Discussion

A literature review disclosed only six patients with abnormalities associated with a deficiency of the long arm of chromosome 4, and five of these had a ring chromosome (Ockey *et al*, 1967; Carter *et al*, 1969; Dallaire, 1969; Faed *et al*, 1969; Hecht, 1969; Surana *et al*, 1971). The only anomalies common to three or more of these patients were low birth weight, radial anomalies, abnormally formed ears, cleft palate and/or hare lip, and cardiac structural defects. The patients with the ring 4 chromosome shared a number of features in common with those having the Wolf syndrome (4p−). This is not surprising since deletion of the short arm is presumably involved in forming the ring chromosome. Although the one other patient with a 4q− deletion had radial anomalies our patient did not. Until many more patients with the 4q− deletion are described it will be impossible to delineate a syndrome associated with the karyotype.

Chromosome polymorphisms have been noted to be more common in American Negroes than in the Caucasian population (Lubs and Ruddle, 1971). In their study of 4482 newborns, polymorphism of the Denver A, C, D, E, and G groups were noted but none were found of the B group chromosomes. The normal karyotype of both our patient's parents excludes a familial marker chromosome or balanced translocation state. This suggests the patient's chromosome deletion is significant and related to her anomalies.

This work was supported by grants from the National Foundation—March of Dimes; the Maternal and Children Health Services (USPHS) and the John A. Hartford Foundation.

MITCHELL S. GOLBUS, FELIX A. CONTE, and DONNA L. DAENTL

Department of Pediatrics, University of California–San Francisco, San Francisco, California, USA

REFERENCES

Carter, R., Baker, E., and Hayman, D. (1969). Congenital malformations associated with a ring 4 chromosome. *Journal of Medical Genetics*, **6**, 224–227.

Dallaire, L. (1969). A ring B chromosome in a female with mutiple skeletal abnormalities. *Birth Defects: Original Article Series*, **5**, pt. 5, pp. 114–116. National Foundation—March of Dimes, New York.

Faed, M., Stewart, A., and Keay, A. J. (1969). Chromosome abnormalities in two cases with bilateral radial element defects. *Journal of Medical Genetics*, **6**, 342–346.

Guthrie, R. D., Aase, J. M., Asper, A. C., and Smith, D. W. (1971). The 4p− syndrome. *American Journal of Diseases of Children*, **122**, 421–425.

Hamerton, J. L. (1971). *Human Cytogenetics: Clinical Cytogenetics*. Vol. 2. Academic Press, New York.

Hecht, F. (1969). Ring-4-chromosome: ring autosomes, Lorelei of clinical-karyotype correlation and deletion mapping. *Birth Defects: Original Article Series*, **5**, pt. 5, pp. 106–113. National Foundation—March of Dimes, New York.

Lubs, H. A. and Ruddle, F. H. (1971). Chromosome polymorphism in American Negro and White populations. *Nature*, **233**, 134–136.

Ockey, C. H., Feldman, G. V., Macaulay, M. E., and Delaney, M. J. (1967). A large deletion of the long arm of chromosome no. 4 in a child with limb abnormalities. *Archives of Disease in Childhood*, **42**, 428–434.

Sumner, A. T., Evans, H. J., and Buckland, R. A. (1971). New technique for distinguishing between human chromosomes. *Nature New Biology*, **232**, 31–32.

Surana, R. B., Bailey, J. D., and Conen, P. E. (1971). A ring-4 chromosome in a patient with normal intelligence and short stature. *Journal of Medical Genetics*, **8**, 517–521.

Monozygotic Twins with Ring Chromosome 22

Summary. Mentally retarded and monozygous twin sisters, with little physical abnormality, are described. Each twin carried a small ring chromosome, identified as a number 22.

Case Report

The twins (J.G. and C.G.) were first seen by us at 4¾ years. They had always been considered 'identical'. They were the last-born in a sibship of five, and their mother had also miscarried an apparently normal female at 6-months' gestation. She was aged 24 when the twins were born. Both parents and all sibs were physically healthy and intellectually normal.

The twins presented as breeches after an uneventful pregnancy, and were delivered at term; birth weights were 2300g and 2350g. The neonatal period was uneventful and their early development normal; they were said to have smiled at 6 weeks, sat unsupported at 7 months, walked alone at 13 months, and spoken two words by 17 months. Retarded intellectual development was noted in the second year of life, and increased in severity, so that at 4¾ years they scored a social age below 2 years (Vineland scale), and had a DQ of 35–40 on the Merrill-Palmer test.

Other clinical data are recorded in Table I. Compared with their sibs, they showed reduced stature and head circumference, but their weights were normal. Fig. 1 shows their facial similarity; at 4¾ years both their noses had a depressed bridge and a bulbous tip, but a year later (when Fig. 1 was taken) they had assumed a

Received 15 September 1972.

TABLE I
PHYSICAL AND PSYCHOLOGICAL FAMILY DATA*

	Parents		Sibs			Twins	
	B.G.	D.G.	E.G.	S.G.	H.G.	J.G.	C.G.
Sex	♂	♀	♂	♀	♀	♀	♀
Birth weight (kg)	—	—	3·64	3·29	4·43	2·30	2·35
Present age (yr)	34	30	12	10 8/12	7½	5¾	5¾
Height (cm)	181 (75–90)	164 (50–75)	146 (25–50)	146·2 (50–75)	126 (25–50)	111 (10–25)	110 (10–25)
Weight (twins at 4¾ years; kg)	82·3 (75–90)	60·6 (50–75)	34·5 (25–50)	35·1 (50–75)	26·5 (75)	19·1 (50–75)	17·9 (50–75)
Head circumference (cm)	56·3 (50–75)	57·3 (90–97)	54·5 (50–75)	52 (25–50)	51·8 (50–75)	49·2 (10–25)	49·2 (10–25)
External anomalies	None	None	None	None	None	Right inguinal hernia; abnormal right upper incisor; fine downy skin; odd cry	
Behaviour and intelligence	Normal	Normal	Normal	Normal	Normal	Hyperkinetic (DQ) Severely retarded (35–40)	

* Figures in brackets show centile range.

FIG. 1. The twin propositae at age 5¾ years. (C.G. on the left; J.G. on the right.)

more adult shape. The ears were normal, but both girls had mild epicanthus, and a congenitally discoloured central incisor; limbs and trunk were finely downy; two small pigmented naevi (1–2 cm) were found on J.G.

The twins were extremely hyperkinetic and excitable; they resorted more often to low-pitched cries than to recognizable words.

Skull radiographs showed a thick featureless vault and early fusing of the sutures, with some apparent overgrowth of ethmoid sinuses and mastoid air cells; there were no recognizable anomalies in radiographs of chest, pelvis, elbow, hand, knee or foot, and no retardation of bone growth in either twin. Haemoglobin, blood film, serum sodium, potassium, calcium, chloride, bicarbonate, phosphate, cholesterol and uric acid, blood urea and urinary amino acids were normal. Electroencephalograms were 'within normal limits'. Finger, palm, and sole dermatoglyphics in the twins, their parents and their sibs were normal, and there were no patterns that were peculiar to the twins alone; their total ridge counts of 133 and 132 compared to a paternal count of 121 and a maternal count of 19.

Serology. The twins were identical for ABO, MNSs, Rhesus, P, Lutheran, Kell, Duffy, transferrin, haptoglobin, Gm_a, cholinesterase E_1 and E_2, phosphoglucomutase (PGM_1), diaphorase, adenyl kinase, and adenosine deaminase; the probability they were monozygotic twins, derived from the above data and from sex, height, total ridge count and *atd* angles was $p_{mz} > 0{\cdot}99988$. There was evidence that loci for Rhesus (Cc), MNSs, haptoglobin, PGM_1, and adenosine deaminase had not been deleted during ring formation.

Cytogenetics. Lymphocyte cultures from both twins showed a 46,XX chromosome constitution, with one of the G-group chromosomes replaced by a ring; the ring chromosome was found also in skin fibroblast cultures. The use of quinacrine dihydrochloride fluorescence and trypsin banding (modified from Seabright, 1971) identified the normal G-group chromosomes as a pair of 21s and a single 22, whilst the ring had a staining pattern compatible with origin from a normal 22 (Fig. 2).

Fifty metaphases from each twin were analysed. Forty-seven cells from C.G. and 48 from J.G. showed 46 chromosomes, with one of the G-group replaced by a small ring chromosome. Two cells from J.G. had a 45,XX,G− constitution; two cells from C.G. had an apparently normal female chromosome constitution,

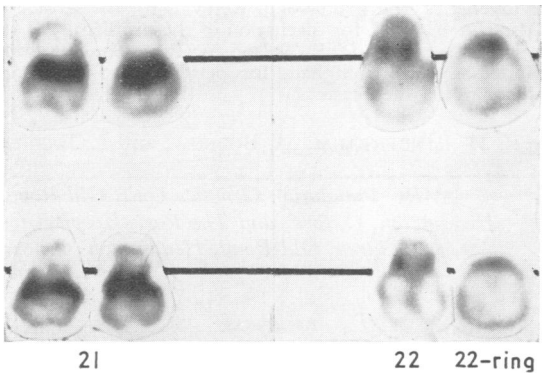

FIG. 2. G-group chromosomes from two metaphases (from C. G.). Each cell was treated with a modified trypsin banding technique. The pairs of normal 21 chromosomes are shown on the left, the normal 22s and the 22-rings on the right.

and one cell had 46 chromosomes with a dicentric ring approximately twice the size of the ring seen in other cells. In preparations not treated with colchicine, 112 anaphases were examined and a double chromatin bridge was seen in one of these. The appearances at metaphase and anaphase gave no indication of great mitotic instability, although some reservations must be made about the technical difficulties of scoring anaphase bridges from very small rings.

The parents and sibs showed normal chromosomes.

Discussion

We have found reports of 23 individuals in whom a G-group chromosome is replaced by a ring (see Table II). We know of three other cases (B. Noël, personal communication—two cases of ring 22; R. Nelson, personal communication—one case of ring 22), in addition to the twins described above. Supernumerary G-ring-like structures have been described by Atkins, Sceery, and Keenan (1966) and Summitt (1969); but the G identity of these rings is not established.

TABLE II

PHENOTYPIC CLASSIFICATION OF G-RINGS

Twenty-three cases from the literature, one personal communication, and twins J.G. and C.G.

Reference	Suggested Ring Origin*	IQ/DQ†	Head Circumference (centile)	Height (centile)
Mongoloid				
Blank and Lorber (1969)‡		↘	3?	<3
Grosse *et al* (1971) case 1	21.L	74	<3	3
Grosse *et al* (1971) case 2	21.L	<50	10	50
Antimongoloid				
J. L. German and A. G. Bearn (1962)**	21.AR	65	?	?
Lejeune *et al* (1964)‡		↘	<3	<3
Reisman *et al*, (1966)	21.L	?	↘	↘
Challacombe and Taylor (1969)††		?	<3	<3
Say *et al* (1970)‡		Slight↘	75	10
Nevin *et al* (1971)		<50	25	<3
Crandall *et al* (1972) case 1	21.CB	76	95	3
Other				
McIlree *et al* (1966)		Normal?	Normal?	Normal?
Benson *et al* (1967)‡‡		Normal?	Normal?	Normal?
Hoefnagel *et al* (1967)	22.AR	↘	?	75
Reisman *et al* (1967)		22	25	25
Weleber *et al* (1968)		54	<3	90,→10
Talvik and Mikelsaar (1969)	22.AR	↘	3	75
Zdansky *et al* (1969)		80	?	<3
Podugolnikova and Blumina (1970)		↘	<3	<3
Dubowitz *et al* (1971) case 1		<50	75	80
Dubowitz *et al* (1971) case 2		↘	?	97
Richards *et al* (1971)		↘	?	<3
Crandall *et al* (1972) case 2	22.CB	10	3	10
Crandall *et al* (1972) case 3	22.CB	22	<3	10
R. Nelson (personal communication)	22.CB	<35	50	<3
Both twins J.G. and C.G. (present report)	22.CB	35–40	10–25	10–25

* *Cytogenetic* attributions—by length (L), autoradiography (AR), or chromosome banding (CB).
† ↘ indicates 'markedly lowered'.
‡ Mosaic: 46,Gr/45,G−.
** Cited in Penrose (1966) and Penrose and Smith (1966).
†† Mosaic: 46,Gr/46,Gq−/45,G−.
‡‡ Mosaic: 46,Gr/46, normal (only 4% of cells had the ring).

Chromosome banding techniques have only recently permitted a definite identification of chromosomes involved in G-ring formation. Quinacrine fluorescence has been used to identify a ring 21 and two cases of ring 22 (Crandall *et al*, 1972); proteolytic treatment has been used to identify two unrelated cases of ring 22 (B. Noël, personal communication), and to identify the ring chromosomes in our twin propositae.

Without knowing the origin of the ring, phenotype-genotype correlations are difficult. Even within the groups of 21 ring and 22 ring phenotypic variability may be expected, due to variable amounts of deletion and duplication within the ring, mosaicism and varying proportions of several cell lines in different tissues at various periods of development, other genetic and environmental factors (eg, expression of recessive alleles due to the partial monosomy occasioned by the ring), and the age at ascertainment.

Some previous cases have been described as 'mongoloid' (Blank and Lorber, 1969; Grosse *et al*, 1971), whilst others have been thought to have 'antimongoloid' features (Lejeune *et al*, 1964; and others, see Table II); it is reasonable to suppose that cases included in these two groups carry a ring chromosome, with duplications or deficiencies, that has arisen from a number 21 chromosome. An attempt at phenotypic classification, based on the presence or absence of mongoloid or antimongoloid features only, is made in Table II; (the group listed as 'other' presumably contains all cases of ring 22 and possibly some atypical ring 21s). Most of the cases in the antimongoloid group have a very small ring, or an associated 45,G− line, and somewhat resemble the cases of 45,G−, described by Thorburn and Johnson (1966), Hindle (1967—cited in Challacombe and Taylor [1969]), and others, and the case of 45,21− of Gripenberg, Elfving, and Gripenberg (1972); they have less in common with the case of Al-Aish *et al* (1967).

The ring 22 cases of Crandall *et al*, of Noël, and the twins we describe, have a paucity of physical signs in common, and fairly normal facies, but all show severe mental retardation; other ring 22 cases show more phenotype abnormality. The G-ring cases with mongoloid or anti-mongoloid features (Table II) appear to show greater growth retardation and perhaps less severe mental retardation than the 'other' group, although the absence of IQ data in many of the published reports makes it difficult to be sure on this latter point.

We have found no other reports of monozygous twins with ring chromosome anomalies.

We wish to thank Dr C. Ounsted for permission to report the twins, Dr Nora Blackwell—for much of the cytogenetics, and Professor J. Renwick for the serology. Also, Dr B. Noël, for discussion of the problem, and of his own cases; and Dr R. Nelson and Professor Charlotte Anderson of Birmingham for permission to mention their unpublished case.

R. H. LINDENBAUM, M. BOBROW, and L. BARBER

MRC Population Genetics Unit, Old Road, Headington, Oxford, and The Park Hospital for Children, Old Road, Headington, Oxford

REFERENCES

Al-Aish, M. S., de la Cruz, F., Goldsmith, L. A., Volpe, J., Mella, G., and Robinson, J. C. (1967). Autosomal monosomy in man. *New England Journal of Medicine*, **277**, 777–784.

Atkins, L., Sceery, R. T., and Keenan, M. E. (1966). An unstable ring chromosome in a female infant with hypotonia, seizures, and retarded development. *Journal of Medical Genetics*, **3**, 134–138.

Benson, P. F., Taylor, A. I., and Gough, M. H. (1967). Chromosome anomalies in primary lymphoedema. *Lancet*, **1**, 461–462.

Blank, C. E. and Lorber, J. (1969). A patient with 45,XX,G−/46,XX,Gr mosaicism. *Journal of Medical Genetics*, **6**, 220–223.

Challacombe, D. N. and Taylor, A. (1969). Monosomy for a G autosome. *Archives of Disease in Childhood*, **44**, 113–119.

Crandall, B. F., Weber, F., Muller, H. M., and Burwell, J. K. (1972). Identification of 21r and 22r chromosomes by quinacrine fluorescence. *Clinical Genetics*, **3**, 264–270.

Dubowitz, V., Cooke, P., Colver, D., and Harris, F. (1971). Mental retardation, unusual facies, and abnormal nails associated with a group-G ring chromosome. *Journal of Medical Genetics*, **8**, 195–201.

Gripenberg, U., Elfving, J., and Gripenberg, L. (1972). A 45,XX, 21− child: attempt at a cytological and clinical interpretation of the karyotype. *Journal of Medical Genetics*, **9**, 110–115.

Grosse, K.-P., Böwing, B., Hopfengärtner, F., Reinhardt, G., and Sitzmann, C. F. (1971). Ring G-Chromosom: zwei kasuistische Beiträge und Literaturübersicht. *Humangenetik*, **12**, 142–155.

Hoefnagel, D., Schroeder, T. M., Benirschke, K., and Allen, F. H., Jr. (1967). A child with a group-G ring chromosome. *Humangenetik*, **4**, 52–58.

Lejeune, J., Berger, R., Rêthoré, M.-O., Archambault, L., Jérôme, H., Thieffry, S., Aicardi, J., Broyer, M., Lafourcade, J., Cruveiller, J., and Turpin, R. (1964). Monosomie partielle pour un petit acrocentrique. *Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences*, **259**, 4187–4190.

McIlree, M. E., Tulloch, W. S., Newsam, J. E., and Barclay, J. (1966). Studies on human meiotic chromosomes from testicular tissue. *Lancet*, **1**, 679–682.

Nevin, N. C., MacLaverty, B., and Campbell, W. A. B. (1971). A child with a ring G chromosome (46,XX,Gr). *Journal of Medical Genetics*, **8**, 231–234.

Penrose, L. S. (1966). Antimongolism. *Lancet*, **1**, 497.

Penrose, L. S. and Smith, G. F. (1966). *Down's Anomaly*, pp. 142–144. Churchill, London.

Podugolnikova, O. A. and Blumina, M. G. (1970). The ring chromosome of G-group of a child with congenital mental deficiency. *Genetika*, **6**, No. 3, 156–161.

Reisman, L. E., Darnell, A., Murphy, J. W., Hall, B., and Kasahara, S. (1967). A child with partial deletion of a G-group autosome. *American Journal of Diseases of Children*, **114**, 336–339.

Reisman, L. E., Kasahara, S., Chung, C-Y., Darnell, A., and Hall, B. (1966). Anti-mongolism: studies in an infant with a partial monosomy of the 21 chromosome. *Lancet*, **1**, 394–397.

Richards, B. W., Rundle, A. T., Hatton, W. M., and Stewart, A. (1971). G-group ring chromosome in a mentally subnormal girl. *Journal of Mental Deficiency Research*, **15**, 61–72.

Say, B., Tunçbilek, E., Yamak, B., and Balci, S. (1970). An unusual chromosomal aberration in a case of Chediak-Higashi syndrome. *Journal of Medical Genetics*, **7**, 417–421.

Seabright, M. (1971). Rapid banding technique for human chromosomes. *Lancet*, **2**, 971–972.
Summitt, R. L. (1969). Cytogenetics in mentally defective children with anomalies: a controlled study. *Journal of Pediatrics*, **74**, 58–66.
Talvik, T. A. and Mikelsaar, A.-V. N. (1969). A new case of ring chromosome of the group 21–22 (G_2?). *Genetika*, **5**, No. 12, 129–133.
Thorburn, M. J. and Johnson, B. E. (1966). Apparent monosomy of G autosome in Jamaican infant. *Journal of Medical Genetics*, **3**, 290–292.
Weleber, R. G., Hecht, F., and Giblett, E. R. (1968). Ring-G chromosome, a new G-deletion syndrome? *American Journal of Diseases of Children*, **115**, 489–493.
Zdansky, R., Bühler, E. M., Vest, M., Bühler, U. K., and Stalder, G. (1969). Familiäres Mosaik mit G-Ring. *Humangenetik*, **7**, 275–286.

An Autosomal Recessive Form of Craniofacial Dysostosis (The Crouzon Syndrome)

Summary. Craniofacial dysostosis, the Crouzon syndrome, occurs sporadically and in families; the clearly heritable form up to now has been autosomal dominant. We ascertained two similarly affected sibs, a brother and a sister, in a sibship of nine. Neither the Negro parents nor any ancestors nor collateral relatives were similarly affected. The parents were not consanguineous. After excluding other genetic and environmental explanations, we concluded that the reasonably typical findings of the disorder in the two sibs were probably genetically determined by a single, autosomal recessive gene.

Craniofacial dysostosis, or the Crouzon syndrome after its describer, generally results in the following phenotype: cranial synostosis or synostoses, bilateral exophthalmos with external strabismus, psitticorhina, and maxillary underdevelopment with relative mandibular prognathism and a drooping lower lip. From the time of the original description most observers have recognized the syndrome to be genetically determined—specifically, monogenically as autosomal dominant—and they have usually attributed sporadic cases to spontaneous mutation. Most authors have ascribed the frequent variability in the manifestations to irregular expression rather than to anomaly of penetrance.

Our purpose in this report is the description of two sibs, a female and a male, with manifestations of the syndrome; however, neither the parents nor the grandparents nor any consanguineous relatives have a similar appearance. After evaluating other explanations, we propose that the craniofacial disorder in the family is monogenically determined as autosomal recessive.

Received 4 April 1972.

Case Reports

The sister of the propositus (Fig. 1) was born on 31 October 1961 and was first referred to the Confederate Memorial Medical Center of Shreveport, Louisiana, at the age of 9 months, because in treating her respiratory symptoms, the family physician noted a prominent anterior fontanelle. Results of the examination of her spinal fluid were normal, and she was treated for bilateral otitis media, the examiners noting no morphological abnormalities. Though the anterior fontanelle bulged on subsequent examinations at 10, 12, and 14 months, she was asymptomatic. She had two examinations in the clinic during the following year, and the anterior fontanelle bulged on each occasion.

At 28 months of age she showed rotatory nystagmus, exophthalmos, and visual defects. Skull radiology showed closed sutures and prominence in the region of the anterior fontanelle. Ventriculograms, made by trephining, demonstrated no abnormalities; but, three months later, her scalp still bulged at the operative sites.

She did not return for examination in our hospital until 9 years of age following the determination of visual difficulty in school. Her height of 132 cm placed her between the 25th and 50th centiles. By this time she manifested scaphocephaly with a slightly ridged sagittal suture; there was also bilateral prominence of the frontal bones (Fig. 2). She had a parrot-beaked nose and a relatively underdeveloped maxilla with a prominent mandible and a drooping lower lip (Fig. 3). Though she appeared to have somewhat shallow orbits and prominent globes, she did not have exophthalmos by measurement. Table I lists pertinent determinations, including her diminished visual acuity presumably from partial optic atrophy; from the cranial and intercanthal measurements we calculated her canthal index to be 43 and her circumference-interorbital index to be 8·3 (Gorlin and Pindborg, 1964). She continued to have rotatory nystagmus. She had no other significant abnormalities: specifically, her ear canals were normal, her nasal septum deviated slightly to the left, and her palate, uvula, and tongue were normal; she had 10 maxillary teeth, missing both canines, and 11 mandibular teeth, missing one first molar; her hands and feet were normal.

Skull radiology at 9 years displayed anterior flattening of the frontal bones and heavy convolutional markings,