Median Facial Cleft Associated with Ring E Chromosome

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The purposes of this report are: (1) to describe the course of a newborn female with a ring E chromosome whose phenotype included microcephaly, median facial cleft, and hypertelorism, and (2) to review briefly reported ring E karyotypes.

Case Report

This term (gestation 42 weeks; weight 2508 g., length 43 cm.) female infant was born to a primiparous 19-year-old Caucasian mother and a 19-year-old Negro father. Pregnancy was complicated by maternal exposure to rubella during the third month of pregnancy, which was treated with 20 ml. γ -globulin. Slight vaginal bleeding occurred during the 7th month of pregnancy and was treated with hydroxyprogesterone

caproate. The infant was a breech delivery. At birth, microcephaly, a palpable parietal skull defect, plus those anomalies apparent in Fig. 1a and b were noted. The infant was floppy, with diminished Moro, absent deep tendon reflexes, and was unable to nurse. She gained weight while being gavage fed, but developmentally remained at the newborn level. Her subsequent course included the onset of continual minor-motor seizures at 4 weeks of age and recurrent respiratory infections beginning at approximately 5 weeks of age. A grade 1/4 parasternal systolic murmur was first heard at 5 weeks of age. Death occurred at 9 weeks of age during the course of a respiratory infection. There was no necropsy. The family history was negative for related disorders.

A chromatin positive buccal smear was obtained. X-rays of the skull showed a 2.5 cm. defect involving the medial aspects of both parietal bones, microcephaly, an

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FIG. 1a and b. Full face and lateral view of patient, showing hypertelorism and median facial cleft.

FIG. 2a and b. X-rays of patient, showing an interorbital distance of less than 1 cm., absence of prelabium and premaxilla, and the posterior parietal defect.

interorbital distance of 0.9 cm., and the absence of a prolabium and premaxilla (see Fig. 2a and b). Club-shaped costal end of the ribs and increased pulmonary vascular markings without cardiomegaly were noted by x-ray. The radiographic appearance of the skull was consistent with arrhinencephaly.

Dermatoglyphic analysis. This revealed the pattern given in the Table.

TABLE
DERMATOGLYPHIC
ANALYSIS*

	Right	Left
Palmar triradius	t	t
Thenar area	O/O	O/Ld
Hypothenar area	O/O	O/O
1 ₂	O	O
1 ₃	O	O
1 ₄	O	Ld
Volar ridges		
1	U	V
2	V	R
3	V	V
4	V	V
5	V	V
Hallucal pattern	W	W
Great toe	A	V

* Dermatoglyphic analysis conducted in accordance with Memorandum on Dermatoglyphic Nomenclature as published in *Birth Defects Original Article Series*, Vol. XV, No. 3, June 1968.

Chromosomal analysis. Chromosomal analysis was conducted upon leucocytes grown in short-term culture. Eighty-seven figures were analysed, and presented a mosaic of 45 and 46 chromosomes. Eleven figures contained 45 chromosomes; the remaining 76 figures contained 46 chromosomes. A chromosomal abnormality in the E group appeared consistently. The E group of chromosomes consists of a pair of small metacentric chromosomes compatible with E16, three sub-metacentric E chromosomes, and a ring chromosome. Each of the 76 figures containing 46 chromosomes is missing one of the sub-metacentric E chromosomes, and contains in its place a ring chromosome of varying morphology (see Fig. 3 a-d). In 21% of the figures there appears a monocentric ring of varying size; 66% contained a metacentric chromosome slightly smaller than an F (see Fig. 4a and b), a few of which formed a single or double ring chromosome. Though autoradiography was not completed, we believe the ring chromosome is derived from E18; however, we have not excluded the possibility of a ring E17.

Eleven of the 87 figures contained 45 chromosomes with an absence of the ring E; however, in 6 of these 11 figures there appeared remnants of what is believed to be the absent ring chromosome (see Fig. 4c and d). The remaining five figures appeared to be intact but contained only 45 chromosomes and were missing one of the sub-metacentric E17 or E18 chromosomes. Karyotyping of the mother and father revealed normal chromosomal complements.

FIG. 3. Varying morphology of a ring chromosome. a, b, and c represent large and small monacentric ring chromosomes. d is an example of a small double ring chromosome.

Discussion

The case described herein is the 10th reported instance of a ring E chromosome and is unique in that the infant's median facial cleft and hypotelorism represent the first reported instance of these two anomalies with a ring E chromosome. The phenotypic characteristics of the 10 cases reported to date include: mental retardation (10/10); microcephaly (5/6); failure to thrive (6/6); deafness (1/5); hypotonia (5/7); seizures (3/7); micrognathia (3/5); hypertelorism (5/9); hypotelorism (1/9); ventricular septal defect (1/9); cleft lip (1/9); cleft palate (2/9). Male to female ratio is 3/7. The ages of the patients at death have ranged from 9 weeks to 18 years, with an average of 6.5 years (the present case also represents the youngest age of death reported to date). The mothers' ages at the times of birth have ranged from 19 to 33 years with an average age of 25.4 years; the fathers' ages at the times of birth have ranged from 19 to 37 years with an average age of 29.2 years. A variation in dermatoglyphic patterns, as in karyotypes, has been observed.

The karyotype in previous reports uniformly shows an abnormal E chromosome of varying

FIG. 4. a and b show 46 chromosomes with E(17 or 18) replaced by a small metacentric chromosome. c and d have 45 chromosomes with an E(17 or 18) replaced by disintegrating chromatin material derived from the altered E chromosome.

morphology including small and large rings, small dicentric rings, or small metacentric chromosomes. The karyotype of the authors' case and of that reported by Gripenberg (1967) and U. Gripenberg (1969, personal communication) showed a loss of the ring chromosome in a few cells either with an E monosomy or remnants of the absent ring chromosome. One case (Lucas *et al.*, 1963) had a mosaicism with coexisting normal and ring E cell lines.

Chromosome involved. Review of the literature and inspection of the published karyotypes reveal that 4 of the previously reported 9 cases of ring E chromosome involve pair E18 (Gropp, Jussen, and Ofteringer, 1964; Lucas *et al.*, 1963; Sinha, 1968; Grouchy, 1965). In 5 of the previously reported cases it is stated that the ring E 'probably' involves E18 (Wang *et al.*, 1962; Aula *et al.*, 1967; Leisti *et al.*, 1968; Feingold *et al.*, 1969; Finley *et al.*, 1968); in these 5 cases, however, photographs of the karyotype are either absent or difficult to interpret.

Amount of chromosomal deletion. A double break must occur in the production of a ring chromosome, and during reunion the acentric fragment is lost. This may influence *a priori* the phenotype observed.

Abnormal chromosomal division. McClintock (1938) described the relation of phenotype to abnormal division of the ring chromosome as it occurred in maize. Not only may there be an unequal mitotic division of the ring chromosome but there may also occur an actual loss of the ring in cell divisions. The above three factors suggest that a stereotyped ring E syndrome will not be seen.

Cause of chromosomal abnormality. The abnormality does not appear to be related to parental age, abnormal parental karyotypes, increased fetal loss, or to intrauterine viral infections. However, the appearance of the remnant of the ring chromosome in our case and that reported by Gripenberg resembles changes in the chromosome(s) in cell culture which has been infected by virus (MacKinnon *et al.*, 1966).

A variation in dermatoglyphic patterns, as in phenotype, has been observed.

The presence of arrhinencephaly in the authors' case is assumed by virtue of radiographic findings. Arrhinencephaly has been described in the D trisomy syndrome (Miller *et al.*, 1963; Smith *et al.*, 1963) and in patients whose karyotypes show deletion of the short arm of E18 (Nitowsky *et al.*,

1966). Arrhinencephaly does occur sporadically (Demyer, Zeman, and Palmer, 1963, 1964) and may exhibit a familial pattern thought to reflect an autosomal recessive mode of inheritance (Gorlin, Yunis, and Anderson, 1968; Haworth, Medovy, and Lewis, 1961). This is the first reported case of arrhinencephaly occurring in association with a ring E chromosome.

Summary

We have presented the case of a female infant in whom a ring E chromosome was found. We believe the ring E chromosome has been formed from an E17 or E18. The phenotype consisted of microcephaly, probably due to arrhinencephaly, median facial cleft, and hypotelorism; she died at the age of 9 weeks. This is the first report describing a ring E chromosome associated with the above phenotypic characteristics. Previous case reports show a conspicuous variation in number and severity of defects.

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