The 13q- Deletion Syndrome

ELIZABETH GRACE,* J. DRENNAN,† DOREEN COLVER, and R. R. GORDON

From The Centre for Human Genetics and the Children's Hospital, Sheffield

Since 1963 intermittent reports have appeared which indicated that deletion of a D chromosome, with or without ring formation, could be associated with various congenital malformations (Bain and Gauld, 1963; Lele, Penrose, and Stallard, 1963; Thompson and Lyons, 1965; Jacobsen, 1966; van Kempen, 1966; Bloom, Gerald, and Reisman, 1967, Gerald *et al*, 1967; Juberg *et al*, 1969; Laurent *et al*, 1967; Mikelsaar, 1967; Sparkes, Carrell, and Wright, 1967; Teplitz *et al*, 1967; Varela and Sternberg, 1969).

Lejeune *et al* (1968) proposed that there was a specific ring D syndrome and Allderdice *et al* (1969) widened this concept to a specific 13q- syndrome since one of their cases had a straight 13q- deletion and the other a 13r. It is also likely that in the cases of Lejeune *et al* (1968) a 13 chromosome was the member of the D group involved.

The clinical features most frequently found in the 23 cases reported were collected by Allderdice *et al* (1969) and are shown in Table I. Since then a further short report has been made by Tolksdorf, Wiedmann, and Goll (1969). Two further cases are reported here which clinically and cytogenetically seem to belong to this specific syndrome.

Case Histories

Case 1 (Fig. 1). Born 23 May 1967, weight 2016g at 40 weeks; illegitimate of Italian/Lithuanian parentage. Both parents had two normal children by different partners. The child was abandoned by both parents at 4 months, and has been in the residential care of a local authority ever since.

He was first seen at 6 months, weight 6692g, skull circumference 37.5 cm. Gross mental retardation; no hypotonia; no hypertonia; abnormal facies. He was able to smile but there was no other development. Skull x-ray showed no craniostenosis. He was seen again at 4 years, when his weight was 9520g, head circumference 43 cm. He was able to see and hear, but unable to sit unsupported. There were no signs of cerebral palsy.

Received 24 September 1970.

* Present address: Department of Pathology, Royal Hospital for Sick Children, Edinburgh.

† National Institute of Health Research Fellow, Children's Hospital, Sheffield.

TABLE I

CLINICAL FEATURES OF THE
13q- DELETION SYNDROME
(Modified from Allderdice *et al*, 1969)

- * Mental retardation (microcephaly)
- Broad prominent nasal bridge
- Hypertelorism
- Microphthalmia
- Epicanthus
- * Ptosis
- Colobomata
- * Retinoblastoma
- Micrognathia
- * Protruding maxilla
- Short neck (with folds)
- Low set (malformed) ears
- Large (malrotated) ears
- * Facial asymmetry
- Congenital heart disease
- * Imperforate anus
- Hypospadias (epispadias)
- Undescended testes
- Bifid scrotum
- * Pelvic girdle anomalies
- Foot and toe anomalies
- Absent thumb
- Short 5th finger
- Short 4th finger

* Important features in our two cases.

He could smile and swallow, but there were no other signs of development. He did not have convulsions. The scrotum was hypoplastic; the testes were undescended (Fig. 2); no heart murmur; skeletal survey normal; WR negative; no abnormal aminoaciduria.

Cytogenetic Studies. Sex chromatin was negative; leucocytes were cultured from peripheral blood on two separate occasions (6 months and 4 years). The karyotype of the major cell line was 46,XY,Dr (see Table II). Results from terminal labelling indicated the ring replaced a number 13. Karyotypes of the parents were not obtained.

Case 2 (Fig. 3a and 3b). A third child of a normal pregnancy, weight 2044g, born at 40 weeks with gross congenital malformations involving the legs and genitalia.

There was arthrogryposis of both legs; rectovaginal fistula (Fig. 4); abnormal facies; and clouding of the cornea which was diagnosed by ophthalmologists as being due to bilateral retinoblastoma.

Examination of her back revealed intact skin with a palpable gibbus at L1. The upper extremities were unremarkable. The lower extremities were fixed in a

FIG. 1. Case 1: full face and profile at the age 6 months. There is no evidence here of the absent frontal nasal depression present in the French case reports (Lejeune *et al*, 1968).

Buddha type position with changes suggesting arthrogryposis. Severe talipes equino varus was also noted. All major muscle groups contracted to pin and faradic stimulation. Pin and touch sensation were intact and she was continent of urine. Bilateral partial syndactylism of the 4th and 5th toes was present. An incidental postnatal femoral fracture healed without incident.

FIG. 2. The genitalia in case 1: hypoplastic scrotum, and undescended testes.

Radiological examination showed agenesis of lumbar vertebra 2, 3, and 4 with resumption of the normal vertebral column caudally (Fig. 5). Failure of fusion of the neural arches of the cervical and upper thoracic vertebrae as well as rib anomalies were also observed.

She refused to feed at the start but was then able to swallow. She never even started to smile. Her parents refused all treatment. She died at six months and a necropsy was refused.

Cytogenetic studies. Sex chromatin was positive. Leucocytes were cultured from the peripheral blood on three separate occasions. The karyotype of the major cell line was 46,XX,Dr and as in case 1 the ring replaced a 13. A sample of skin failed to grow. Karyotypes of the parents were normal.

Results

Cytogenetics (Fig. 6). The formation of ring chromosomes results in monosomy for the deleted terminal regions. If the ring forms or subsequently becomes twisted, a breakage-fusion-bridge cycle occurs (McClintock, 1938). This instability results in rings of varying sizes, dicentric rings and cells where the ring has been lost due to anaphase lag (ie, 46,Drdic and 45,D-).

These two types of cell were observed in both cases (Table II). Cells of case 2 were harvested without colcemid at intervals of 30 minutes for three hours in order to examine anaphases. If a breakage-fusion-bridge cycle was occurring, one would expect to see anaphase bridges. None were observed, however the proportion of dicentrics in case 2 was only 4%.

The D chromosome pairs were identified by autoradiographic techniques using tritiated thymi-

FIG. 3. Case 2: full face and half profile. The facial asymmetry is obvious and the resemblance to case 1 is clear. The legs are in plaster but it was impossible to correct the deformity completely.

TABLE II
RESULTS OF CHROMOSOME ANALYSIS ON TWO OCCASIONS

Case	45,D -	46,Dr	46,Dr +	47,Dr,Dr	47,Dr + ,Dr +	Total
1	0	50	4	0	0	54
	2	38	7	0	1	48
2	11	227	18	1	3	260
	3	175	10	0	0	185

dine. Both density and pattern of silver grains indicated the missing D group chromosome to be a number 13 (Gianelli and Howlett, 1966). Little emphasis was placed on the grain counts on the ring as these were presumed to be artificially low. When chromatids overlap the β particles emitted by the radioactive thymidine from the obscured chromatid are prevented from impacting on the autoradiographic emulsion and initiating the development of silver grains. In these cases, the rings were usually contorted and sister chromatids were overlapping.

Cells, where the D group could be well separated 7—J.M.G.

autoradiographically, were photographed and printed to a constant enlargement. The lengths were measured by running a toothed wheel or opisometer over the image and counting the indentations. These units were then converted to μ .

TABLE III
RESULTS OF AN ANALYSIS OF VARIANCE ON TOTAL CHROMATID LENGTH OF RING AND THE NORMAL 13

Case	CSS		df	V	VR
<i>Small ring size-class</i>					
1	R	174.006	21	8.286	2.726*
	13	63.819	21	3.039	
2	R	110.649	21	5.269	1.564 (NS)
	13	70.749	21	3.369	
<i>Large ring size-class</i>					
1	R	304.956	17	17.939	5.903**
	13	63.819	21	3.039	
2	R	75.083	17	4.417	1.31 (NS)
	13	70.749	21	3.369	

* Significant at 0.05% level.

** Significant at 0.001% level.

FIG. 4. The genitalia in case 2: a rectovaginal fistula and absent anus.

Estimations of the length of the small rings are less accurate than those of the normal 13 because of the contorted appearance, but it was assumed that the length of the ring was as often overestimated as it was underestimated. The conformation of the large rings were usually clear and so measurements of the large rings were less prone to error.

Statistical analyses were used to estimate to what extent the operation of the breakage-fusion-bridge cycle was affecting the size of the ring. On examination of the measurements, the rings seemed to fall into two classes depending on their lengths. These classes were treated separately and the variation within each size class was compared to that of the normal 13. The results are set out in Table III.

The behaviour of the ring was different in each case. In case 2 the ring was stable within its class. The stability could be attributed to either a selection for certain sizes or the infrequency of occurrence of the breakage-fusion-bridge cycle. The results of a *t* test on the difference in length between the small ring and the normal 13 was significant in case 2 and revealed a reduction in length of

FIG. 5. Case 2: lateral x-ray of the spine to show focal lumbar agenesis.

0.4 μ or 7% of the total chromatid length of the normal 13. The ring was unstable in case 1. The *t* test was not significant because the ring was as often larger as it was smaller than the normal 13 (Table IV).

TABLE IV
RESULTS OF *t* TEST ON DIFFERENCE
IN TOTAL CHROMATID LENGTH
BETWEEN SMALL RING AND THE
NORMAL 13

Case	$\bar{d}$	V	df	t
1	0.03	5.004	21	0.057 (NS)
2	0.76	1.517	21	2.89**

** Significant at 0.001% level.

FIG. 6. Autoradiographs of group D chromosomes from selected cells in both cases.

FIG. 7. Diagrammatic representation of the dermatoglyphic patterns in both cases.

Similar variability in ring D size has been reported previously (Lejeune *et al*, 1968; Ayraud and Szepetowski, 1969) and the gene-dosage effects have been discussed.

Dermatoglyphs (Fig. 7). There was only one unusual feature in case 1, and that was a small tri-radius at the base of digit 1 on the right hand. In case 2 the feet showed severe talipes; there were open fields on the hallucal areas, but the remaining area was dry and scaly so that no patterns could be detected.

Discussion

The clinical features present in our cases seem to resemble those already described, but they differed considerably in the two cases. Thus, although the facies were similar and there was gross mental retardation in each, case 1 had gross malformations of the spine, eyes, and genitalia. Such differences in clinical presentation have been described in previous cases in this and other chromosomal abnormalities. The differences could be due to 3 main effects. Firstly, the D group is made up of 3 pairs and until recently the individual mem-

FIG. 8. Case 1: at the age 2½ years. The resemblance to case 2 of Lejeune *et al* (1968) is obvious.

bers could not be recognized. Secondly, the extent of the deletion may differ even in the same chromosome. Thirdly, in the case of ring chromosomes duplication and/or deletion of additional segments of the ring can occur.

Certain clinical features of interest do however keep recurring in this syndrome and are relatively rare in others (see Fig. 8).

Retinoblastoma. The original case of Dq— was in a child who was only slightly mentally retarded and who had bilateral retinoblastoma. One of our cases also had this condition and its association with a D chromosome deletion has now been recognized in 6 cases but in one (Wilson, Melnyk, and Towner, 1969) it was apparently a 14 chromosome which was involved and not a 13.

Pelvic Girdle Anomalies. These have been variable and usually only detectable by radiology. In our second case there was gross clinical abnormality with complete absence of the lumbar spine on x-ray, which was no doubt responsible for the neurological defect in the legs, which was very similar to the clinical state of arthrogryposis which is often associated with myelodysplasia.

Complete lumbosacral agenesis is a well recognized congenital abnormality. Pairs of somites are serially added as the embryo grows in size. The resumption of normal vertebral growth pattern caudal to focal lumbar agenesis has not been described in the literature. Experimental studies (Holtzer, 1963) suggests that the neural tube has a primary influence on the formation of the neural arch whilst the notochord has a direct effect on the development of the vertebral body. Excision of either of these neural elements prevents the formation of the corresponding part of the vertebral structure. The clinical demonstration in this case of motor and sensory function in the lower extremities indicates that the spinal cord itself was uninterrupted.

Absent Thumbs. Absent thumbs have been reported in 8 out of 24 cases of Dq—, 13q—, and 14r. This clinical feature is not, of course, restricted to Dq— and is found in other chromosome abnormalities (Faed, Stewart, and Keay, 1969). However, it may be a useful pointer to the possible diagnosis of 13q— syndrome in a child with multiple congenital malformations.

However much the clinical features may vary in this syndrome, it seems that the combination of abnormalities which occurs along with the facial features will make it likely that it can be clinically recognized, or at least suspected, in the future.

Our thanks are due to Mr R. B. Zachary and Professor R. S. Illingworth for permission to report cases originally admitted to their care.

REFERENCES

- Allderdice, P. W., Davis, J. G., Miller, A. J., Klinger, H. P., Warburton, D., Miller, D. A., Allen, F. H., Abrams, C. A. L., and McGilvray, E. (1969). The 13q— deletion syndrome. *American Journal of Human Genetics*, **21**, 499–512.
- Ayraud, N. and Szepietowski, G. (1969). Un cas de chromosome D en anneau. *Annales de Génétique*, **12**, 259–261.
- Bain, A. D. and Gauld, I. K. (1963). Multiple congenital abnormalities associated with ring chromosome. *Lancet*, **2**, 304–305.
- Bloom, G. E., Gerald, P. S., and Reisman, L. E. (1967). Ring D chromosome. A second case associated with anomalous haptoglobin inheritance. *Science*, **156**, 1746–1748.
- 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.
- Gerald, P. S., Warner, S., Singer, J. D., Corcoran, P. A., and Umansky, I. (1967). A ring D chromosome and anomalous inheritance of haptoglobin type. *Journal of Pediatrics*, **70**, 172–179.
- Gianelli, F. and Howlett, R. M. (1966). The identification of the chromosomes of the D group (13–15). Denver. An autoradiographic and measurement study. *Cytogenetics*, **5**, 186–205.
- Holtzer, H. (1963). *Comments on Induction during Cell Differentiation in Induction and Morphogenesis*, pp. 127. Springer, Berlin.
- Jacobsen, P. (1966). A ring chromosome in the 13–15 group associated with microcephalic dwarfism, mental retardation and emotional immaturity. *Hereditas, Genetiskt Arkiv*, **55**, 188–191.
- Juberg, R. C., Adams, M. S., Venema, W. J., and Hart, M. G. (1969). Multiple congenital anomalies associated with a ring-D chromosome. *Journal of Medical Genetics*, **6**, 314–321.
- Laurent, C., Cotton, J. G., Nivelon, A., and Freycon, M. T. (1967). Déletion partielle du bras long d'un chromosome du groupe D(13–15):Dq—. *Annales de Génétique*, **10**, 25–31.
- Lele, K. P., Penrose, L. S., and Stallard, H. B. (1963). Chromosome deletion in a case of retinoblastoma. *Annals of Human Genetics*, **27**, 171–174.
- Lejeune, J., Lafourcade, J., Berger, R., Cruveiller, J., Rethoré, M. O., Dutrillaux, B., Abonyi, D., and Jérôme, H. (1968). Le phénotype (dr): étude de trois cas de chromosomes D en anneau. *Annales de Génétique*, **11**, 79–87.
- McClintock, B. (1938). The production of homozygous deficient tissues with mutant characteristics by means of the aberrant mitotic behaviour of ring shaped chromosomes. *Genetics*, **23**, 315.
- Mikelsaar, A.-V. N. (1967). The mosaicity with respect to the deletion of a part of the long arm of one of the chromosomes of group D (in man). *Genetika (Moscow)*, No. 4, 142–145.
- Sparkes, R. S., Carrell, R. E., and Wright, S. W. (1967). Absent thumbs with a ring D₂ chromosome: a new deletion syndrome. *American Journal of Human Genetics*, **19**, 644–659.
- Teplitz, R. L., Miller, D., Hansson, K. M., and Rundell, T. S. (1967). A human ring D chromosome associated with multiple congenital abnormalities. *Journal of Pediatrics*, **70**, 936–941.
- Thomson, H. and Lyons, R. B. (1965). Retinoblastoma and multiple congenital anomalies associated with complex mosaicism with deletion of D chromosome and probable D/C translocation. *Human Chromosome Newsletter*, No. 15, 21.
- Tolksdorf, J., Wiedmann, H.-R., and Goll, U. G. (1969). Ring D₁ chromosome and multiple malformations. *Lancet*, **2**, 1009.
- Van Kempen, C. (1966). A case of retinoblastoma, combined with severe mental retardation and a few other congenital anomalies, associated with complex aberrations of the karyotype. *Maandschrift voor Kindergeneeskunde*, **34**, 92–95.
- Varela, M. A. and Sternberg, W. H. (1969). Ring chromosomes in 2 infants with congenital malformations. *Journal of Medical Genetics*, **6**, 334–341.
- Wilson, M. G., Melnyk, J., and Towner, J. W. (1969). Retinoblastoma and deletion D(14) Syndrome. *Journal of Medical Genetics*, **6**, 322–327.