Retinoblastoma and Deletion D (14) Syndrome*

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Retinoblastoma has been reported in 3 subjects whose karyotypes showed partial deletion of the long arm of a D (13-15) chromosome (Lele, Penrose, and Stallard, 1963; Thompson and Lyons, 1965; Van Kempen, 1966). The child reported here is an additional case of retinoblastoma with partial deletion of the long arm of chromosome 14.

Case Report

A Caucasian girl was first seen at this hospital at 18 months of age with bilateral retinoblastoma, complete midline cleft of the secondary palate, and eczematoid dermatitis. There was moderate retardation of development and growth.

This child had been born at term, weighing 3150 g., after an uncomplicated gestation and delivery. She was born to a healthy 20-year-old primigravida mother. The age of the father is unknown. Since the birth of this child, the mother has had two normal children. The three children have had different fathers.

There was no maternal family history of retinoblastoma, congenital malformations, or mental retardation. Information about the father was unknown or withheld.

The infant ate poorly and gained weight slowly. At 1 year of age, clouding of the right pupil was noted. The child crawled at 15 months, stood with support at 17 months, and walked alone at 20 months. Medical history included two episodes of uncomplicated pneumonia, recurrent otitis media, intermittent asthma, and persistent eczematoid dermatitis.

On admission at 18 months of age, the child's right eye, which was extensively invaded by tumour, was enucleated. Post-operative treatment included irradiation with 3250 rads (total) to both orbits, intracarotid artery injection of triethylenemelamine (0.08 mg./kg.), and photocoagulations of the tumour in the left eye, followed by enucleation. Microscopical examination of the enucleated tissue from both eyes showed active retinoblastoma extending into the choroid and vitreous.

Physical Examination. At this time (January, 1968) the child is 5½ years of age and presents an attractive appearance, except for temporary orbital prostheses (Fig. 1). Height and weight are less than the 3rd percentile for age. The teeth are at a normal developmental stage for age, but are irregularly shaped, stubby, and carious. There are transverse palmar creases. The only other evident anomaly is the cleft palate. She feeds herself without assistance and is toilet trained. Her motor abilities represent her least retarded behaviour; she runs and participates in games. Her vocabulary, however, is less than 10 words, and her general behavioural quotient is estimated at 30-50 by Gesell developmental testing.

Laboratory and Investigative Studies. Normal laboratory studies included blood counts, urine analysis, serum proteins, serum bilirubin, prothrombin, and alkaline phosphatase. Blood type was A₁Rh positive. Normal percentages of haemoglobins F and A₂ in peripheral blood were found by column chromatographic techniques. Amino acid screening tests of urine and plasma yielded normal results. X-rays of the skull,

FIG. 1. Patient at 5½ years of age. Temporary orbital prostheses are in place.

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FIG. 2. Karyotype of leucocyte culture from the patient. The arrow indicates the deleted D chromosome.

cervical and thoracic vertebrae, chest, and limbs were normal. An electroencephalogram was normal.

Cytogenetic Studies. The buccal smear was sex chromatin positive. The Barr bodies in the positive cells were single and of normal size. Karyotypes were examined from three peripheral blood cultures; the results are summarized in Table I. The modal number of chromosomes was 46, and the karyotype showed an XX female pattern. In all 87 cells analysed, there were only 5 normal appearing chromosomes of the D (13-15) group. An unpaired acrocentric chromosome which

was intermediate in size between a D-group and G-group chromosome was assumed to be a D chromosome with about one-quarter deletion of the long arm (Fig. 2).

Autoradiographic studies were done on the peripheral blood cultures by the technique described by Schmid (1965) which uses continuous labelling with tritiated thymidine. A total of 30 cells was considered satisfactory for analysis. Autoradiography did not always clearly differentiate the three labelling patterns of the D chromosomes; however, the majority of analyses indicated that the deleted D was most likely chromosome 14 (Table II). These interpretations were based on the previously described labelling patterns of the D-group chromosomes (Yunis, Hook, and Mayer, 1964; Giannelli, 1965). Autoradiographic labelling of the D-group of chromosomes from 5 cells is illustrated in Fig. 3.

The karyotype of the patient is expressed as 46,XX, 14q-, according to the notation of the Chicago

TABLE I
CHROMOSOME ANALYSIS FROM PATIENT AND MOTHER

	Chromosome No./Cell				No. of Cells		Analysis
	44 or fewer	45	46	47	Counted	Analyzed	
<i>Patient</i> Leucocyte cultures (No. = 3)	4*	4*	57	0	65	87	46,XX, ?14p-
<i>Mother</i> Leucocyte culture (No. = 1)	1*	0	23	0	24	24	46,XX

*Random loss.

TABLE II
AUTORADIOGRAPHIC IDENTIFICATION OF DELETED D CHROMOSOME

	Chromosome					
	13	13 or 14	14	14 or 15	15	
No. of Cells	3	4	19	3	1	Total = 30

Conference (1966). Cytogenetic studies from other tissues of the patient were not permitted.

Chromosomal analysis from the mother's peripheral blood culture showed a normal 46,XX pattern (Table I). The father and the two half-sibs were not available for examination.

Dermatoglyphs. The dermatoglyphs of the patient are illustrated in Fig. 4. The dermatoglyphs were unusual in that the total ridge count was only 31, average for females being 127, with a standard deviation of 53 (Holt, 1961). The low ridge count was due to arches on five fingers, a vestigial radial loop on the second finger of

the right hand, and a vestigial ulnar loop on the fifth finger of the right hand. The case reported by Lele *et al.* (1963) had four arches. Only the thumbs and the fourth right finger of our patient had patterns; these were small ulnar loops. There were a single transverse palmar crease and a less developed transverse crease distally on both palms. The proximal axial triradii were not elevated distally. Both hypothenar regions showed loops opening towards the ulnar side. There was a loop in the third interdigital area.

The hallucal area of both feet showed distal loops. The case reported by Lele *et al.* (1963) showed a whorl on one foot and a loop opening towards the tibial margin on the other.

Discussion

Descriptions of the four children with retinoblastoma associated with partial deletion of a D chromosome are in Table III. These children were retarded in growth and development, with the possible exception of the patient described by Lele *et al.* (1963), who appeared normal except for an initial delay in development. The extent of follow-up is, however, not known in this instance. Cleft palate and transverse palmar creases were found in our patient and in the patient described by Thompson and Lyons (1965). An increased proportion of arches on the fingers was found in our patient and the child described by Lele *et al.* (1963). There were no other congenital anomalies that these patients had in common.

Our patient and the child described by Lele *et al.* (1963) were the least affected. Except for poor feeding and slow weight gain, these two children seemed generally healthy up to the time that the diagnosis of retinoblastoma was made. It has been believed that detectable autosomal deletions are usually associated with non-viability or severe abnormality in the affected subject (*Lancet*, 1965). The relatively few congenital defects in these two patients show that a detectable amount of chromosomal material may be missing from chromosome 14 without severe, multiple abnormalities. An alternative explanation is that some of the deleted material has been translocated to another chromosome where it is not noticeable.

The cases reported by Thompson and Lyons (1965) and Van Kempen (1966) showed many congenital anomalies. Karyotypes from peripheral blood cultures from these two patients were interpreted as showing abnormalities in addition to the deleted D chromosome.

Chromosomal analyses of the parents and sibs in the above cases were not always reported. The

FIG. 3. Autoradiographs of five D-group chromosomes. Labelling pattern is most consistent with chromosome 14.

FIG. 4. Dermatoglyphs from hand and foot prints.

TABLE III
DESCRIPTION OF 4 CASES OF RETINOBLASTOMA AND DELETION-D SYNDROME

	Present Case	Lele <i>et al.</i> (1963)	Thomson and Lyons (1965)	Van Kempen (1966)
Sex	F	F	M	M
Maternal age (yr.)	20	33	19	22
Paternal age (yr.)	Unknown	29	20	30
Gestation	Term	Not stated	40 wk.	Term
Birthweight (g.)	3150	Not stated	2580	3000
Status at time of report	Alive at 5½ yr.	Alive at 10+ mth.	Death at 3 yr.	Alive at 6 yr.
Abnormalities*	<i>Retinoblastoma, bilat. (Dx at 18 mth.); mental retardation (est. IQ 30-50); growth retardation; cleft palate; transverse palmar creases; eczematoid dermatitis; dental dysplasia</i>	<i>Retinoblastoma, bilat. (Dx at 10 mth.); slow development</i>	<i>Retinoblastoma, OD (Dx at 19 mth.); mental retardation (severe); Growth retardation; hypotonia; convulsions; hirsutism; microcephaly; microphthalmia; colobomata; malformed ears; high arched and cleft palate; cryptorchidism; hypospadias; multiple skeletal anomalies; transverse palmar creases</i>	<i>Retinoblastoma, bilat. (Dx at 6 mth.); mental retardation (moderate to severe); Growth retardation; antimongoloid slants; epicanthal folds; dental caries; high arched palate; small testes; multiple skeletal anomalies</i>
Dermatoglyphs	Arches on 5 fingers	Arches on 4 fingers; arch tibial on one foot	Stated to be abnormal	Not reported
Chromosome studies				
Tissue	Blood	Blood, skin, tumour, conjunctiva	Blood	Blood
Analysis	46,XX,D(14)q -	46,XX,Dq -	46,XY,Dq - /46,XY,t(C;D)	46,XY,Dq -,t(2;C)
Sex chromatin	Positive	Not reported	Not reported	Negative
Chromosome studies on parents	Mother normal; father not available	Normal	Mother 46,XX/46,XX,Dq -; father normal	Not reported

*Significant features found in more than one patient are in italics.
Dx = diagnosis.

father of our patient was not available for examination. Van Kempen (1966) reported no chromosomal studies from the parents of his case. The karyotypes of the parents of the case reported by Lele *et al.* (1963) were normal. The mother of the child reported by Thompson and Lyons (1965) showed a partial deletion of one of the D chromosomes in some cells; therefore, in this instance it is assumed that the deleted D was an inherited abnormality.

Retinoblastoma has not been associated with deletion short arm D (Grouchy *et al.*, 1966; Bias and Migeon, 1967), deletion of long arm D (Bloom, Gerald, and Diamond, 1966; Laurent *et al.*, 1967; Taylor, 1968); and ring-D chromosomes (Wang *et al.*, 1962; Turner, 1963; Bain and Gault, 1963; Macintyre *et al.*, 1964; Adams, 1965; Reisman, Darnell, and Murphy, 1965; Jacobsen, 1966; Gerald *et al.*, 1967; Teplitz *et al.*, 1967; Sparkes, Carrel, and Wright, 1967; Lejeune *et al.*, 1968). Autoradiography was done in 5 cases; two deletions and two ring chromosomes appeared to consist of a No. 13 (Bias and Migeon, 1967; Bloom *et al.*, 1966; Gerald *et al.*, 1967; Reisman *et al.*, 1965; Bloom, Gerald, and Reisman, 1967); while the ring reported by Sparkes *et al.* (1967) was a chromosome 14. Presumably a ring chromosome is formed after deletions at both ends of a single chromosome; the ends then unite in a ring. A different portion of the chromosome may be lost if a deletion is intercalary in position. The clinical features of the child described by Sparkes *et al.* (1967) did not resemble our patient.

Retinoblastoma is usually inherited as an autosomal dominant trait. This is the fourth report in which the tumour has been found in association with a gross chromosomal abnormality. In these patients, congenital abnormalities and mental retardation were found, but were not always so severe as to interfere with reproduction by the affected subject. Most patients with retinoblastoma do not show congenital abnormalities and those who have been studied have normal karyotypes; thus the syndrome of deletion of chromosome D (14) does not contribute significantly to the total number of cases of retinoblastoma (Lele *et al.*, 1963; Wiener, Reese, and Hyman, 1963; Fraser and Friedmann, 1967).

Summary

A girl with retinoblastoma, cleft palate, and retardation of growth and development is described. All the karyotypes from peripheral blood cultures of the patient showed a partial deletion of the long arm of a D chromosome. This is the fourth reported instance in which retinoblastoma has been

associated with this chromosomal structural defect, and the first in which the deleted chromosome was shown by autoradiography to be chromosome 14. Retinoblastoma and deletion of chromosome D (14) appears to be a verified chromosomal deletion syndrome, in which there may not be multiple severe anomalies.

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