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## Abstract

A cytogenetic study was performed on 74 children with at least three major or minor congenital malformations and mental retardation, and whose phenotypes did not fit any well-defined syndrome. The chromosomes were examined routinely using banding techniques. A total of 11 patients (14.9%) was found to have a major chromosome abnormality: one patient had a sex chromosome structural abnormality and 10 patients had an autosomal structural abnormality, including 4 patients with partial trisomies, 4 patients with partial monosomies, and 2 patients with tertiary trisomies. Two of them had probable intrachromosomal duplication which would not have been identified by conventional staining alone. Familial transmission was ascertained in 5 of 10 cases in which both parents were studied. In addition, 5 patients (6.8%) were noted to have the following chromosome heteromorphisms: partial inv 1qh, inv 9qh, 9qh+, and Yqh+. These results show that chromosome abnormalities contribute much to the etiology of unclassifiable multiple malformations associated with mental retardation. Furthermore, the demonstration of subtle chromosome rearrangements by means of banding techniques provides important implications in medical practice for the diagnosis of affected patients as well as for the genetic counseling of the families.

**KEYWORDS:** chromosome abnormality, multiple malformations, banding techniques, intrachromosomal duplication.

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## A CYTOGENETIC STUDY OF CHILDREN WITH CLINICALLY UNCLASSIFIABLE MULTIPLE CONGENITAL MALFORMATIONS AND MENTAL RETARDATION

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**Abstract.** A cytogenetic study was performed on 74 children with at least three major or minor congenital malformations and mental retardation, and whose phenotypes did not fit any well-defined syndrome. The chromosomes were examined routinely using banding techniques. A total of 11 patients (14.9%) was found to have a major chromosome abnormality: one patient had a sex chromosome structural abnormality and 10 patients had an autosomal structural abnormality, including 4 patients with partial trisomies, 4 patients with partial monosomies, and 2 patients with tertiary trisomies. Two of them had probable intrachromosomal duplication which would not have been identified by conventional staining alone. Familial transmission was ascertained in 5 of 10 cases in which both parents were studied. In addition, 5 patients (6.8%) were noted to have the following chromosome heteromorphisms: partial inv 1qh, inv 9qh, 9qh+, and Yqh+. These results show that chromosome abnormalities contribute much to the etiology of unclassifiable multiple malformations associated with mental retardation. Furthermore, the demonstration of subtle chromosome rearrangements by means of banding techniques provides important implications in medical practice for the diagnosis of affected patients as well as for the genetic counseling of the families.

**Key words:** chromosome abnormality, multiple malformations, banding techniques, intrachromosomal duplication.

Interest in multiple congenital malformations associated with mental retardation has been increasing particularly in the field of pediatrics. The conditions may be the result of gene mutations, intrauterine teratogens, or chromosome abnormalities. The etiology, however, remains unknown in the great majority of cases. The advent of banding techniques has enabled us to identify each chromosome and provides a means for recognition of subtle chromosome changes. The identification of a previously unrecognized chromosome abnormality in such a patient would lead to a better understanding of the causes of the conditions.

There have been a few cytogenetic surveys on patients with unclassifiable multiple malformations and mental retardation, in which the chromosomes were examined routinely using banding techniques (1-4). The results of these surveys, however, did not appear to represent accurately the incidence of chromosome abnormalities in affected patients, since the subjects studied were for the most part

school-aged children or young adults and chromosome abnormalities resulting in early mortality might go undetected. This prompted us to investigate chromosomes mainly from infants or preschool children with those phenotypic abnormalities. The present paper reports data on the frequency and types of chromosome abnormalities found in 74 such patients.

#### MATERIALS AND METHODS

*Subjects.* The subjects were 74 patients, consisting of 38 males and 36 females. They were brought to the out-patient or in-patient services of the Department of Pediatrics, Okayama University Medical School Hospital between January, 1975, and December, 1979. The majority (78.0%) came from Okayama or neighboring prefectures. Their ages at examination ranged from 3 days to 11 years (Table 1). Selection of a patient was based on the presence of clinically recognizable mental or psychomotor retardation as well as the presence of at least three major or minor congenital malformations, which were developmentally unrelated each other. Individuals with classical chromosome syndromes (trisomy 13, 18 or 21), any known Mendelian genetic malformation syndrome, or malformations due to intrauterine exposure to known teratogens were excluded from the sample. All newborn patients, except for chromosomally abnormal patients who died in early infancy, were found later to show definite psychomotor retardation. When a chromosome abnormality was detected, available relatives were also studied.

*Chromosome analysis.* Whole blood was cultured by a modification of the method described by Hungerford (1965) (5), using Eagle's MEM medium supplemented with 15% bovine calf serum, phytohemagglutinin and antibiotics. Cultures were set up at 37 °C for 70-72 h, and colchicine was added two hours before harvest. Hypotonic treatment was done with 0.075 M KCl for 10 min. The cells then were fixed in Carnoy's solution (3 parts absolute methanol: 1 part glacial acetic acid). Air-dried slides were prepared and allowed to age for 2-5 days before staining. A minimum of 15 cells per patient was counted, and at least 3 banded metaphases from each patient were photographed and karyotyped. G-banding analysis was carried out routinely in all patients, using the technique of Seabright (1971) with minor modifications (6). Where necessary, Q-banding (7), R-banding (8), or C-banding (9) methods were further applied. Karyotype designation was made according to the International System for Human Cytogenetic Nomenclature (1978) (10).

TABLE 1. AGE AND SEX DISTRIBUTION OF THE PATIENTS.

| Age         | Male | Female | Total |
|-------------|------|--------|-------|
| 0-4 weeks   | 12   | 5      | 17    |
| 2-12 months | 9    | 18     | 27    |
| 2-5 years   | 10   | 10     | 20    |
| 6-12 years  | 7    | 3      | 10    |
| Total       | 38   | 36     | 74    |

## RESULTS

A total of 11 patients was found to have a major chromosome abnormality, and the overall frequency of abnormalities was 14.9% (Table 2). The abnormalities consisted of one patient with a sex chromosome structural abnormality (Case 1) and 10 patients with an autosomal structural abnormality, including 4 patients with partial trisomies (Cases 2-5), 4 patients with partial monosomies (Cases 6-9), and 2 patients with tertiary trisomies (Cases 10 and 11). It should be noted that two of them (Cases 2 and 3) had structural rearrangement which would not have been identified by conventional staining method alone. Familial transmission was ascertained in 5 of 10 cases where both parents were studied. In addition, the following rare chromosome heteromorphisms were detected in 5 patients: a partial inversion of 1qh (Case 3); an inversion of 9qh (Case 14); an elongation of 9qh (Case 15); and a long Y (Cases 12 and 13). These heteromorphisms are shown in Fig. 1. Phenotypically, Case 12 had encephalocele with hydrocephaly, ear malformation, and some facial dysmorphia: Case 13 had cleft palate, ear malformation, duodenal atresia, inguinal hernia and cryptorchidism: Case 14 had congenital contractures of multiple joints, ear malformation, high-arched palate, and arachnodactyly: and Case 15 had trigonocephaly, antimongoloid eye slants, redundant nuchal skin,

TABLE 2. MAJOR AND MINOR CHROMOSOME ABNORMALITIES FOUND IN THE PATIENTS.

| Case No.                                    | Sex | Age at examination | Karyotype                            | Origin of chromosome abnormalities |
|---------------------------------------------|-----|--------------------|--------------------------------------|------------------------------------|
| Sex chromosome structural abnormality       |     |                    |                                      |                                    |
| 1.                                          | M   | 3 d                | 46,XY,der(15),t(15;Y)(p11;q11)pat    | Paternal unbalanced translocation  |
| Unbalanced autosomal structural abnormality |     |                    |                                      |                                    |
| 2.                                          | M   | 1y 1m              | 46,XY,dir dup(1)(p11→p22)            | De novo occurrence                 |
| 3.                                          | F   | 2y 5m              | 46,XX,inv dup(1)(q32→q44),inv 1qh    | De novo occurrence                 |
| 4.                                          | M   | 41 d               | 46,XY,der(15),t(13;15)(q14;q26)pat   | Paternal balanced translocation    |
| 5.                                          | M   | 2m                 | 46,XY,der(13),t(13;18)(q34;q12)pat   | Paternal balanced translocation    |
| 6.                                          | F   | 11m                | 46,XX,del(4)(p13)                    | De novo occurrence                 |
| 7.                                          | F   | 14 d               | 46,XX,del(7)(q32),t(4;7)(q27;p22)    | De novo occurrence                 |
| 8.                                          | M   | 9 d                | 46,XY,del(11)(q21)                   | Unknown                            |
| 9.                                          | F   | 2m                 | 46,XX,del(18)(q22)                   | De novo occurrence                 |
| 10.                                         | F   | 4m                 | 47,XX,+ der(9),t(4;9)(q25;q13)mat    | Maternal balanced translocation    |
| 11.                                         | F   | 7m                 | 47,XX,+ der(22),t(11;22)(q25;q13)mat | Maternal balanced translocation    |
| Chromosome heteromorphisms                  |     |                    |                                      |                                    |
| 12.                                         | M   | 2m                 | 46,XYqh+                             |                                    |
| 13.                                         | M   | 2y 8m              | 46,XYqh+                             |                                    |
| 14.                                         | M   | 2m                 | 46,XY,inv 9qh                        |                                    |
| 15.                                         | M   | 3y 0m              | 46,XY, 9qh+                          |                                    |

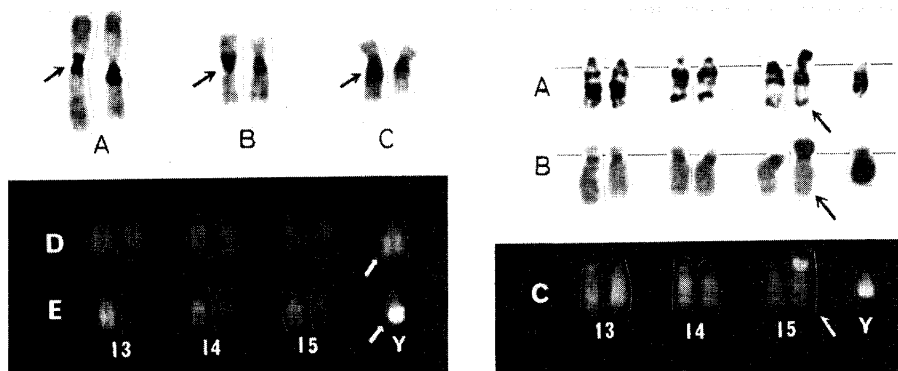


Fig. 1. (left) Chromosome heteromorphisms found in 5 patients: Case 3 (A), Case 14 (B), Case 15 (C), Case 12 (D), and Case 13 (E). Arrows indicate chromosomes with heterochromatic variants.

Fig. 2. (right) Partial karyotypes of Case 1: G-banding (A), C-banding (B), and Q-banding (C). Arrows indicate translocated chromosomes 15.

cubitus valgus and sacral sinus.

Three patients with a major chromosome abnormality (Cases 7, 10 and 11) have already been reported elsewhere (11-13). Brief descriptions of clinical and cytogenetic data in the remaining 8 cases with a major chromosome abnormality are as follows.

*Case 1.* 46, XY, der(15), t(15;Y)(p11;q11)pat.

*Clinical findings.* The patient was born at term to a 27-year-old mother and an unrelated 34-year-old father. The birth weight was 2,890 g. Physical abnormalities included small ears with hypoplastic antihelix, heart murmurs, genital abnormalities with bifid scrotum and perineal hypospadias, and pes valgus. Dermatoglyphic findings were not remarkable. Death from cardiac failure occurred at 2 months of age.

*Cytogenetic findings.* In every cell examined, a chromosome 15 was replaced by a C-group-like chromosome. G-, Q- and C-banding analyses showed that the heterochromatic portion of the long arm of Y chromosome was additionally translocated to the short arm of a chromosome 15 (Fig. 2). The father was found to be carrying the same chromosome abnormality.

*Case 2.* 46, XY, dir dup(1)(p11→p22).

*Clinical findings.* The patient was the product of the first full-term pregnancy of a 23-year-old mother and an unrelated 24-year-old father. The pregnancy and delivery were uneventful, and the birth weight was 2,130 g. At 8 months of age, he was diagnosed as being a Dandy-Walker syndrome. When examined at 13 months, the body weight was 5,780 g, length 64.8 cm, and head circumference 42.8 cm. He had prominent occiput, hypertelorism, with bilateral epicanthic folds and blepharoptoses, malformed ears with preauricular pits, bilateral cryptorchidism, skin tag on the medial side of the left thumb, hypoplasia of the middle phal-



Fig. 3. (left) The appearance of Case 2 at the age of 13 months.

Fig. 4. (right) Three pairs of chromosome 1 in Case 2 (G-banding). Arrows indicate abnormal chromosomes 1.

anges of the 5th fingers, and pes valgus (Fig. 3). Dermatoglyphic study showed fingertip patterns consisting of 5 whorls and 5 ulnar loops, a total finger ridge count of 171, and absence of the left digital triradius d and right digital triradius c. Psychomotor development was profoundly retarded with no head control or visual following.

*Cytogenetic findings.* In every cell examined, the short arm of a chromosome 1 was found to be somewhat elongated. G-banding analysis of the chromosomes from early metaphases revealed that this elongation appeared to be due to a serial duplication of the segment 1p11→1p22 within the short arm of chromosome 1 (Fig. 4). The detailed karyotype was designated as 46, XY, dir dup(1)(pter→p22::p22→p11::p22→qter). Another possible karyotypic interpretation was an inverted duplication of the same segment at 1p23. The parents had normal chromosomes.

*Case 3.* 46, XX, inv dup(1)(q32→q44), inv 1qh.

*Clinical findings.* The patient was the product of the first pregnancy of a 28-year-old mother and an unrelated 35-year-old father. The delivery occurred at term, and the birth weight was 2,700 g. Psychomotor development was very slow: she could sit unsupported at 2 years, but could not stand or speak any meaningful words. Physical examinations at 2 years and 5 months revealed that her body weight was 8,000 g, length 75.0 cm, and head circumference 47.5 cm. The anterior fontanel was still widely open. She had dolichocephaly, antimongoloid eye slants, epicanthic folds, bushy eyebrows and long eyelashes, low-set and malformed ears, narrow and high-arched palate, microstomia, micrognathia, widely set nipples, systolic heart murmurs, long slender fingers with flexion deformities, umbilical hernia, prominent calcaneus, and excessive hair on the forehead, back and extremities (Fig. 5). Dermatoglyphic study showed 10 whorls with extralimital triradii on the fingertips.

*Cytogenetic findings.* In every cell examined, the long arm of a chromosome 1 was found to be slightly elongated. Based upon the G-banding patterns of the



Fig. 5. (left) The appearance of Case 3 at the age of 2 years and 5 months.



Fig. 6. (right) Three pairs of chromosome 1 in Case 3 (G-banding). Arrows indicate abnormal chromosomes 1.

chromosomes from early metaphases, this elongation was interpreted as being due to an inverted duplication of the segment  $1q32 \rightarrow 1q44$  at the distal end of the long arm of chromosome 1 (Fig. 6). The detailed karyotype was 46, XX, inv dup(1) (pter $\rightarrow$ q44::q44 $\rightarrow$ q32::q44 $\rightarrow$ qter). The parents had normal chromosomes.

*Case 4.* 46, XY, der(15), t(13;15)(q14;q26)pat.

*Clinical findings.* The patient was the product of the second term pregnancy of a 26-year-old mother and an unrelated 30-year-old father. The first pregnancy ended in a spontaneous abortion. The birth weight was 2,250 g. When examined 41 days after birth, the body weight was 2,860 g. He had hypertelorism, epicanthic folds, right internal strabismus, malformed ears with prominent antihelix and hypoplastic lobules, cleft palate, long philtrum, short neck, heart murmurs, small umbilical hernia, small penis with bilateral cryptorchidism, and limited abduction

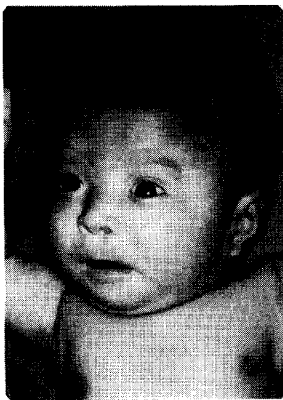


Fig. 7. (left) The appearance of Case 4 at the age of 41 days.

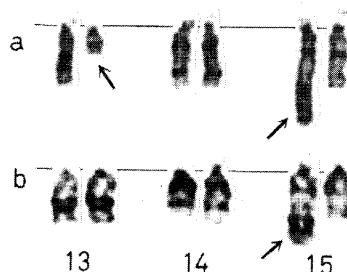


Fig. 8. (right) Partial G-banded karyotypes of Case 4 (b) and his father (a). Arrows indicate translocated chromosomes.

of the hip joints (Fig. 7). Death from cardiac failure occurred at 4 months.

*Cytogenetic findings.* In every cell examined, a chromosome 15 was found to be replaced by a longer acrocentric chromosome (Fig. 8b). The father was found to have a balanced translocation between the long arms of chromosomes 13 and 15,  $t(13;15)(q14;q26)$  (Fig. 8a). The patient was, therefore, trisomic for  $13q14 \rightarrow 13qter$ .

*Case 5.* 46, XY,  $der(13)$ ,  $t(13;18)(q34;q12)$  *pat.*

*Clinical findings.* The patient was born at term to a 26-year-old mother and an unrelated 31-year-old father. The mother had previously had 4 early trimester miscarriages and one stillbirth. The pregnancy was complicated by a threatened abortion in the first trimester. The delivery was uneventful, and the birth weight was 2,560 g. When examined at 2 months of age, the baby's body weight was 3,740 g. He had microcephaly with flat occiput, low-set and malformed ears, prominent nasal bridge, downturned corners of mouth, high-arched palate, micrognathia, redundant nuchal skin, overlapping fingers with flexion deformities, heart murmurs, left cryptorchidism, rocker-bottom feet, and hammer toes (Fig. 9). Dermatoglyphic study showed fingertip patterns consisting of 7 arches and 3 obscure configurations, a transitional simian crease on the right palm, and arch proximal patterns on the hallucal areas. Intravenous pyelography disclosed hydronephrosis of the left kidney with double ureters. Subsequent development was profoundly retarded. Death occurred suddenly at 13 months.

*Cytogenetic findings.* In every cell examined, a chromosome 13 was found to be replaced by a longer acrocentric chromosome (Fig. 10b). The father was found to be a carrier of a balanced translocation between the long arms of chromosomes 13 and 18,  $t(13;18)(q34;q12)$  (Fig. 10a). The patient, therefore, was trisomic for  $18q12 \rightarrow 18qter$ . Cytogenetic studies of his relatives showed that the translocation was transmitted through three successive generations (paternal grandfather, father and patient).

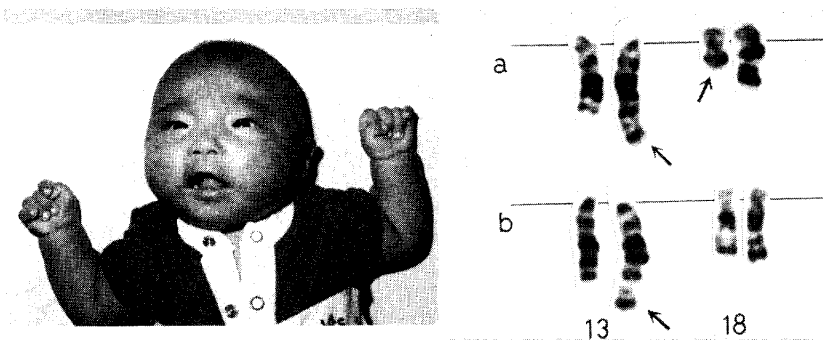


Fig. 9. (left) The appearance of Case 5 at the age of 2 months.

Fig. 10. (right) Partial G-banded karyotypes of Case 5 (b) and his father (a). Arrows indicate translocated chromosomes.

*Case 6. 46, XX, del(4)(p13).*

*Clinical findings.* The patient was born at term to a 27-year-old mother and an unrelated 30-year-old father. The birth weight was 2,460 g. Psychomotor development was severely delayed, and epileptic seizures appeared from the age of 8 months. When examined at 11 months, the baby weight was 7,360 g, length 66.5 cm, and head circumference 41.4 cm. She had frontal bossing, hemangioma on the glabella, hypertelorism, thick eyebrows, divergent strabismus, small nose with short philtrum, low-set and malformed ears, small mouth, micrognathia, high-arched palate, and sacral sinus. Intravenous pyelography showed ectopia of the right kidney. Dermatoglyphics of the patient were not remarkable.

*Cytogenetic findings.* In every cell examined, a partial deletion of the short arm of a chromosome 4 was observed. The breakpoint appeared to occur at 4p13 (Fig. 11).

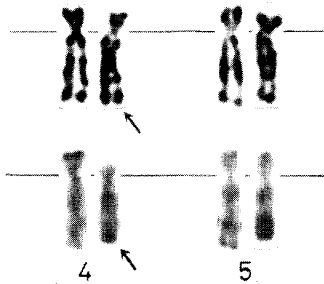


Fig. 11. Partial karyotypes of Case 6: G-banding (top) and R-banding (bottom). Arrows indicate deleted chromosomes.

*Case 8. 46, XY, del(11)(q21).*

*Clinical findings.* The patient was born after 34 weeks' gestation to a 30-year-old mother and an unrelated 36-year-old father. The father had been oligospermic for the previous several years. The birth weight was 2,035 g. He had hyper-

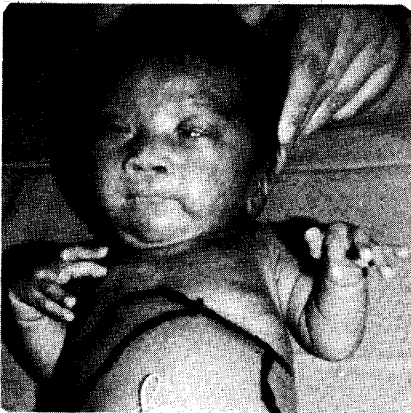


Fig. 12. (left) The appearance of Case 8 at the age of 9 days.

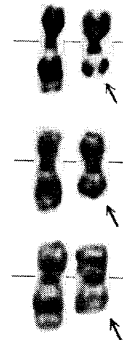


Fig. 13. (right) Three pairs of chromosome 11 in Case 8 (G-banding). Arrows indicate deleted chromosomes 11.

telorism with mongoloid eye slant, blepharoptoses and right microphthalmos, flat nasal bridge, low-set and malformed ears, micrognathia, cleft palate, heart murmurs, sacral sinus, and bilateral cryptorchidism (Fig. 12). Dermatoglyphic study showed fingertip patterns consisting of 6 ulnar loops, 3 whorls, and one radial loop (unusually on the right thumb), and a total finger ridge count of 94. Obstructive jaundice appeared at 7 days. Autopsy disclosed incomplete extrahepatic biliary atresia with hypoplasia of the gallbladder, patent ductus arteriosus, and Meckel's diverticulum.

*Cytogenetic findings.* In every cell examined, partial deletion of the long arm of a chromosome 11 was observed. The breakpoint appeared to occur at 11q21 (Fig. 13). Chromosome analysis of the parents was not granted.

*Case 9. 46, XX, del(18)(q22).*

*Clinical findings.* The patient was born at term to 33-year-old nonconsanguineous parents. The mother had previously had 3 spontaneous abortions. The birth weight was 2,700 g. When examined at 2 months, her body weight was 3,420 g. She had hypertelorism, narrow palpebral fissures, malformed ears with a right postauricular skin tag, midface hypoplasia, bilateral cleft lips and cleft palate, micrognathia, short neck, heart murmurs, umbilical hernia, and prominent calcaneus. Dermatoglyphic study showed fingertip patterns consisting of 9 whorls and one ulnar loop, a total finger ridge count of 160, hypothenar patterns on both hands, and high axial triradii (t").

*Cytogenetic findings.* In every cell examined, a partial deletion of the long arm of a chromosome 18 was detected. The breakpoint appeared to occur at 18q22 (Fig. 14).

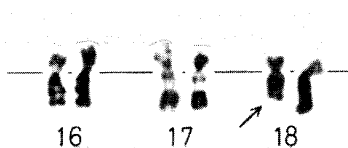


Fig. 14. Partial G-banded karyotype of Case 9. Arrow indicates a deleted chromosome 18.

## DISCUSSION

The present study showed that an appreciable proportion (14.9%) of patients with unclassifiable multiple malformations and mental retardation had a major chromosome abnormality. There have been at least 9 published cytogenetic surveys concerning patients with those phenotypes, irrespective of whether banding techniques were used or not (1-4, 14-18). The results of these surveys, together with those of the present study, are summarized in Table 3. For comparison, cases with trisomy 13 or 18 were excluded from the survey of Coco and Penchaszadeh (1976)(1). The incidence of chromosome abnormalities in these surveys varied, ranging from 3.0% to 17.8%. It seems likely that differences in sample size, selection criteria, and cytogenetic methods used were responsible for the variation. The

TABLE 3. SUMMARY OF CYTOGENETIC SURVEYS CONCERNING MENTALLY RETARDED PATIENTS WITH MULTIPLE MALFORMATIONS.

| References                  | Population studied |        |       | Sex chromosome abnormality |     | Autosomal abnormalities |      |                 |     | Total |      |
|-----------------------------|--------------------|--------|-------|----------------------------|-----|-------------------------|------|-----------------|-----|-------|------|
|                             | Male               | Female | Total | No.                        | %   | Unbalanced <sup>a</sup> |      | Balanced        |     | No.   | %    |
| Summitt, 1969               | 27                 | 23     | 50    | 0                          | 0   | 3                       | 6.0  | 1               | 2.0 | 4     | 8.0  |
| Daly, 1970                  | —                  | —      | 50    | 1                          | 2.0 | 4                       | 8.0  | 2               | 4.0 | 7     | 14.0 |
| Jacobsen and Dupon, 1971    | —                  | —      | 102   | 3                          | 2.9 | 8                       | 7.8  | 0               | 0   | 11    | 10.8 |
| Carrel et al., 1973         | 61                 | 60     | 121   | 1                          | 0.8 | 17                      | 14.1 | 1               | 0.8 | 19    | 15.7 |
| Erdtmann et al., 1973       | 32                 | 19     | 51    | 1                          | 2.0 | 4                       | 7.8  | 0               | 0   | 5     | 9.8  |
| Coco and Penchaszadeh, 1976 | —                  | —      | 124   | 2                          | 1.6 | 17                      | 13.7 | 3               | 2.4 | 22    | 17.7 |
| Doyle, 1976                 | —                  | —      | 90    | 1                          | 1.1 | 4                       | 4.5  | 0               | 0   | 5     | 5.6  |
| Magnelli, 1976              | —                  | —      | 50    | 0                          | 0   | 6                       | 12.0 | 0               | 0   | 6     | 12.0 |
| Tharapel and Summitt, 1977  | 108                | 92     | 200   | 0                          | 0   | 3                       | 1.5  | 3               | 1.5 | 6     | 3.0  |
| Total                       |                    |        | 838   | 9 <sup>b</sup>             | 1.1 | 66                      | 7.9  | 10 <sup>c</sup> | 1.2 | 85    | 10.2 |
| Present study               | 38                 | 36     | 74    | 1                          | 1.4 | 10                      | 13.5 | 0               | 0   | 11    | 14.9 |

<sup>a</sup> : This includes trisomies, partial trisomies or monosomies. <sup>b</sup> : This includes 3 patients with XYY, 3 patients with XO mosaicism, and each patient with XXX, XXXX, or XXY/XXYY.

<sup>c</sup> : This includes 2 patients with D/D translocation and 8 patients with reciprocal translocations.

relatively high frequency in the present study may be due to detection of chromosomally abnormal patients who died in early infancy. In previous surveys, on the other hand, most of the subjects were school-aged children or young adults, and chromosome aberrations resulting in early mortality would be rare.

Combination of the previous surveys reveals that the overall incidence of chromosome abnormalities is 10.2 % (Table 3). Unbalanced autosomal abnormality is the most common type of aberration, occupying 7.9 % of this figure. The frequency of sex chromosome abnormalities and balanced autosomal abnormalities are 1.2 % and 1.1 %, respectively. In the present study, a sex chromosome abnormality was found in one case (1.4%), while an unbalanced autosomal abnormality was observed in 10 cases (13.5 %). These results are consistent with the combined data. The lack of a balanced autosomal abnormality in this study may be explained by the small sample size.

A causal relationship between chromosome abnormality and a phenotype in the 10 cases with unbalanced autosomal rearrangements is evident, since such rearrangements are consistently associated with net loss or gain of vital genetic material. In the case with an unbalanced Y/15 translocation, however, the heterochromatic nature of the duplicated segment along with the absence of phenotypic abnormalities in the father carrying the same chromosome abnormality suggest

that this chromosome rearrangement is in fact coincidental. Indeed, Nielsen and Rasmussen (1976) noted that 5 infants with this translocation found in a consecutive newborn survey showed no abnormal phenotype (19).

The improbable phenotypic effect also holds true for the heterochromatic variants found in the present study. These variants involve only heterochromatic regions, that are, by definition, genetically inert. Moreover, the frequency of each variant in the patient sample is not significantly different from that reported in the general Japanese population (20).

The most remarkable finding in this study is the demonstration of two patients (Cases 2 and 3) with a probable intrachromosomal duplication, which would not have been identified by conventional staining alone. This has important implications in medical practice for the diagnosis of patients with unclassifiable multiple malformations and mental retardation. Banding techniques are particularly useful in detecting certain structural rearrangements, including paracentric inversions, pericentric inversions with breakpoints equidistant from the centromere, interchromosomal exchanges involving approximately equal amount of chromosome material, and small deletions or duplications. In the last rearrangement, when there is no parental chromosome abnormality, it is often difficult to determine with certainty the origin of duplicated segments. The parents of the two cases had normal chromosomes. Their karyotypic interpretations, therefore, were based on banding patterns of the abnormal chromosomes from early metaphases. The validity of the interpretation of Case 3 is further supported by the close resemblance of the clinical features to those of earlier cases with trisomy for the same segment (21-24). On the other hand, Case 2 is not conclusive, because no comparable case is available yet. Further study of dose effects for certain gene markers presumed to be located on the short arm of chromosome 1 might clarify this question.

Although the present study provides further evidence that chromosome abnormalities contribute much to the etiology of unclassifiable multiple malformations associated with mental retardation, in the majority of the affected patients the cause is still unknown. There is a report of cases in which a chromosome abnormality is restricted exclusively to skin fibroblasts (25). Furthermore, a banding technique with a higher resolution has recently been developed, facilitating the detection of even more subtle chromosome changes (26). Future study using this high-resolution technique, coupled with simultaneous analysis of cultured skin fibroblasts, will lead to more accurate assessment of the role of chromosome abnormalities in the etiology of the above-mentioned conditions.

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