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Ring Chromosome 18 in a Patient with Multiple Anomalies*

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Ring chromosomes, long of interest in cytogenetics, have been intensively studied in corn and *Drosophila* (McClintock, 1932, 1938; Morgan, 1933; Battacharya, 1950) and also described in *Crepis*, *Tulipa*, *Tradescantia*, and other species. In the past few years, a number of reports of ring chromosomes in man have appeared (Table I). We recently encountered a mentally retarded patient with multiple congenital anomalies, in a high proportion of whose cells we found a ring chromosome 18.

The clinical expression of patients with 18 long (Lejeune, Berger, Lafourcade, and Rethore, 1966) and short arm deletions (Grouchy, Bonnette, and Salmon, 1966) are contrasted and compared with the findings in our patient and other patients with ring 18 chromosomes. The variability in size and frequency of ring chromosomes in human subjects and in this patient are discussed.

Case Report

The patient was a 10-year-old white boy with mental retardation and multiple congenital anomalies, who had been followed at the Indiana University Medical Center since the age of 16 months.

He was the fourth child of a healthy, non-consanguineous marriage of a 29-year-old father and 26-year-old mother. Four sibs are healthy; a fifth died of 'cord strangulation' at birth. The pregnancy and delivery were uncomplicated except for an upper respiratory infection during the fourth month of gestation. The patient was cyanotic at birth and weighed 3·97 kg. The unusual findings known to the mother at birth were 'clubbed feet, a heart murmur, and decreased movements of the elbow joints'. Developmentally, he sat at 9 months, pulled up at 12 months, crawled at 14 months, said 'mama' at 16 months, walked at 3 years, and was toilet-trained at 5 years.

At the time of evaluation, the patient (Fig. 1) was 10 years old, mentally retarded, and hyperactive. He was co-operative and able to speak with a three-word syntax. He had a kyphotic posture and broad-based, balanced gait. The height was 126 cm., weight 21·2 kg. (both below the third centile).

His occipital-frontal circumference was 49 cm. (two standard deviations below the normal). There was bony roughness over the posterior occipital region. The neck had a slight extra fold of skin over the trapezius muscles suggesting webbing, and there was a low hairline posteriorly. Ocular findings included an antimongoloid slant, hypertelorism, exotropia, nystagmus, and a normal fundoscopic appearance. Unusual facial features were large, well-differentiated, low-set ears, prominent supraorbital ridges, and a broad-bridged, upturned nose (Fig. 1). Otoscopic examination was normal. The angles of the mouth had a downward slope. The tongue was fissured. The chest had a slight anterior protuberance and a praecordial bulge. There was cardiomegaly and a grade 3/4 systolic blowing murmur, best heard along the left sternal border. The liver was palpable 3 cm. below the right costal margin. The spleen was not palpable.

Examination of the extremities revealed limitation of elbow extension at 160 degrees on the right and 170 degrees on the left. Supination and pronation were decreased by 15 degrees on the right and 10 degrees on the left. The wrist joints had ulnar deviation. The hands were hyperextensile and spade-like, with broad palms, short fingers (especially the index and the fifth), and proximally placed thumbs (Fig. 1). The lower extremities were thin, and could best be described as stork-like, with prominent knees and thin lower legs. The knee joints had a full range of motion, but the ankle joints could be moved only 5 to 10 degrees in any direction. The feet were planovalgoid with callus formation anterior to the usual calcaneal pad resulting from talipes calcaneovalgus. Bilaterally, the third toes were long and flexed beneath the second toes; the fourth and fifth toes were also moderately flexed and the first toes were broad (Fig. 1). Pulmonary osteoarthropathy and mild cyanosis were present in all fingers and toes. The external genitalia were those of a normal prepubescent male with both testes palpable in the scrotum.

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TABLE I

RING CHROMOSOMES IN CONGENITAL MALFORMATIONS

Chromosome No. or Group	Tissue	Cells with Ring (%)	Size Variation in Rings	Reference
1	Leucocytes	87	x	Gordon and Cooke (1964)
2	Bone-marrow	90		DiGrado, Mendes, and Schroeder (1964)
3	Leucocytes	—		Mukerjee and Burdette (1966)
5	Leucocytes	100		Rohde and Tompkins (1965)
C	Leucocytes	50		Fisher (1965)
	Skin	20		
C	Leucocytes	80		Turner, Jennings, Den Dulk, and Stapleton (1962)
	Skin	89		
	Bone-marrow	100		
X	Leucocytes	66		Pfeiffer and Büchner (1964)
X	Leucocytes	12		Hustinx and Stoelinga (1964)
	Skin	< 1		
X	Leucocytes	35		Lindsten and Tillinger (1962)
	Skin	0		
X	Leucocytes	7	x	Lüers, Struck, and Nivinny-Stickel (1963)
X	Leucocytes	14	x	Bishop, Blank, Simpson, and Dewhurst (1966)
	Skin	11		
X	Leucocytes	14		Paolini, Berger, Rethore, Lafourcade, and Lejeune (1966)
X	Leucocytes	41	x	Bain and Gauld (1963)
D	Leucocytes	100		Reisman, Darnell, and Murphy (1965)
D	Leucocytes	—		Adams (1965)
D	Thymus	93		Bain, Gauld, and Farquhar (1965)
D	Leucocytes	100	x	Wang *et al.* (1962)
E	Leucocytes	100	x	Wang *et al.* (1962)
17–18	Skin	66–72	x	Lucas *et al.* (1963)
	Leucocytes	55–76		
18	Leucocytes	100		Gropp *et al.* (1964)
16	Leucocytes	80		E. Pergament, T. Kadotani, A. Walczak, and L. Brando, 1965, personal communication
17–18	Leucocytes	100		Grouchy *et al.* (1964)
18	Leucocytes	100		This paper
18	Leucocytes	87·3		Genest *et al.* (1963)
*	Leucocytes	26·8*		
	Skin	10		Atkins, Sceery, and Keenan (1966)

* Unidentified ring as extra chromosome showing progressive loss with time.

Laboratory Studies. Repeated urine analyses revealed no abnormalities, and there was no chromatographic (paper) evidence of abnormal amino acid excretion. Haemoglobin 16 g./100 ml.; leucocyte counts and differentials normal. Blood urea nitrogen consistently below 15 mg./100 ml., fasting blood glucose 74 mg./100 ml., serum acid phosphatase 0·65 Bessy-Loury units, serum alkaline phosphatase 4·1 and 4·8 Bessy-Loury units (normal 2·8–6·7 units for this age-group), serum glutamic oxaloacetic and glutamic pyruvate transaminase, 27 and 21 units, respectively. C-reactive protein and antistreptolysin-O titres negative. Total serum proteins 7·4 g./100 ml. (albumin 3·2 g. and globulin 4·2 g./100 ml.). Paper electrophoresis of serum revealed albumin 44·5%, α_1-globulin 5·3%, α_2-globulin 5·3%, β-globulin 10·6%, and γ-globulin 33·3%. Serum iron was 110 μg./100 ml. with a total iron-binding capacity of 375 μg./100 ml.

Radiological Studies. These revealed microcephaly, generalized cardiomegaly, engorged pulmonary vasculature, bilateral congenital vertical talus leading to rocker-bottom feet and valgus deformities (Fig. 2). There was posterior dislocation of the head of the radius and medial dislocation of the ulnar trochlear joint on the right side. The terminal phalanges were small and the thumb was very low set (Fig. 3). The lower spine was unusual. The normal increase in the interpedicular distance that occurs on the lumbar area, craniocaudally, was reversed in that the distance at the first lumbar vertebra was 24 mm. and at the fifth 18 mm., a finding also seen in achondroplasia. The odontoid process was present. The femoral neck could only be described as massive and the femoral condyles were slightly flattened.

The conclusions derived from cardiac catheterization with cine-angiograms were: total pulmonary venous drainage into the right ventricle probably via the coronary sinus, left ventricle small with an intact interventricular septum, and a moderate left-to-right atrial shunt. All heart chambers had almost equal oxygen concentrations, and there was a moderate increase in the right ventricular and pulmonary artery pressures. The electrocardiogram had tall P waves suggestive of cor pulmonale.

An audiogram revealed a moderate high frequency loss.

Dermatoglyphics showed that the axial triradii were in the t position and 6 out of 10 fingers had whorls. The remaining fingers had ulnar loops (the left index, and the first, second, and third fingers of the right hand). There was no pattern in the thenar, hypothenar, or in the first interdigital spaces. The digital ridge count was normal. The footprints showed that the left hallucal area had a distal loop with a proximal arch in the right foot. All toes had fibular loops.

Blood from the patient, his parents, and sisters was typed for erythrocytic antigens, erythrocytic acid phosphatase, phosphoglucomutase, and serum haptoglobin. The data are shown in Table II. On the basis of heterozygosity of the patient for the MN, Kidd, and red cell acid phosphatase loci we can exclude these loci from localization in the deleted segment. The other blood group, haptoglobin, and phosphoglucomutase loci do not contribute evidence for or against inclusion in the deleted segment.

Cytogenetic Studies. Chromosome studies were made on leucocyte cultures utilizing the method of Moorhead, Nowell, Mellman, Battips, and Hungerford (1960), with modifications previously described (Palmer and Funderburk, 1965). Chromosomes of cells derived from cultures of skin specimens obtained by punch

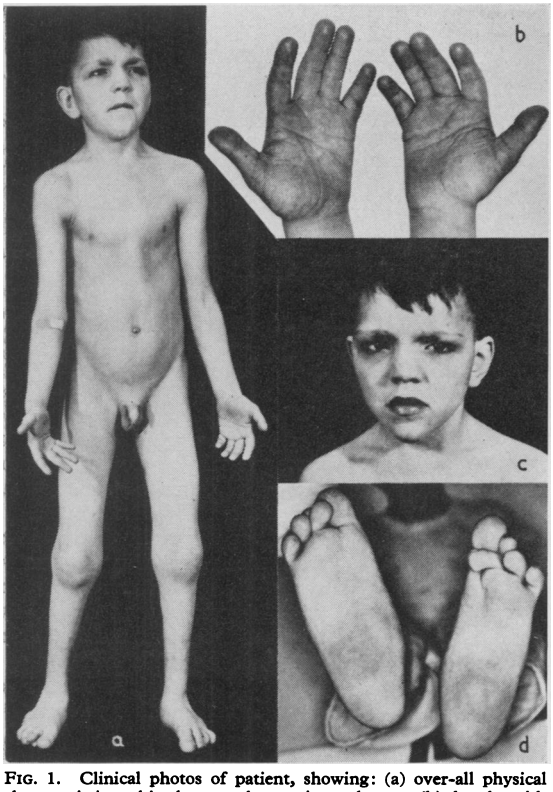

FIG. 1. Clinical photos of patient, showing: (a) over-all physical characteristics, thin legs, and prominent knees; (b) hands with broad palms, short fingers, and proximally placed thumbs; (c) hypertelorism, anti-mongoloid slant, and extropia; and (d) flexion of long third toe beneath second toe and callosity beneath the head of the vertical talus.

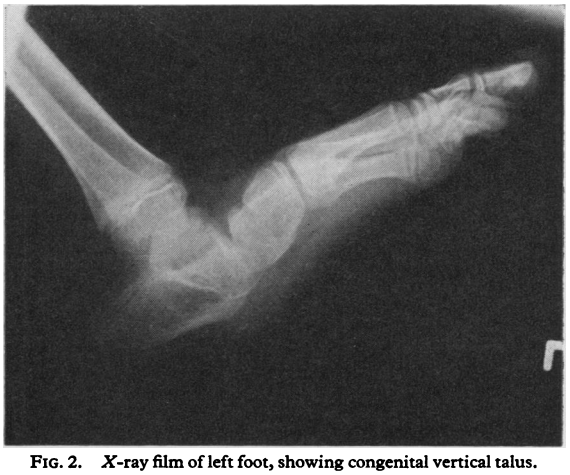

FIG. 2. *X*-ray film of left foot, showing congenital vertical talus.

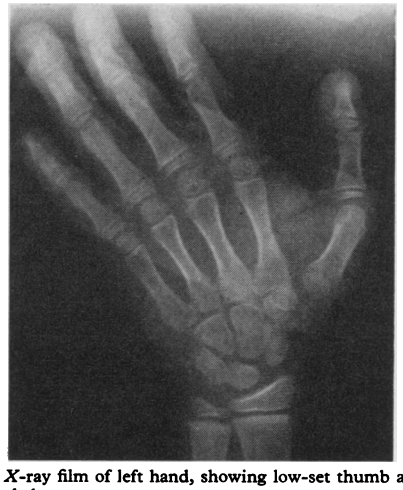

FIG. 3. *X*-ray film of left hand, showing low-set thumb and small terminal phalanges.

biopsy and grown in plasma clot were also studied. Of 146 cells of leucocyte cultures counted, 121 were observed to have 46 chromosomes, one of which was a ring replacing an absent chromosome 18. The remaining 14 cells had 45 chromosomes and, when karyotyped, all but one were shown to contain the ring chromosome and one 18 chromosome, but to have random loss of other chromosomes. Of 18 cells studied from fibroblast cultures, all had 46 chromosomes, including the ring.

A typical karyotype from leucocyte culture is shown in Fig. 4. The ring chromosome assumed various shapes in the cell, depending on the degree of contraction of chromosomes, twisting of the chromatids, and the angle

TABLE II

RESULTS OF BLOOD GROUP ANALYSIS, RED CELL ENZYME STUDIES, AND SERUM HAPTOGLOBIN DETERMINATIONS

	ABO	Rh	MNSs	K	Fy^a	Kidd	P_1	Hp*	AcPh†	PGM‡
Patient	B	r	MsNs	−	−	JK^a/JK^b	+	2-2	BA	1-1
Mother	O	R_0r	MsNs	−	+	JK^a/JK^b	+	2-1	BA	2-1
Father	AB	r	MsMs	−	−	JK^a/JK^b	+	2-1	BA	1-1
Sisters 19 yr.	A	R_0r	MsMs	−	+	JK^a/JK^b	+	1-1	BA	2-1
8 yr.	A	r	MsNs	−	−	JK^b/JK^b	−	2-1	BA	1-1
2 yr.	A	r	MsMs	−	+	JK^b/JK^b	+			

* Haptoglobin.
† Red cell acid phosphatase.
‡ Phosphoglucomutase.

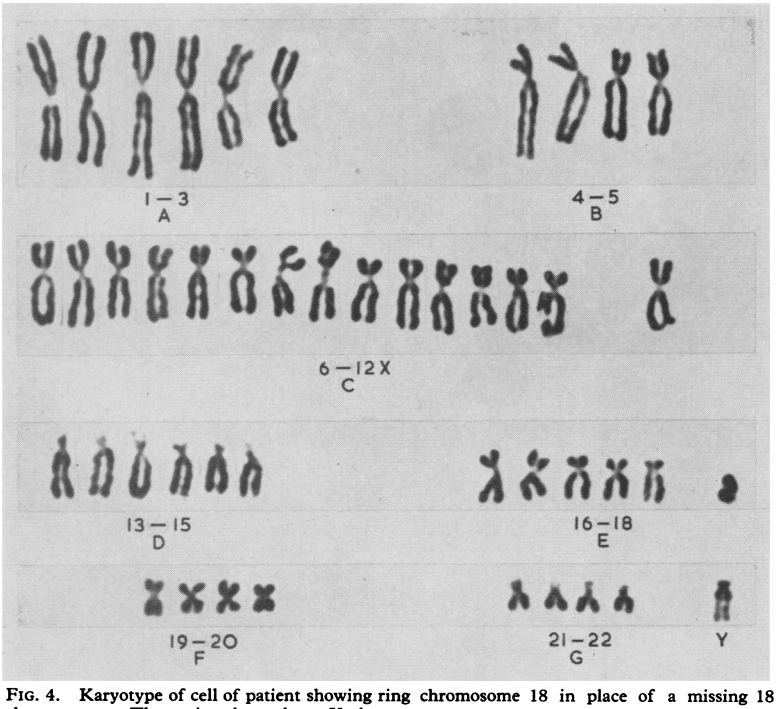

FIG. 4. Karyotype of cell of patient showing ring chromosome 18 in place of a missing 18 chromosome. The patient has a large Y chromosome.

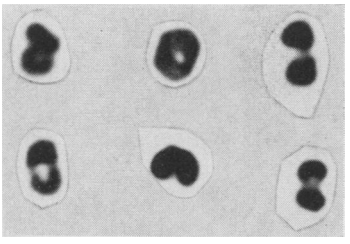

FIG. 5. Variable shapes of ring chromosome in different cells.

from which the chromosome was observed. Some of these variations are shown in Fig. 5. The ring chromosome was small in all the cells observed, and we could not discern any great variation in size other than that attributable to differences in stage of mitosis.

Autoradiographic studies on leucocyte cultures from this patient showed the ring to replicate with one unaltered 18 chromosome. It could also be readily distinguished from the late-labelling Y chromosome (Fig. 6). Cultures of peripheral leucocytes of the mother and father showed normal chromosome morphology and a number with no evidence of chromosomal rearrangement in either parent.

Discussion

Patients bearing ring chromosome 18 have a number of common clinical findings. A summary of these findings in five such patients reported in the

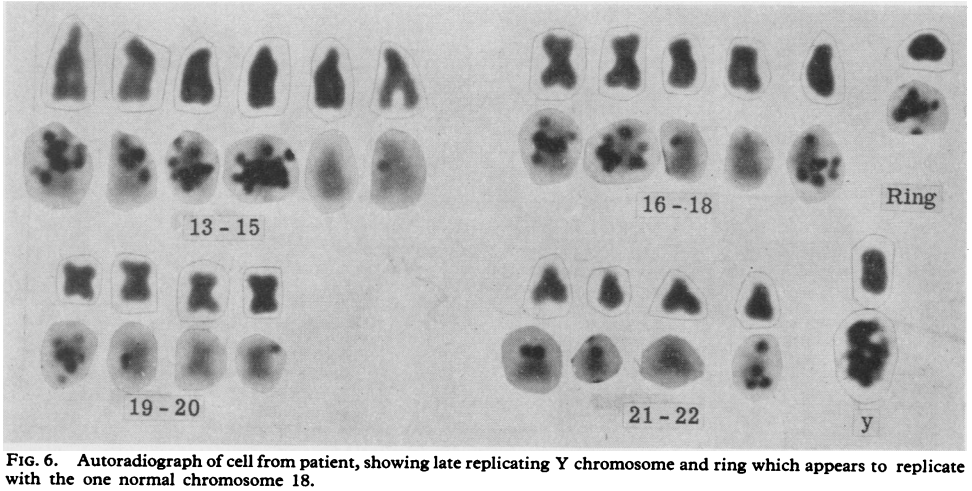

FIG. 6. Autoradiograph of cell from patient, showing late replicating Y chromosome and ring which appears to replicate with the one normal chromosome 18.

literature and our patient is shown in Table III. All patients bearing the ring 18 are characterized by mental retardation. The one reported by Lucas, Kemp, Ellis, and Marshall (1963) and our patient

TABLE III

CLINICAL FINDINGS IN RING CHROMOSOME 18 SYNDROME

	Wang *et al.* (1962)	Genest *et al.* (1963)	Lucas *et al.* (1963)	Grouchy (1965)	Gropp *et al.* (1964)	Current Paper
Sex	M	F	F	F	?	M
Mental retardation	+	+	+	+	+	+
Microcephaly			+			+
Dolichocephaly					+	
Bilateral pterygium colli				+		
Low hairline				+		+
Ear malformation	+	+			−	−
Low set					+	+
Deafness	+					
Atresia of middle ear	+	+				
Epicanthal folds	+	+		+		−
Antimongoloid slant						+
Hypertelorism	+	+		+	−	+
Strabismus						+
High arched palate					+	−
Cleft palate			+			−
Hypoplasia of mandible			+		+	−
Speech defect		+				+
Heart defect					+	+
Broad chest with widely spaced nipples				+		−
Abnormal dermatoglyphs			−	+	−	+
Single palmar creases t axial triradius				+		+
Short fingers		−	−	+		+
Thumb implantation						Low
Syndactyly of toes	+					−
Club feet		+				+
Rocker-bottom feet		+			+	+
Other toe abnormalities		+				+
Congenital dislocated hips			+			−
Kidney anomalies					+	
Hypotonia				+		
Seizures		+				−

+ = present; − = absent; blank = not received.

have the common finding of microcephaly. A number of ring-chromosome bearing subjects have abnormalities in the formation of the ears, atresia of the middle ear (Wang, Melnyk, McDonald, Uchida, Carr, and Goldberg, 1962; Gropp, Jussen, and Ofteringer, 1964), and low-set ears. Our patient's ears have normal external conformation, though they are somewhat large and low set and there is a loss of acuity in the high range at audiometric testing. Hypertelorism and epicanthic folds are not found in our patient. Oral defects in these patients may include mandibular hypoplasia, cleft palate, and high-arched palate. Foot anomalies include syndactylism (Wang *et al.*, 1962), overlapping toes, rocker-bottom feet, and club feet (Genest, Leclerc, and Auger, 1963; Gropp *et al.*, 1964). Our patient has the overlapping toes, clubbed feet, and rocker-bottom feet. One of the previously reported patients had abnormal dermatoglyphics with t axial triradius and whorls on all fingers (Grouchy, Lévêque, Debauchez, Salmon, Lamy, and Marie, 1964); similar findings were present in our patient (t axial triradius and whorls on 6 out of 10 fingers). Other specific malformations are found in individual cases.

Some of the findings in the ring-18 bearing patients discussed above are similar to those with the 18-deletion syndromes. In the formation of the ring chromosome by breakage at both ends of the chromosome and refusion of the broken ends, segments of both ends are deleted. Thus, the ring 18 chromosome may lack different segments depending on the extent of the deletion. Patients bearing the 18-ring chromosome should have features in common with both the 18 short and long arm deletion syndromes. Common findings in three patients with a deleted segment of the long arm of chromosome 18 include hypoplasia of the middle area of the face, projecting chin, and ear anomalies, including prominent antihelix, deep scaphoidal dimples, and thickly bordered helix (Lejeune *et al.*, 1966). Additional findings of subacromial dimples, small nodules in the jugular area or in the cheeks, hyperabduction of the thighs, tapering fingers, and an increase in the number of whorls on the fingers have also been reported in some patients. Although only the dermatoglyphic findings of the common characteristics of 18-L deletion syndrome were noted in our patient, he had findings in common with individual patients with the 18-L deletion syndrome, including abnormal insertion of the toes, so that there is flexion of several of the toes beneath the others, turned-down corners of the mouth, low-set ears, and cardiac malformations, i.e. interatrial septal defect and anomalous pulmonary venous drainage.

While there have been more patients reported with deletion of segments of the short arm of chromosome 18, some 13 in all, there is more inconsistency in the clinical findings (Grouchy *et al.*, 1966). Mental retardation of these patients varies in severity. There are frequent ocular signs, including hypertelorism, ptosis, strabismus, and epicanthic folds. Prosencephalic defects which have been noted in patients with a deleted short arm chromosome 18 include one case of hypertelorism and two infants with cyclopian malformations (S. Faint and F. J. W. Lewis, 1965, personal communication; Nitowsky, Sindhvananda, Konigsberg, and Weinberg, 1966). The ears are usually abnormal and low set. Micrognathia has been observed in

some cases. The hands are short, with the thumb inserted high. Malformed feet and a webbed neck have been found in a few instances. The dermatoglyphics were not unusual, with only an increase in ridge intensity found with any frequency (7 of 13 patients) and a t triradius with transverse palmar crease observed in only one patient. Of these characteristics, our patient has mental retardation, hypertelorism, nystagmus, neck webbing, and malformed feet.

Thus, our patient has some characteristics in common with both 18 L and 18 S deletion syndromes, as one might predict from loss of segments of both long and short arms of the 18 in ring formation, and indeed resembles closely those patients already reported bearing a ring 18.

Ring chromosomes have been studied extensively in corn (McClintock, 1932, 1938, 1941; Schwartz, 1953) and *Drosophila* (Sandler, 1965; Morgan, 1933; Brown and Hannah, 1952; Battacharya, 1950). It is from the behaviour of rings in these organisms that information about ring chromosomes in man has been extrapolated. Levan (1956) first described ring chromosomes in effusions of patients with malignancies. In his material, he observed variation in ring size, as well as dicentric, monocentric, and interlocked rings. At anaphase separation, both interlocked rings and dicentric rings were observed. These figures may lead to bridges resulting in chromosome breakage or in non-disjunctive distribution of ring chromosomes. The latter would then result in elimination of the ring from one daughter cell and an increase in the number of rings in the other. In the hypertriploid tumours described by Levan (1956), such variations might readily survive, while in diploid cells they may not. Ring chromosomes have also been described in other malignancies (Ising and Levan, 1957; Ishihara, Moore, and Sandberg, 1962; Baikie, Court Brown, Jacobs, and Milne, 1959; Sandberg, Ishihara, Crosswhite, and Haushka, 1962), and in leucocytes of patients exposed to irradiation (Tough, Buckton, Baikie, and Court-Brown, 1960; Bender and Gooch, 1962; Buckton, Jacobs, Court Brown, and Doll, 1962), some of these persisting for years.

To date, more than 20 patients with congenital defects have been found to have ring chromosomes in groups A–E. It is possible that rings of F and G groups also occur, but microscopically these might be difficult to differentiate from a small fragment. A summary of the frequency of ring-bearing cells in these patients is shown in Table I.

Ring instability resulting from sister strand crossing-over within the ring or replication of a ring having a half twist in the original strand, both of which lead to dicentric formation, has occurred frequently in maize (McClintock, 1938). In corn, these dicentrics or interlocking rings may undergo breakage and refusion to produce rings of varying size. Monocentric rings may fail to be incorporated into one or the other nucleus and give rise to cells lacking rings or with multiple rings. In *Drosophila*, errors in replication of ring chromosomes leading to dicentrics also occur, but at anaphase these rings do not regularly undergo breakage and refusion, as in corn. Instead, both or neither ring may be incorporated into daughter cells, resulting in loss or gain of rings at division (Griffen and Lindsley, 1946; Battacharya, 1950).

Human ring chromosomes tend to vary in size and may also be lost from the cells. This may be evidenced by the proportion of ring-bearing cells observed in a patient (Table I). On the other hand, in several patients, including ours, the ring has been observed in most of the cells. In these cases, either the ring is small enough to avoid mechanical difficulties resulting from twisting during replication, or cells lacking the ring are nonviable. If the latter were the case, we might expect to see cells with multiple rings and we do not. In corn, where both large and small rings are available for comparison, the larger rings show greater variation in size in somatic cells. The smaller rings are less likely to be involved in abnormal mitoses (McClintock, 1938), such as we find in the human material. In corn and *Drosophila*, the loss of chromosome segments or the entire ring can be followed genetically as well as cytologically. In man, this has not yet been possible since suitable markers are not available. The fact that a ring chromosome has a deleted segment has been used, however, to demonstrate the possible localization of the haptoglobin locus at the end of the long arms of one of the D chromosomes (Gerald, Warner, Singer, Corcoran, and Umansky, 1964). Our studies of red cell antigens and enzymes and serum haptoglobin indicated that the MN, Kidd, and red cell acid phosphatase genes were not in the deleted segments, but no positive evidence for localization of a gene in the deleted regions was obtained. It is in this area of relating genes to chromosomes that the ring chromosome bearing patients may provide useful material for continued study.

Summary

A 10-year-old boy is described, with psychomotor retardation, microcephaly, facial, eye, cardiac, dermatoglyphic, and skeletal anomalies, including brachydactyly, subluxation of the radio-ulnar joint, and bilateral vertical talus.

The patient had a ring chromosome 18 in a high proportion of cells of cultures of leucocytes and skin. The findings of other patients with ring chromosome 18 are summarized and compared with the present patient and with the two syndromes manifested by deletions of the long or short arm of chromosome 18. The patient had characteristics of both syndromes, thus suggesting the loss of segments of both long and short arms.

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