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Ring chromosome 15

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Ring chromosome 15 was found unimodally in the blood cells and in mosaic form in the skin fibroblasts of a female patient. Observations made in the reported case supported the assumption that the instability of ring formation is responsible for the most common clinical symptoms, the intrauterine and postnatal growth retardation.

Ring chromosome 15 is a rare chromosome aberration. To our best knowledge only 18 patients with r(15) have been described in the literature after banding techniques had allowed an exact individualization of chromosomes in the human karyotype [1–7, 10, 11, 13–19]. In this paper we report an additional case with r(15) aberration and the findings are compared with those occurring in the cases published in the literature.

Report of a Case

The female patient T. J. was born in the 39–40th gestational week from the 2nd pregnancy when the mother was 31 years and the father 32 years old. The parents were healthy and unrelated. From the first and the third pregnancy healthy boys were born.

The birth weight was 2500 g (small for gestational age), body length was 55 cm, head circumference was 35 cm. No perinatal problem occurred.

The patient was seen first at 2 months of age. At that time her weight was 3000 g, body length 55 cm, head circumference 35 cm. These parameters remained below the 25th and 3rd percentile values throughout her life.

Clinical examination revealed a delay in motor development, generalized muscular hypotonicity and grand mal type epilepsy with corresponding EEG alterations. Only a few signs of craniofacial dysmorphism could be observed; they were a high forehead and triangular face, narrow palpebral fissures, bulbous tip of the nose, thin lips, high arched palate and sparse hair. There were a coloboma of the iris on the right side and coloboma of the retina and choroid on both sides. The body shape was disproportionate to the long upper extremities and trunk. The hands and feet were small (Figs 1 and 2).

Urography, ECG and laboratory examinations did not reveal any pathological changes.

After gradual deterioration, the patient died with bronchopneumonia in the 36th month of life. Necropsy

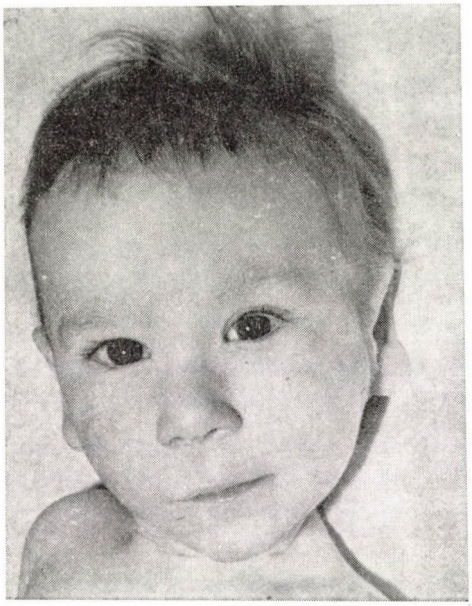

FIG. 1. The patient at 1 year of age

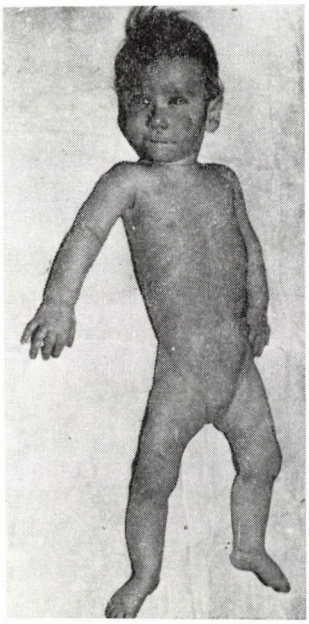

FIG. 2. The patient at 1 year of age

showed unilobar lungs on both sides and microcephaly accompanied by striking microgyria and moderate dilatation of the ventricles (Fig. 3).

Cytogenetic studies. In routinely cultivated blood cells, ring formation of chromosome 15 was found (Fig. 4). In 50 investigated metaphases neither a derivate structure nor loss of r(15) chromosome could be observed. In cultivated skin fibroblasts, out of 66 metaphases 6 displayed the loss of the ring chromosome. On the basis of these findings, a mosaicism was stated.

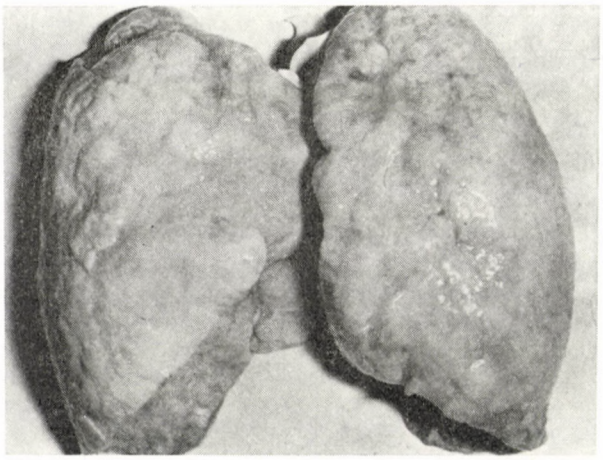

FIG. 3. Unilobar lungs of the patient

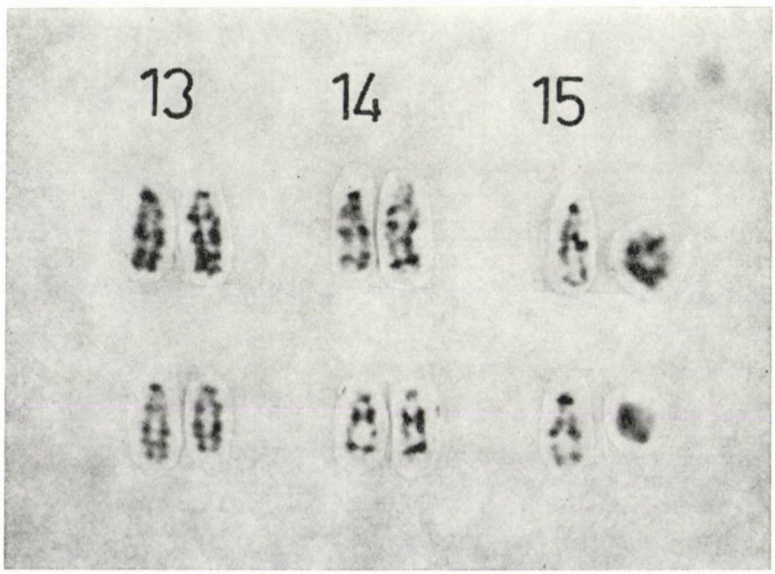

FIG. 4. Ring chromosome 15 with GAG banding

The karyotype of the parents as well as that of the two other children proved to be normal.

Discussion

Ring chromosomes are produced by breakage in each of the two arms of chromosomes and a subsequent reunion of the broken ends. The loss of genetic material depends on the site of breakage. The exact identification of the break points in cell samples during postnatal life is usually difficult; it did not succeed in most of the reported cases of r(15) including the present case. Short arm deletion was identified only in two cases with r(15) chromosome [16, 18] by NOR staining. From the practical point of view, a deficiency of the short arm is without importance, since a monosomy of the short arms of acrocentric chromosomes does not affect the phenotype. Long arm deletion in r(15) chromosome could also be evidenced [16, 4]. An explanation for the failure of exact identification, even in the best banded metaphases, lies probably in the circumstance that there is no significant loss of genetic material in most of the cases [18].

In spite of the minimum deficiency of chromosome material, the phenotype is usually seriously involved and there seems to be no correlation between the clinical findings and the primary deletion. Several investigators emphasized that the phenotypic

Table I

Clinical data and symptoms

Data and symptoms	Emberger et al [1]	Ferrante et al [2]	Forabosco et al [3]	Fryns et al [4] 1	Fryns et al [4] 2	Jacobsen et al [7]	Ledbetter et al [10]
Sex	M	F	F	F	F	M	F
Age	8.5y	15m	16m	18m	6.5y	4ly	15m
Birth weight			2300	2200	2700	1800	
Growth retardation	+	+	+	+	+	+	+
Mental deficiency	+	mild	mild	mild	mild	mild	+
Microcephaly	+			+	+		+
Triangular face	+	+	−	−	+	−	−
High forehead	−	−	−	−	−	−	−
Hypertelorism	−	+	−	+	−	−	−
Epicanthus	−	−	−	−	−	−	−
Microor retrognathia	−	+	−	+	+	−	−
Small hands and feet	−	+	+	+	+	−	
Finger anomaly	−	+	+	+	+	+	+
Major malformation	−	−	+	−	−	+	−

manifestation and variation could rather be connected to the structural instability of ring formation [9, 8]. The instability of ring chromosomes is due to the specific behaviour in the mitotic anaphase. A ring formation with minimum primary deficiency can result in daughter cells with a severe unbalanced genome. Firstly, the ring chromosome can be lost and the daughter cells will be monosomic. Secondly, ring formation can be recombined and daughter cells will contain different derivates that mean partial duplication and/or deficiency in their genomes. Derivates of a ring chromosome have excellently been demonstrated by Niss and Passarge [12]. As a result of these events, mosaicism arises and a certain proportion of the cells will probably be lost at cell division and a significant reduction in the number of viable cells will occur prenatally and postnatally alike. Kjessler et al. (8) assumed that the presence of a ring chromosome per se can predispose to a significantly retarded intrauterine and postnatal growth reflected in low birthweight, growth retardation, delay of development and mental retardation. In the light of this hypothesis, one may understand why all cases with ring chromosome 15 have a low birthweight and postnatal delay in growth and mental development (Table I).

In addition, it is likely that difficulties occur in the anaphase and, as a consequence, the proportion of unviable cells varies from case to

of patients with r(15)

Meinecke and Koske–Westphal [11]	Pfeiffer et al [13]	Rumenic et al [14]	Scheibenreiter and Frisch [15]	Schmid et al [19]	Stoll et al [17]	Yunis et al [18]	Wisniewski et al [19]	Present case
M	F	F	M	F	F	F	M	F
37y	3y	11y	5.5y	14y	2.2 y	46m	19m	⊞ 36m
	2420			2250	2310	1800	2460	2500
+	+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+	+
+	+			+	+	+	+	+
−	−	+	+	−	+	−	−	+
−	−	−	−	−	+	−	−	+
−	−	+	+	+	−	+	−	−
+	−	−	−	−	−	+	−	−
−	−	−	+	+	+	−	−	+
+	+	+	+	+	+	−	−	+
+	+	−	−	+	−	+	−	−
−	−	−	+	−	−	−	−	+

TABLE II

Cytogenetic data in patients with r(15)

	Material	Number of cells investigated					Size of r(15)
		all	with r(15)	without r(15)	with derivate	normal	
Emberger et al [1]	blood	151	138	13	0	0	variable
Forabosco et al [3]	blood	80	79	1	0	0	constant
Fryns et al 1. [4]	blood	41	39	0	0	2	constant
2.	blood	60	29	4	27	0	variable
Jacobsen et al [7]	blood	76	76	0	0	0	
Meinecke and Koske–Westphal [11]	blood	45	41	4	0	0	variable
Pfeiffer et al [13]	blood	50	30	0	0	20	variable
	fibro-blasts	50	26	0	0	24	
Rumenic et al [14]	blood	50	50	0	0	0	variable
Schmid et al [16]	blood	200	197	0	3	0	variable
Stoll et al [17]	blood	100	58	42	0	0	variable
Wisniewski et al [19]	blood	216	207	0	9	0	variable
Present case	blood	50	50	0	0	0	variable
	fibro-blasts	66	60	6	0	0	

ase. The variation in ring stability can then cause variations in the phenotype of the patient. It is not only the degree of the somato-mental retardation that varies from patient to patient, but the cranio-facial dysmorphism, too. Signs of dysmorphism such as a narrow forehead, mongoloid slants, hypertelorism, epicanthus, flattened nasal root, micro and retrognathia, etc., have been mentioned in some cases with r(15) but, except for the triangular face and small hands and feet with finger anomaly, none of them can be regarded as a characteristic dysmorphic symptom. Gross internal anomalies are not frequent. Out of 16 patients, 5 had heart malformations; in one case it was accompanied by renal anomaly. In the present case, the necropsy revealed a pulmonary anomaly.

Constancy of ring formation in 50–100 cells investigated in postnatal samples could hardly be a convincing proof against a mosaicism in the patient; it only means that no mosaicism could be detected. Therefore, it is not possible to evaluate the cytogenetic findings of the reported cases. (Table II.) It is, however, remarkable that mosaicism could be observed in many patients.

Another object of further studies is the dominance of females. Out of 16 patients, there were only 5

males. A female excess could be found in other chromosome aberrations, too, e.g. in the 4p and 5p deletion syndromes, but it seems that the sex ratio in the case of r(15) is much more overbalanced.

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