1	+				
III.5	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-1	+	8-23	765	242	250
III.6	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-2	+	7-78	765	225	141
III.7	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-2	+	9-88	1107	389	141
III.8	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-2	+	8-05	855	203	190
III.9	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-1	+	9-4	1062	110	127
III.10	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-1	+	8-5	900	173	247
III.11	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-1	+	9-8	720	173	93
IV.1	O	+	-	-	+	+	-	+	+	+	+	+	-	-	2-1	+	8-90	648	89	90
IV.2	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-1	+	5-11	900	48	79
IV.3	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-2	+	4-21	630	50	71
IV.4	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-1	+	7-78	974	110	130
IV.5	O	+	-	-	+	+	-	+	+	+	+	+	-	+	2-2	+	7-48	972	84	120
IV.6	O	+	-	-	+	+	-	+	+	+	+	+	-	+	1-1	+	10-94	810	58	82

TABLE III
DERMATOGLYPHIC ANALYSIS

	Normal Karyotype*	46,16-,C+†
Total finger ridge count		
Mean ± 1 SD	161.86 ± 34.94	169.33 ± 41.68
a-b ridge count		
Mean ± 1 SD	92.87 ± 10.24	92.28 ± 11.62
Palmar axial triradius (%)		
Mean ± 1 SD	24.85 ± 12.39	22.85 ± 9.61
atd angle (°)		
Mean ± 1 SD	52.71 ± 20.06	49.46 ± 6.48

* 16 cases; † 7 cases.

(Ferguson-Smith *et al*, 1962; Court Brown *et al*, 1966).

It is of interest that our index case was detected fortuitously, and that the examined members of this family were all phenotypically normal. Several reports have associated a variety of congenital malformations with morphological autosomal variations, and specifically, an elongation of one chromosome no. 16 (Jennings and Turner, 1961; Anders *et al*, 1965; German, Chlers, and Engle, 1966; Moors, Anders, and Emanuel, 1966; Emerit *et al*, 1967;

Fraumeni, Geiser, and Manning, 1967; Grimaud, Gilgerenkrantz, and Bemal, 1967; Stewart *et al.*, 1969). In some of these reports, the chromosomal structural anomaly has been followed for several generations in the same kindred. On the other hand, the same anomaly has been reported in families without phenotypical abnormalities (Carr, 1963; Rowley and Hodges, 1967; Therkelsen, Lamm, and Henningsen, 1967; Guanti, Balacco-Gabrieli, and Battaglia, 1969), in normal newborn infants (Walzer, Breau, and Gerald, 1969), and in normal, unselected populations (Jacobs, Brunton, and Court Brown, 1964; Court Brown, Jacobs, and Brunton, 1965; Court Brown *et al.*, 1966; Court Brown, 1967). The fact that the proportion of secondary constrictions observed in a given specimen may vary with the technique used (Sasaki and Makino, 1963; Palmer and Funderburk, 1964), diminishes the significance that can be placed on correlations between the proportion of cells affected and phenotype.

The biological significance of this particular anomaly is not understood. In certain chromosome pairs, secondary constrictions—especially those that are consistently found—can be shown to be in specific, late DNA-replicating regions (Schmid, 1963; German, 1964; Giannelli and Howlett, 1967), suggesting that DNA synthesis is completed before coiling is terminated (Schmid, 1963). An alternate possibility proposed by Schmid (1963) is that both delayed replication and a special type of spiralization are the consequence of a structural change in these regions, such as duplication or deletion. The fact that areas bearing secondary constrictions are late replicating has, by analogy with the X-chromosome, also suggested the possibility of autosomal genic inactivation of such regions (Beutler, 1963; German, 1964; Wald and Turner, 1964). There is, however, no evidence for this assumption, nor does our study demonstrate any relationship of the genetic markers to this structural variant.

Homozygosity for a secondary constriction is rare (Herrerros *et al.*, 1964). Recently, Berg *et al.* (1969) and Hirschhorn (1969) reported homozygosity of chromosomal structural variations—a satellited chromosome no. 17, and enlarged short arms of a D-group chromosome, respectively—that were detected during the study of normal relatives of patients with abnormalities.

It is reasonable, then, to assume that the presence of this marker chromosome is due to a genetically determined anomaly in coiling (a single uncoiling gene?) (Crippa, Schwartz and German, 1969), although the possibility of structural rearrangements cannot be ruled out. Thus far, the evidence suggests that these marker chromosomes

are polymorphisms whose value to the organism, if any, remains unexplained.

Summary

A kindred is reported in which a structural anomaly of one chromosome no. 16 has segregated in 4 generations. The family demonstrated no phenotypic abnormalities which might be related to this variant. A variety of genetic markers were examined and revealed no linkage relationships with the marker chromosome.

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