Multiple Congenital Anomalies Associated with a Ring-D Chromosome

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Ring chromosomes have now been observed in all except one group of the human karyotype, though, as yet, a syndrome has not been recognized which is characterized by the presence of a ring. Ring chromosomes have been observed in group A (Gordon and Cooke, 1964), in group B (Rohde and Tompkins, 1965), in group C (Lindsten and Tillinger, 1962; Turner *et al.*, 1962; Lüers, Struck, and Nevinny-Stickel, 1963; Bain, Gauld, and Farquhar, 1965; Bishop *et al.*, 1966), in group D (Bain and Gauld, 1963; Turner, 1963; Reisman, Darnell, and Murphy, 1965; Jacobsen, 1966; Gerald *et al.*, 1967; Sparkes, Carrel, and Wright, 1967), in group E (Wang *et al.*, 1962; Genest, Leclerc, and Auger, 1963; Lucas *et al.*, 1963; Gropp, Jussen, and Ofteringer, 1964; Gripenberg, 1967), in group G (Lejeune *et al.*, 1964; Hecht, Weleber, and Giblett, 1967), and when the group of origin could not be determined (Atkins, Sceery, and Keenan, 1966). They have also been reported in association with a specific disease (Di Grado, Mendes, and Schroeder, 1964), in tumours (Levan, 1956; Sandberg *et al.*, 1967; Miles, 1967), and after radiation (Tough *et al.*, 1960; Buckton *et al.*, 1962).

This report describes in detail an infant with multiple congenital anomalies and a ring chromosome in group D, for which a preliminary report has already been published (Juberg *et al.*, 1965). Previously, the association of a ring-D chromosome with anomalies similar to those of our patient had been reported in a stillborn infant (Bain and Gauld, 1963), and since then it has been reported in a 5-year-old child (Sparkes *et al.*, 1967). In our earlier report we suggested the existence of a syndrome based upon our case and the case of Bain and Gauld (1963). Sparkes *et al.* (1967) have made a similar

proposal. The syndrome would be the first to be associated with a ring chromosome.

Case Report

A white female was referred to The University of Michigan Medical Center at the age of 1 month for evaluation of multiple congenital anomalies. She was the product of the mother's first pregnancy and weighed 1365 g., after a full-term, uncomplicated pregnancy and normal delivery. The mother received prenatal care from the fifth month of her pregnancy. She stated that she neither took medications nor had x-ray examinations during the gestation. After delivery, the infant cried immediately, and she was not cyanotic. She remained in the hospital for 3 weeks and gained 603 g., weighing 1968 g. when she left.

Both parents were 21 years of age and in good health. The mother had worked as a waitress, and the father was employed in a foundry. He had not been exposed to irradiation or industrial toxins. Family history revealed no evidence of hereditary disease or consanguinity. The parents themselves were not consanguineous. One first cousin of the mother, a 28-year-old man, was mentally retarded. The only relative known with a congenital anomaly was another first cousin of the mother, also a male, who had a cleft lip.

At admission the infant's weight was 2390 g. (Fig. 1). Her cry was considered to be unusual both because of its high pitch and its brief duration. The head circumference was 29.5 cm., and the diameter of the anterior fontanelle was 1 cm. She had a hairy naevus, measuring 3 mm. × 3 mm., in the midline of the cranium over the occipital bone.

Her eyes were widely separated, and there was ptosis of the right eyelid, with a right epicanthal fold. Her pupils were equal in size, and they responded briskly to light. By funduscopic examination, the optic discs were small and dark with normal vascularity. The right pinna was angulated posteriorly. The mandible appeared underdeveloped (Fig. 2). Both external auditory canals were patent, and the tympanic membranes were intact. The child gave a startled response to loud noise.

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The bridge of her nose was broad and flat, and both nares were patent. Her neck was short and thick, especially on the left side.

Her left nipple was hypoplastic, and it was situated about 0.5 cm. lower than the right nipple which appeared to be normal. A systolic thrill was palpable along the left sternal border. The heart was not enlarged to percussion. There was a harsh, pansystolic murmur (grade 3/6), typical of an interventricular septal defect, which was heard best along the left sternal border and was widely transmitted to the back and axillae. The abdomen was normal except for a slight diastasis recti abdominis. Genitalia were normal.

The most unusual finding was the bilateral absence of thumbs without rudiments. The fifth digits were short and incurved. There were asymmetrical skin folds in the thighs, deep dimples in the lateral aspects of the buttocks, and limitation of abduction of the hips. The feet were flat, and the first and second toes were widely separated.

The infant showed spontaneous, jerking movements, but she had fair head control with normal muscular tone. The Moro, tonic neck, suck, and grasp reflexes were present, and the plantar response was extensor. The deep tendon reflexes were brisk and equal bilaterally.

When she was re-examined at 5 months of age, weight was 4119 g., head circumference was 33.3 cm., and anterior fontanelle measured 1 cm. in diameter. Motor development was retarded; she did not smile, roll over, or reach for objects.

Results of complete blood count and urinalysis were normal, and a ferric chloride test on the urine was negative. Chest x-ray showed several hemivertebrae in the cervical and thoracic regions, and the pulmonary vascular markings were prominent, though the heart was not enlarged. X-rays of the hands and wrists showed fusion of the fourth and fifth metacarpals bilaterally,

FIG. 1. Dr chromosome patient at 3 months. Asymmetrical palpebral fissures were a constant finding.

FIG. 2. Dr chromosome patient at 3 months. Note incomplete rotation of ear, small mandible, narrow palpebral fissure.

FIG. 3. X-ray of hands of Dr chromosome patient at 1 month. Note absence of thumb and first metacarpal, fused fourth and fifth metacarpals, absence of middle phalanx of fifth digit.

FIG. 4. Pneumoencephalogram at 5 months, showing single midline ventricle and absence of septum pellucidum. Note the hemivertebrae.

absence of the middle phalanx of both fifth digits, and absence of the first metacarpals as well as the thumbs (Fig. 3). They also revealed, however, that the bone age was normal. X-rays of the hips confirmed the diagnosis of bilateral dislocation. The kidneys appeared normal in size and configuration by intravenous pyelograms. An air contrast study of the central nervous system at 5 months of age revealed a single midline ventricle without evidence of a septum pellucidum. Other portions of the ventricular system were normal without evidence of thinning of the cortex. The corpus callosum was present (Fig. 4). The bony structure of the cranium was small. The position of the orbits was considered normal in relation to the skull.

Chromosomal Analyses. Leucocyte cultures were established from the patient, the mother, and the father (Table I). In all of the patient's cells there were 45

TABLE I
RESULTS OF CHROMOSOMAL ANALYSES ON
PROPOSITA, MOTHER, AND FATHER

Subject	Tissue	Chromosome No.						Analysis
		44	45	46	47	48	Total	
Proposita	Blood	0	2	39 (9)*	0	0	41 (9)	46,XX,Dr
Mother	Blood	0	2 (1)	40 (7)	0	0	42 (8)	46,XX
Father	Blood	0	2	37 (6)	0	0	39 (6)	46,XY

* Figures in parentheses represent cells analysed either visually or photographically.

distinct chromosomes plus another structure, which was interpreted as a ring chromosome. In many cells it

assumed the form of a figure-eight, with symmetrical and equal halves. In some cells there was a circle with a small cleft. In a few cells only a round mass was apparent. In cells with long thin chromosomes, the ring configuration could be seen most clearly. In these cells the unbroken circumference and a single centromere were visible. The karyotype of the patient is illustrated in Fig. 5. The group D chromosomes from selected cells, which show the more common appearances of the ring chromosome, are illustrated in Fig. 6. Parental karyotypes were normal.

Blood Group, Saliva, and Serum Types. The results of these determinations are presented in Table II and provide no evidence of linkage with the abnormal chromosome.

Dermatoglyphic Analyses. The finger configurations and ridge counts of the patient and her parents are

summarized in Table III. The parental patterns were not unusual except for the occurrence of ulnar loops on all fingers of the mother. The patient had a single low arch on the ii digit of the left hand and tented arches on the ii and iii digits of the right hand.

The palmar patterns of the patient were much more irregular (Fig. 7). The *t* triradius was missing from both palms, and the ridges crossed the palms horizontally. The *t* triradius is occasionally absent in the normal population, but the ridges in these cases usually part at the base of the palm and run vertically.

Four triradii are normally situated at the bases of digits ii, iii, iv, and v. In the patient, *c* and *d* were absent bilaterally. There were no other patterns on the palm. The occasional absence of palmar digital triradii in normal prints is almost always confined to the iv digit. This has been seen in some deletion and trisomy patients (Punnett, Carpenter, and DiGeorge,

FIG. 5. Karyotype prepared from peripheral blood culture. Arrow indicates the ring chromosome, in this instance resembling a 'figure 8'.

TABLE II
BLOOD GROUP, SALIVA, AND SERUM TYPES

Subject	ABO	Rh	MNSs	P	K	Fy ^a	Jk ^a	Le	ABH Secretor	Hp	Tf	Gc
Proposita	A ₁	CDe/cDE	MNSs	+	-	-	+	a+b+	+	2-2	C	1-1
Mother	O	CDe/cde	MMSS	+	-	-	+	a-b+	+	2-1	C	1-1
Father	A ₁	CDe/cDE	NNss	+	-	+	+	a-b+	+	2-2	C	1-1

TABLE III
FINGERPRINT CONFIGURATION AND RIDGE COUNT

Subject		Fingers									
		Left					Right				
		V	IV	III	II	I	I	II	III	IV	V
Proposita	Configuration	U	W	W	A	—	—	T	T	W	U
	Ridge count	17	22	3	0	—	—	0	0	30	14
Mother	Configuration	U	U	U	U	U	U	U	U	U	U
	Ridge count	18	18	13	14	23	22	15	13	14	18
Father	Configuration	U	U	U	R	U	W	R	U	R	U
	Ridge count	11	17	6	4	10	21	2	9	5	18

A, simple arch; T, tented arch; R, radial loop; U, ulnar loop; W, whorl; —, absent digit.

FIG. 6. Group D chromosomes from selected cells. Arrow indicates the ring chromosome.

1964). The palmar patterns of both parents were normal.

The palmar main lines were transverse and parallel. There was a single interphalangeal crease on digit v bilaterally. The parents' main lines were normal.

Patterns of the soles were unremarkable in the patient and did not resemble those that have been described in D_1 -trisomy (Uchida, Patau, and Smith, 1962).

Discussion of the implications of these unusual der-

matoglyphic findings has been already presented (Adams, 1965).

Discussion

In order to establish the identity of a new syndrome as the result of a specific chromosomal aberration, the phenotypic manifestations of the patients must be reasonably similar. Uniqueness of either individual features or a constellation may contribute to its recognition and definition. Unusual malformations involving the central nervous system and the skeletal system appear to be the most significant in the 3 patients with a Dr chromosome, which at least suggests the possibility of a syndrome.

Evidence for a Syndrome. The characteristics of the three patients with similar anomalies and a Dr chromosome are listed in Table IV. Some of these

TABLE IV
CHARACTERISTICS OF 3 PATIENTS WITH A Dr CHROMOSOME

Feature	Bain and Gauld (1963)	Sparkes <i>et al.</i> (1967)	Present Report
Sex	Female	Male	Female
Birthweight (g.)	1347	1900	1365
Maternal age (yr.)	24	18	21
Paternal age (yr.)	a	23	21
Sibship position	3	1	1
Microcephalus	a	+	+
Ocular hypertelorism	a	+	+
Ocular anomaly	+	+	+
Epicanthi	a	+	+
Auricular anomaly	a	+	+
Micrognathia	a	+	+
Holistic prosencephalon	+	+	+
Short neck	a	+	+
Hypoplastic nipple	a	+	+
Congenital heart disease	+	+	+
Congenital hip dysplasia	a	+	+
Defective or absent thumbs	+	+	+
Bilateral simian crease	+	+	+
Anomalous feet	+	+	+
Renal hypoplasia	+	+	+
Genital anomaly	+	+	+
Mental retardation	+	+	+
Growth retardation	+	+	+

+, present; —, absent; a, not stated; —, not evaluated.

FIG. 7. Schematic representation of palm- and fingerprint patterns.

features are commonly observed in patients with multiple congenital anomalies, and, therefore, they are frequently present in patients with the syndromes associated with chromosomal aberrations. These include low birthweight, ocular hypertelorism, epicanthal folds, anomalous ears, micrognathia, and congenital heart disease. Either alone or in combination these abnormalities are not sufficiently uncommon that they contribute appreciably to the definition of a new syndrome. Likewise, growth retardation is not unusual, and is seen in many patients who have neither multiple congenital anomalies nor a chromosome aberration.

By pneumoencephalography we showed a single midline ventricle without evidence of a septum pellucidum in our patient. This is evidence of defective differentiation of the primitive forebrain, a degree of holistic prosencephalon (DeMyer, Zeman, and Palmer, 1964). The stillborn reported by Bain and Gauld (1963) had 'an anterior defect of the falx with fusion of the cerebral hemispheres in this region; arrhinencephaly was present.' Therefore, two patients with a Dr chromosome have shown a similar central nervous system anomaly. While the patient reported by Sparkes *et al.* (1967) was neurologically severely defective, there was no detailed investigation of the central nervous system. A primary brain defect, such as failure of cleavage, may result not only in defective growth of the brain but also in deficient cranial expansion. Our patient had microcephalus which is further evidence of internal

abnormality. Bain and Gauld (1963) did not report the head circumference of the stillborn infant, but because of the defects present, it seems highly probable that the head was significantly small. The patient of Sparkes *et al.* (1967) had microcephalus. Varying degrees of holoprosencephaly seem to occur frequently in patients with chromosomal aberration (Miller *et al.*, 1963; Snodgrass *et al.*, 1966; Ishmael and Laurence, 1965; Shaw, Cohen, and Hildebrandt, 1965). As yet, there is not a particular brain defect invariably associated with a specific chromosomal aberration, and the holistic prosencephalon is clearly not pathognomonic of a Dr chromosome. Nevertheless, one consequence from the loss of part of this D chromosome may be malformation of the brain.

Aplasia or extreme hypoplasia of the thumbs might be pathognomonic for the presence of the Dr chromosome. The patient reported by Bain and Gauld (1963) had a rudimentary thumb with four fingers on the left hand and no thumb with four fingers on the right hand. The patient of Sparkes *et al.* (1967) had no thumbs, while the fifth fingers were short and had a single flexion crease. The incidence of this specific anomaly has apparently never been determined. Barsky (1959) states that 'absence of the entire thumb ray is not uncommon', but this is difficult to resolve with a frequency of 1 in about 90,000 for ectrodactyly (Birch-Jensen, 1949), which in this instance referred to distal phalanx defects, commonly the absence of one or more digits. This estimate was for all ectrodactyly, not just for

thumbs, and included unilateral as well as bilateral defects. Potter (1952) stated that absence of the thumb is not often bilateral and that absence of the radius is usually associated with absence of the thumb. Both radii in our patient were present and normal. Bain and Gauld (1963) do not comment upon the radii in their patient, while the heads of the radii were dislocated in the patient of Sparkes *et al.* (1967). An E_1 -trisomy patient has been reported with an absent radius and a rudimentary thumb unilaterally (Voorhess, Aspillaga, and Gardner, 1964). We have seen a normal male karyotype in a patient with multiple congenital anomalies, severe mental retardation, and absence of both thumbs (R. C. Juberg and M. G. Hart, unpublished). The three patients with the Dr chromosome suggest that aplasia or hypoplasia of the thumbs may be a necessary, but not sufficient, sign of its presence.

A constellation of bone defects might be considered to be diagnostic of the syndrome. Since congenital dislocation of the hip is not uncommon, the significance of the presence of this defect is diminished. Hemivertebrae are not common, but they are often present in patients with central nervous system malformation (Potter, 1952). Anomalous feet have been frequently observed in both the D_1 - and the E_1 -trisomy syndromes. It has become apparent that chromosomal aberration results in defects involving several systems, and the skeletal system is frequently included.

Relation of Karyotype to Phenotype. Demonstration of a causal relation between a specific phenotype and a chromosomal aberration requires that the association be observed in sufficient cases to render coincidence unlikely. In the present situation, though only three cases are reported, the phenotype and chromosomal aberration are both so rare that their association in the patients cannot be ascribed to chance, and we propose a cause-and-effect relation. We suggest that the same group D chromosome is involved in the cases described by Bain and Gauld (1963), by Sparkes *et al.* (1967), and in our case. Sparkes *et al.* (1967) by autoradiography identified the chromosome in their case as D_2 . Since the origin of a ring is through loss of chromatin material at both ends of the chromosome, the deletions may account for the multiple defects. We believe that these three cases show that the loss of chromatin material in the formation of a ring has led to malformation of several systems: the central nervous, where at least normal cleavage of the brain has been disrupted; the skeletal, where the thumbs may be specifically affected; and the cardiovascular, where normal septal closure has been

impaired. We could not show any urogenital system anomaly in our patient, though the patient of Bain and Gauld (1963) had renal hypoplasia and a bicornuate uterus, and the patient of Sparkes *et al.* (1967) had anomalies of the external genitalia. The urogenital system is frequently involved in other patients with chromosomal aberrations.

Other Dr Chromosomes. The phenotype of other patients who have been reported with a ring chromosome in group D has been very different from the three cases we believe define the syndrome, which suggests that either another member of the group is involved, or the extent of the deletion is different in the same chromosome. A male child was described by Wang *et al.* (1962) with five large acrocentric chromosomes and a ring. The mode was 46, but one member of chromosomal pair 3 had a submedian centromere and was larger than its homologue. Because of the child's similarity to the E_1 -trisomy patients, the authors concluded that there was translocation of a piece of chromosome 18 to chromosome 3. One alternative explanation is that the difference in size of the large metacentric chromosomes was not more than might be expected by normal variation, while the causative aberration was the ring. Even so, the different phenotypic manifestations suggest that the ring originated from a different pair than the ring of the present syndrome.

Turner (1963) reported an adult with a Dr chromosome. She was a triple mosaic, since 95% of her cells had 46 chromosomes, half of which contained a ring in group D, and the other half was normal for a female, while the remaining 5% had 45 chromosomes. No further details on this case are available. Even if the same chromosome were involved as in our patient, the different manifestations could be ascribed to the mosaicism.

Reisman *et al.* (1965) found a ring chromosome in group D in a male infant who had developmental and growth retardation, several congenital malformations, but normal dermal patterns. Jacobsen (1966) studied a patient with microcephalic dwarfism, mental retardation, emotional immaturity, and a ring chromosome in group D. Both these cases are clearly different from the three we believe will establish the syndrome.

Summary

A female infant, with birthweight of 1365 g. after a term pregnancy, possessed the following anomalies: microcephalus, asymmetrical ears, asymmetrical palpebral fissures, short neck, micrognathia, hypoplastic nipple, congenital heart disease, hemivertebrae, absence of both thumbs, single

flexion crease in the fifth digit bilaterally, bilateral congenital hip dislocation, and anomalous feet. At 5 months she showed growth and developmental retardation. Pneumoencephalography showed a single midline ventricle. Leucocyte culture revealed a mode of 46 chromosomes, but only 5 large acrocentrics; a ring chromosome was present in all cells, and the remainder of the karyotype was normal. Karyotypes of the parents were normal. Linkage studies using various red cell blood groups, saliva, and serum protein types showed segregation for only the MNSs system, and the patient was doubly heterozygous. Palmar dermatoglyphs were abnormal and did not resemble those reported for autosomal trisomy or deletion syndromes. In humans, ring chromosomes have been infrequently reported; thus no syndrome has heretofore been associated with a ring. To date, two other patients have been reported with a ring-D chromosome and a strikingly similar phenotype. These three cases may represent a new autosomal syndrome.

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