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CYTOGENETIC STUDIES IN PATIENTS WITH CLEFT LIP AND/OR CLEFT PALATE (IV)

(SCREENING STUDIES OF CHROMOSOMES, FROM AUGUST 1973 TO AUGUST 1977)

Jun-ichi AZUMI,[1,*] Gen-iku KOHAMA,[1] and Motomasa SASAKI*

Department of Oral Surgery, Sapporo Medical College, Sapporo
**Department of Stomatology, Nagasaki University School of Medicine, Nagasaki*

Summary Chromosome studies were carried out in 110 patients with cleft lip and/or cleft palate. Major chromosome abnormalities were found in four cases (3.6%). They included two cases of 46, XX, 4p−, one case of 47,XY, +21 and one case of 46,XX, inv(1) (p32q12). The incidence of chromosome abnormalities in patients with cleft lip and/or cleft palate was about 5.2 times higher than that in newborn children.

INTRODUCTION

Cleft lip and/or cleft palate is one of the most common abnormalities among congenital oral diseases and the etiology of its development seems to be attributed to various genetic and non-genetic factors. In a small percentage of cases, cleft lip and cleft palate are directly associated with chromosome abnormalities. With advances in the chromosome banding techniques, it has become possible to identify minor or complicated chromosome abnormalities.

Since December 1971, screening studies of chromosomes have been carried out in patients with cleft lip and/or cleft palate in order to evaluate the role of chromosome abnormalities in the etiology of the disease. In the previous papers, three cases with various chromosome abnormalities were detected among 155 patients with cleft lip and/or cleft palate (Sasaki *et al.* 1974a,b, 1975). In the present communication, screening data on additional 110 patients with cleft lip and/or cleft palate were described. They represent unselected population who visited the Department of Oral Surgery, Sapporo Medical College during 4-year period starting August 1973.

MATERIALS AND METHODS

Chromosome preparations were obtained by the standard leukocyte culture

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[1] Present address: Department of Human Genetics, National Institute of Genetics, Mishima

technique and karyotypes were examined using Giemsa stained preparations. In order to identify abnormal chromosomes, Q-band analyses were carried out in all patients with structural and/or numerical chromosome abnormalities according to the method of Caspersson *et al.* (1970). The Y chromosome which exceeded apparently the average length of F group chromosomes was defined as the long Y chromosome (Yq+).

The patients included in this study involved 58 cases of cleft lip and cleft palate, 24 cases of cleft lip (with or without alveolus), and 28 cases of cleft palate. Fifty-six cases were male and 54 were female.

RESULTS

Chromosomal features of the 110 patients are summarized in Table 1. Major chromosome abnormalities were found in four cases (3.6%) out of 110 studied. One of them had a numerical and three had structural abnormalities.

Seven of the 56 male patients had a long Y chromosome (Yq+). One case showed an increase in the length of the secondary constriction of the long arm of chromosome No. 16 (16qh+). Both of them were known as normal chromosome variants in man. The remaining 98 cases had a normal karyotype (46,XY in male or 46,XX in female). The chromosome findings of the four cases are described in some detail as follows:

Case 1 was a 21-year-old female with cleft lip and cleft palate (without associated malformations). The father was 27 years old and the mother was 24 years old at the time of birth. Her birth weight was 2,800 g and she was 49.0 cm long. There was neither a history of prenatal irradiation in her mother nor a family history of

Table 1. Cytogenetic features of 110 patients with cleft lip and/or cleft palate (August 1973 to August 1977).

Types of cleft	No. of patients examined	Karyotype	No. of patients
Lip and palate	58	46, XY	28
		46, XX	23
		46, XYq+	5*
		46, XX, inv(1) (p32q12)	1
		47, XY, +21	1
Lip	24	46, XY	11
		46, XX	11
		46, XYq+	1*
		46, XY, 16qh+	1*
Palate	28	46, XY	8
		46, XX	17
		46, XYq+	1*
		46, XX, 4p−	2

*Normal variants.

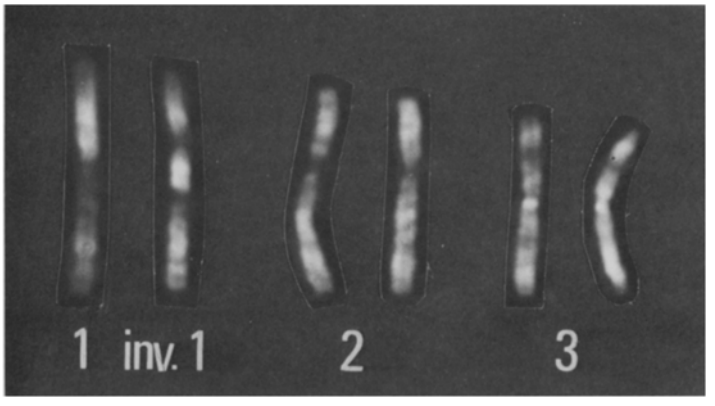

Fig. 1. Partial karyotype of Case 1 (Q-banding), showing pericentric inversion of chromosome 1, inv(1) (p32q12).

malformations. Chromosome analyses of peripheral blood showed a modal chromosome number of 46 and heteromorphic chromosome No. 1. Examination of six Q-band karyotypes revealed pericentric inversion in one chromosome No. 1 showing 46,XX, inv(1) (p32q12) (Fig. 1). The karyotypes of the parents were normal.

Case 2 was a one-month-old male. His birth weight was 3,340 g and he was 47.5 cm long. The maternal and paternal ages at the time of his birth were 32 and 35 years, respectively. The pregnancy and delivery were uneventful. Both parents were healthy and phenotypically normal. He was characterized by cleft lip and cleft palate, flat occiput, flat facial profile, epicanthal folds, flat nasal bridge, small penis, simian crease (bilateral) and single crease of the fifth finger (bilateral). The chromosome analysis revealed a modal chromosome number of 47, with an extra No. 21.

Case 3 was a 2-year-old female. The patient was the only child of a 21-year-old mother and a 18-year-old father who were unrelated and in good health. There was neither a family history of malformations nor a history of abortions in the mother. Resuscitation was required at birth. The main clinical features were: low birth weight (2,000 g at full term), cleft palate, failure to thrive, severe mental deficiency, hypotonia, seizures, microcephaly and hypertelorism. She died at two years and five months from pneumonia and severe seizures. Conventional chromosome analysis disclosed the presence of an abnormal B-group chromosome with a deleted short arm. Q-banding study revealed that the karyotype of the patient was 46,XX, del(4) (p14) (Fig. 2). The karyotype of the parents were normal.

Case 4 was a 14-month-old female. The patient was the second child of healthy parents. The maternal and paternal ages at the time of birth were 33 and 26 years, respectively. She was characterized by the following abnormalities; small birth

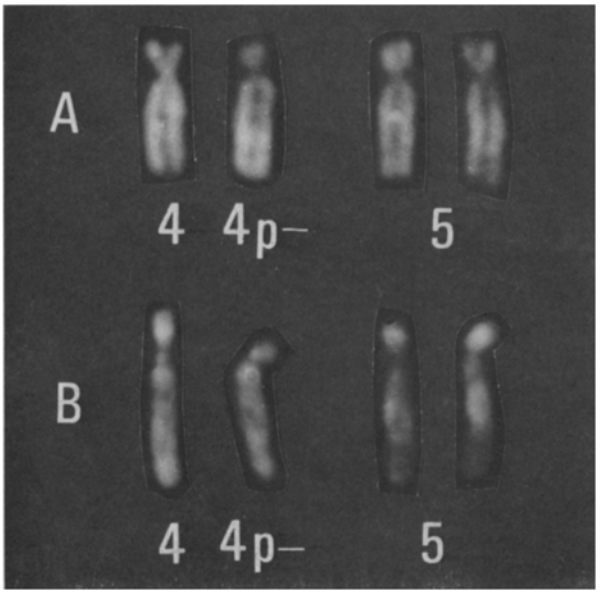

Fig. 2. A: Partial karyotype of Case 3 (Q-banding), showing, del(4) (p14).
B: Partial karyotype of Case 4 (Q-banding), showing, del(4) (p16).

weight (2,050 g at full term), growth failure, psychomotor retardation, cleft palate, seizures, microcephaly, hypertelorism, heart malformation and micrognathia. Q-banding studies demonstrated a 46,XX,del(4)(p16)karyotype in this patient(Fig. 2).

DISCUSSION

Chromosome studies in patients with cleft lip and/or cleft palate have been reported from several laboratories. However, the relationship between cleft lip and/or cleft palate and the chromosome abnormalities is not yet clear. With the use of various banding techniques it is now possible to determine precisely both numerical and structural abnormalities.

Gropp *et al.* (1964) reported a 3.5-month-old boy with cleft lip and palate (without other malformations). Epithelial-like cell cultures from palatal mucosa showed 72 chromosomes which were composed of three haploid sets each of which contained an extra chromosome. In short term culture of peripheral lymphocytes the chromosome number was 46. They suggested that their results could be explained as local chromosome abnormalities in the tissues of the malformed region. On the contrary, in a total of 22 cases examined by Soukup and Warkany (1966), Jackson (1966) and Muramoto *et al.* (1966), no chromosomeabnor malities were detected in cultured cells from malformed tissues.

Leukocyte culture studies have been carried out in patients with cleft lip and/or cleft palate by Makino *et al.* (1964), Subrt *et al.* (1966), Surine and Tajmirova

Table 2. Incidence of chromosome abnormalities of patients with cleft lip and/or cleft palate.

Author	No. of patients examined	No. with chromosome abnormalities
Makino (1964)	6	0
Subrt *et al.* (1966)	11	1
Surine and Tajmirova (1968)	18	0
Chang *et al.* (1970)	22	0
Hirakawa and Adachi (1970)	100	4
Akasaka (1970)	85	3
Sasaki *et al.* (1974a, b, 1975)	155	3
Subtotal	397	11 (2.8%)
Present report	110	4 (3.6%)
Total	507	15 (3.0%)

Table 3. Chromosome abnormalities found in 507 patients.*

Types of chromosome abnormality	Karyotype	No. of patients
Aneuploid		
Sex chromosome	47, XXY	1
	47, XYY	1
	45, X/47, XXX	1
Autosomes	47, XY, +21	4
	47, XX, +21	1
	46, XY/47, XY, +r?	1
Structural abnormalities		
Autosomes	46, XX, t (Dp+; Ep−)	1
	46, XY, 1q+	1
	46, XX, t (1 ; 2)?	1
	46, XX, inv (1) (p32q12)	1
	46, XX, 4p−	2
Total		15

*See also Table 2.

(1968), Chang *et al.* (1970), Hirakawa and Adachi (1970), Akasaka (1970) and Sasaki *et al.* (1974a,b, 1975). Out of a total of 397 cases examined, 11 (2.8%) showed chromosome abnormalities (Table 2). They included four cases of 21 trisomy, two cases of translocation, one case of long No. 1 chromosome, one case of XXY, one case of XYY, one case of 45,X/47,XXX and one case of 46,XY/47,XY+r? The remaining 386 cases showed normal karyotypes. The present study adds results on 110 patients. Four of them showed gross abnormalities. When results of all these studies were combined, 15 chromosome abnormalities were found in a total of 507 patients (Table 2). Types of abnormalities observed were quite variable (Table 3), and no single chromosome abnormality was prevailing. The cleft lip and/or cleft palate is often found as a partial symptom of many chromosomal syndromes. It is, in fact, nearly a constant finding in the 13-trisomy syndrome. No

patient of 13-trisomy syndrome has so far been found in the present series (Sasaki *et al.* 1974a,b, 1975). Probably because they might have died from severe congenital malformations before they could be examined by us. Although, the cleft lip and/or cleft palate are rare among patients with trisomy 21, they have been found more frequently than in the general population (MacMahon and McKeown, 1953).

According to Friedrich and Nielsen (1973) the incidence of chromosome abnormalities was 0.572% based on 31,801 newborn children examined in Boston, New Haven, London, Ontario, Edinburgh, Winnipeg and Denmark. It appears that the incidence of chromosome abnormalities in patients with cleft lip and/or cleft palate is about 5.2 times higher than that in newborn children.

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