FIG 2 Partial karyotype showing the $\text{del}(5)(\text{q}13\text{q}15)$. QFQ banding (left), RBA banding (middle), and diagrammatic representation of the two chromosomes 5 (right). Arrows indicate where breakages occurred. The abnormal chromosome 5 is on the right.

When seen at 6 months of age mental development was delayed. Weight was 4250 g (-4 SD), length 59 cm (-3 SD), and head circumference 40 cm (-3 SD).

Dermatoglyphs were unremarkable except that there were seven whorls and three ulnar loops located on the 2nd and 3rd finger on the right hand and the 2nd finger on the left hand.

CHROMOSOME STUDIES

Chromosome preparations from short term peripheral blood leucocyte cultures were stained with orcein and treated for RHG banding, CBG banding, and QFQ banding. In one culture flask BRdU was added at a concentration of 0.09 mmol/l for the last 8 hours of cultures. Mitoses were photographed with UV after acridine orange staining. These techniques showed an interstitial deletion of the long arm of chromosome 5 $\text{del}(5)(\text{q}13\text{q}15)$ (fig 2).

The karyotypes of the parents were normal.

The following genetic markers of the parents and of the child were studied but were not informative: hexosaminidase B, arylsulphatase B, HLA antigen, blood groups.

Discussion

The abnormalities found during clinical examination of the proband and his mental retardation are obviously the result of chromosomal abnormality.

Interstitial deletions are rare chromosomal mutations resulting from two breaks with loosening of the intermedial segment and rejoining of the two parts. According to the Repository of Chromosomal

Variants and Anomalies in Man, 32 interstitial deletions are known¹⁻³ and Kucerova and Polivkova⁴ found three cases with $\text{del}(5)(\text{q}15\text{q}23)$, $(\text{q}21\text{q}23)$, and $(\text{q}15\text{q}22)$. The segment of the chromosome 5 that was lost in these three cases was different from the one in our patient. The clinical abnormalities of the patient of Pescia *et al*³ also differed from those of our patient.

Studies attempting to map genes on the fragment which was lost in our patient were inconclusive.

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Neurological and neuropathological findings in ring chromosome 4

SUMMARY Despite the fact that mental retardation, microcephaly, seizures, and hyperactivity are common in patients with ring chromosome 4, little has been written about the underlying neuropathology. We describe a 6-year-old girl whose neuropathological findings included low brain weight, abnormal gyral development, and heterotopic neurons. The significance of these findings in regard to other retardation syndromes is discussed.

Microcephaly, mental retardation, seizures, and hyperactivity are frequently present in patients with

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a ring chromosome 4. The single description of the neuropathological findings in this disorder was in an infant. We report our findings of the changes in the nervous system in a 6-year-old girl with ring chromosome 4.

Case report

This patient was the 2 kg term product of a healthy, gravida 3, para 1, aborta 1 28-year-old mother. During the third month of pregnancy, the mother had a monilial infection which was treated with metronidazole. There were no other complications during pregnancy or delivery.

At birth, the child appeared dysmorphic with brachymicrocephaly (31 cm), small simple helices, short neck, high arched palate, and micrognathia. In addition, she had short digits, medial deviation of the distal phalanx of the second toes, dislocated hips, and a deep sacral dimple. Chromosomal analysis showed a ring chromosome 4 (fig 1).

On neurological examination at 6 months of age, the child could not sit independently or roll over. Although she was extremely quiet, she had good visual attention and social smile. She followed past the midline. Oral secretions were handled poorly. Motor evaluation revealed normal tone and crude pincer grasp and transfer. At 18 months of age, evaluation for persistent vomiting confirmed a malrotation of both small and large bowel. Radiographs also showed spina bifida occulta.

Her subsequent neurological development was felt to be slow and at the age of 6 she functioned at

FIG 2 Lateral surface of the brain shows poorly developed superior temporal gyrus (S).

the level of a 4-year-old child. She underwent tonsillectomy at the age of 6, but died of post-operative complications.

NEUROPATHOLOGICAL FINDINGS

The fresh brain was brachymicrocephalic, diffusely swollen, and weighed 800 g (normal, 1200 g). The gyral pattern was simplified and the left superior and middle frontal gyri were quite broad. The right superior temporal gyrus was poorly formed and did not fully extend posteriorly (fig 2). The temporo-occipital gyri were also poorly developed. A deep sulcus was present in the inferior right occipital lobe. The spinal cord, brainstem, and cerebellum appeared normal.

Multiple microscopical sections were stained with luxol fast blue, haematoxylin and eosin, and cresyl violet. A normally laminated six layer cortex was present. There appeared to be many heterotopic neurons in the white matter, most prominent at the crowns of the gyri (fig 3). The border between grey and white matter appeared indistinct. The neurons seemed sparse at the depths of the sulci. In the cerebellum, the Purkinje cells were indistinct in distribution. Sections of the brainstem and spinal cord were normal.

Discussion

Although exceptional cases of normal intellectual functioning have been reported, the majority of children with ring chromosome 4 are mentally retarded to a variable degree (table). Other evidence of neurological involvement includes seizures, epileptiform electroencephalograms, and hyperactivity. Microcephaly is consistently found in patients with ring chromosome 4. While not of the extreme degree

FIG 1 Banded karyotype shows ring chromosome 4.

FIG 3 A cluster of heterotopic neurons (arrow) can be seen within the white matter. (Cresyl violet, original magnification, $\times 160$).

TABLE Neurological and neuropathological findings in ring chromosome 4

Reference	Age (yr)	Sex	Head/skull	Seizures	Mental function	Neuropathology
Bofinger (<i>Am J Dis Child</i> 1973;125:135)	Infant	M	Dolichocephaly			No external abnormalities seen
Carter (<i>J Med Genet</i> 1969;6:224)	Infant	M	30 cm 30 cm			Brain 296 g, poor fissuring, poor neuronal differentiation
Faed (<i>J Med Genet</i> 1969;6:432)	Infant	M	Brachycephaly			
Pathak (<i>Ann Hum Genet</i> 1972;35:471)	1	M	Abnormal skull			
Hecht (<i>Birth Defects</i> 1969;5:106)	1	M	3rd centile		IQ 35	
Bernstein (<i>J Med Genet</i> 1978;15:310)	3	M	46 cm	Abnormal EEG	Hyperactive, mentally retarded	
Bobrow (<i>J Med Genet</i> 1971;8:235)	4	M	40 cm	+	IQ 50	
McDermott (<i>J Med Genet</i> 1977;14:228)	4	M	43 cm		IQ 50	
Chavin (<i>Ann Genet Paris</i> 1977;20:105)	5	F	43 cm		"Near normal"	
Surana (<i>J Med Genet</i> 1971;8:517)	5	F	50 cm		IQ 99	
Present case	6	F	31 cm (at birth)		Mild-moderate retardation	Brachymicrocephaly, abnormal gyri, heterotopic neurons
Fraisse (<i>Ann Genet Paris</i> 1977;20:101)	8	M	42 cm		Moderate retardation	
Parker (<i>Am J Dis Child</i> 1974;128:371)	9	F	41 cm	+	IQ 27, hyperactive	
Niss (<i>Humangenetik</i> 1975;28:9)	12	M	48 cm		IQ 40	
Dallaire (<i>Birth Defects</i> 1969;5:114)	16	F	32 cm		IQ 100	

present in microcephaly vera, head circumference measurements are always below the 3rd centile for age (table). Brachycephaly and dolichocephaly have also been reported.^{4 5}

Despite the frequency of neurological findings in this disorder, there have been only two reports of the underlying neuropathology. Bofinger *et al*⁵ described a newborn with a "long, narrow skull" and a head circumference of 30.5 cm. No external abnormalities of the brain were seen.⁵ Carter *et al*⁴ described an infant with microcephaly, low brain weight (296 g, normal, 400 g), and poorly developed secondary fissuring. Microscopical examination revealed primitive lamination and poor differentiation of neurons in the cerebral cortex.⁴

It is important to interpret both microscopical and macroscopic findings cautiously. The brachycephaly and poor superior temporal gyral development seen in our patient are non-specific and may be present in 50% of patients with Down syndrome.⁶ Microscopical findings may similarly be non-specific or artefactual as a result of tangential sectioning. Heterotopic neurons have been reported in association with mental retardation syndromes as diverse as myotonic dystrophy or lissencephaly.^{7 8}

It is impossible at present to correlate the degree of neurological involvement and the amount of chromosomal deletion. McDermott's patient had no more than the telomeres deleted, yet had an intelligence quotient of 50. In contrast, Surana's patient

had a short arm deletion, yet had normal intelligence (table). Finally, most patients with ring chromosomes are mosaics and may have a variety of ring shapes with differing amounts of chromatin.² Patients may show an increase in the number of ring forms with advancing age.^{1,9}

In summary, neurological and neuropathological abnormalities are frequently present in patients with ring chromosome 4. Because these abnormalities are non-specific, the mechanism of the mental deficiency will require further study.

We are grateful for the advice of Dr Lewis B Holmes. The patient's chromosomes were studied in the laboratory of Dr Leonard Atkins.

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Corrections

On page 336 of the paper 'Medical genetics in China' by Bodmer and Clarke (*JMG* 1979;**16**:330-7), the Medical College in Cheng Chow should read Hunan Medical College, Changsha.

On page 310 of the paper 'Pericentric inversion (13) with two different recombinants in the same family' by Williamson *et al* (*JMG* 1980;**17**:309-12), the chromosomes in fig 3 were inadvertently printed upside down.