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Duplication 8p Syndrome: Studies in a Family With a Reciprocal Translocation Between Chromosomes 8 and 12

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We report a family in which six individuals were carriers of a translocation between chromosomes 8 and 12. The balanced carriers had a chromosome constitution: 46,XX or 46,XY,t(8;12)(021;p13). Six individuals in five generations were mentally retarded. Three of them were examined; their chromosome constitution was 46,XX or 46,XY,der(12),t(8;12)(p21;p13); thus they had a duplication of 8pter→8p21 and possible deficiency of 12pter→12p13. The activities of the enzymes that are coded by genes on 8p (glutathione reductase, GSR, E.C. 1.6.4.2.) and 12p (triosephosphate isomerase, TPI, E.C. 5.3.1.1.; lactate dehydrogenase-B, LDH-B, E.C. 1.1.1.27.; and glyceraldehyde-3-phosphate dehydrogenase, G3PD, E.C. 1.2.1.12.) were normal in these individuals. These findings helped in interpreting the position of the break points in the respective chromosomes. The phenotypic findings in our patients are discussed.

Segregation analysis indicates no significant variation from a 25% recurrence risk for each of the possible genotypes in the offspring of balanced carriers.

Key words: **duplication/deficiency syndrome, familial translocation, recurrence risk, segregation ratio, multiple congenital anomalies/mental retardation (MCA/MR) syndrome**

INTRODUCTION

Several balanced and unbalanced carriers of a chromosome translocation 8;12 were ascertained through the examination of a mentally retarded 23-year-old woman, whose brother, the propositus, required genetic counselling. The retarded sister of the prospositus, two of her cousins, and possibly three other mentally retarded individuals in this family were shown to have a duplication of a portion of the short arm of chromosome 8, and were likely deficient for the terminal segment of 12p. We report the phenotypic findings in these individuals and compare them to those of previously reported cases. An attempt was made to locate more precisely the breakpoints by assaying the activities of the enzymes whose loci are known to be located on 8p and 12p for evidence of gene dosage effects.

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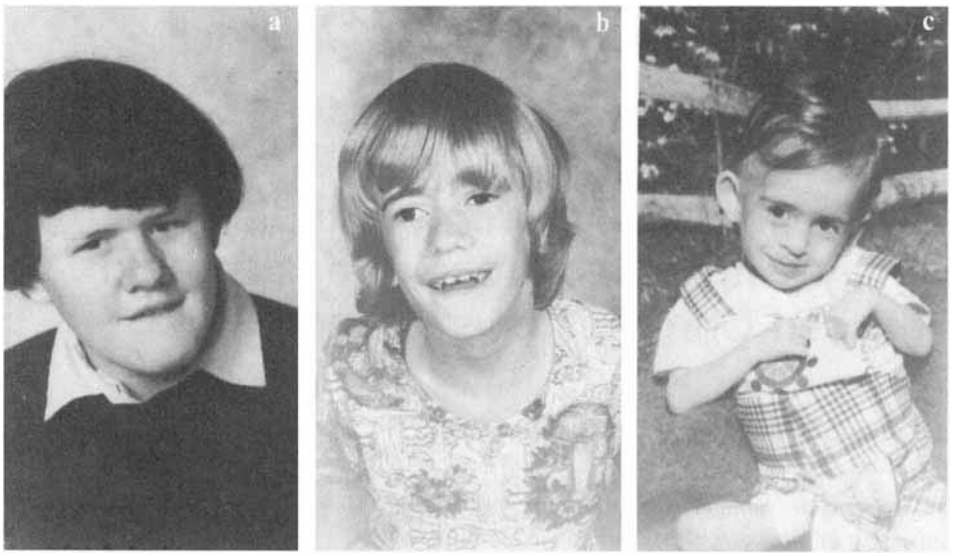

Fig. 1. a: Patient 1, sister of the propositus. b: Patient 2. c: Patient 3.

REPORTS OF PATIENTS

Patient 1

MW 121056 (Fig. 1a; V-2 in Fig. 2), sister of the propositus, a 23-year-old woman, was the product of an uneventful pregnancy and delivery, born to a 23-year-old gravida 2 mother who had had a previous spontaneous abortion. Since birth she had been hypoactive and had had feeding difficulties. Strabismus was evident. She had an atrial septal defect and electrocardiogram (ECG) signs of atrioventricular block, complicated later in infancy with left atrial enlargement, and left ventricular hypertrophy. Mental retardation (MR) was evident since early infancy. Her IQ (Stanford-Binet) was estimated to be around 20 at 23 years. Middle-ear infections were frequent during infancy. She also had a "square" face, prominent glabella, antimongoloid slant of the palpebral fissures, bulbous nose, open mouth with malocclusion, highly arched palate, prominent mandible, prominent and malformed ears, and low posterior hairline. Normal breast development, mild scoliosis, and holosystolic murmur were present. The hands were slender and short with tapering of the fingers and hyperextensible middle phalanges. The patient had rocker-bottom feet with limited movement at ankles and overlapping first and fifth toes. There was constant flexion at most major joints.

Patients 2 and 3

MP 072369, female, age 11 years, and RG 031975, male, age five years (Fig. 1b,c). Both of these similarly affected half-sibs (V-12 and V-13 in Fig. 2) had MR, the same abnormal facial appearance as patient 1, and semiflexion at the major joints. V-12 had clinodactyly of the left fifth finger; club feet had been corrected previously. Atrial and ventricular septal defects were present. V-13 had bilateral clinodactyly, a pectus excavatum, a diaphragmatic hernia, cleft lip and palate, and cryptorchidism. This child had

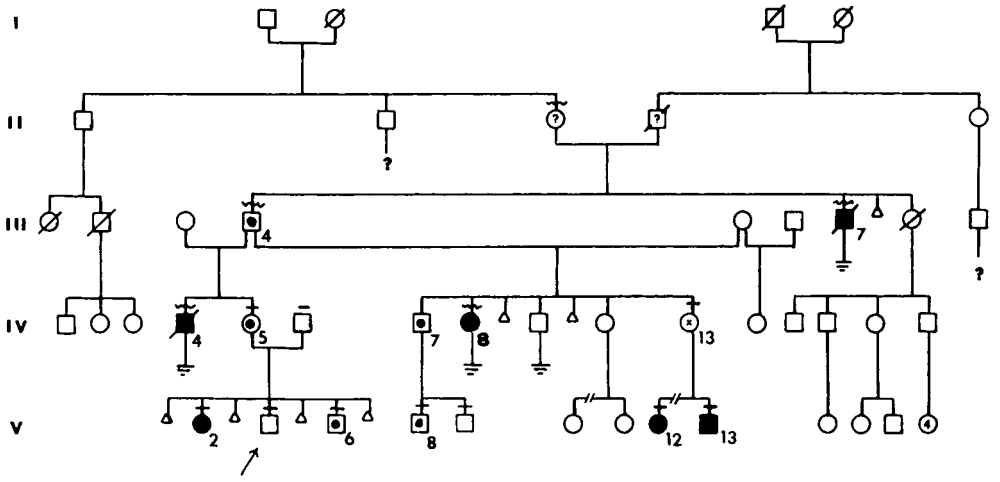

Fig. 2. Pedigree. Affected individuals are denoted as black symbols. Karyotyped balanced carriers as dots inside the symbol. X = obligate carriers. ? = information unknown. Personally examined individuals are identified with a straight line above the symbol. Photograph examined with a wavy line. "Grounded" symbol represents lack of offspring.

no evidence of heart disease. Middle-ear infections were frequent during infancy. EEGs were not specifically abnormal. A CAT scan was normal in V-12; that of V-13 was compatible with dilatation of the posterior horns of the lateral ventricles. These individuals had the same chromosome defect as the sister of the propositus.

Patients 4 to 6

Three other family members were known to be mentally retarded (III-7, IV-4, and IV-8 in Fig. 2). Photographs of these individuals suggested that they had the same clinical syndrome, but they were not examined.

DERMATOGLYPHIC STUDIES

The palmar dermatoglyphics of the three patients examined were unusual and dissimilar from those of their parents. These findings are depicted in Table I. V-2 had a simian crease in the left hand. V-12 had a double triradius *a*, interdigital loops in the second and third spaces of the right hand, and bilateral absence of the *c* triradii. V-13 had a bilateral Sydney line. The triradii *b* and *c* appeared too close together in patients 1 and 3, which may account for the narrow *atd* angle in all three patients (Table I).

CHROMOSOME STUDIES

Cytogenetic analysis was performed in ten individuals; six phenotypically normal individuals (III-4, IV-5, IV-7, IV-13, V-6, and V-8; Fig.2) were balanced carriers of a translocation 8;12(8pter→8p21::12p13→12pter; 12pter→12p13::8p21→8pter) (Fig. 3). All three of the six mentally retarded individuals who were examined (V-2, V-12, and V-13) were found to have a duplication of the segment 8pter→8p21, and a possible deletion of

TABLE I. Palmar Dermatoglyphics

	Digital patterns[a]		Total ridge count	*atd* Angle[a]	Palmar patterns[a]
Patient 1	$UL^1\ A^2\ A^3\ A^4\ A^5$	$UL^1\ A^2\ A^3\ A^4\ A^5$	28	40/45	H: A^c/A^c T: 0/0
Patient 2	$UL^1\ W^2\ W^3\ W^4\ UL^5$	$UL^1\ W^2\ W^3\ UL^4\ UL^5$	147	44/47	H: A^c/A^c T: 0/0
Patient 3	$UL^1\ UL^2\ UL^3\ W^4\ UL^5$	$UL^1\ W^2\ UL^3\ W^4\ UL^5$	105	35/43	H: A^u/A^u T: 0/0

[a]Right hand first.
H = hypothenar; T = thenar.

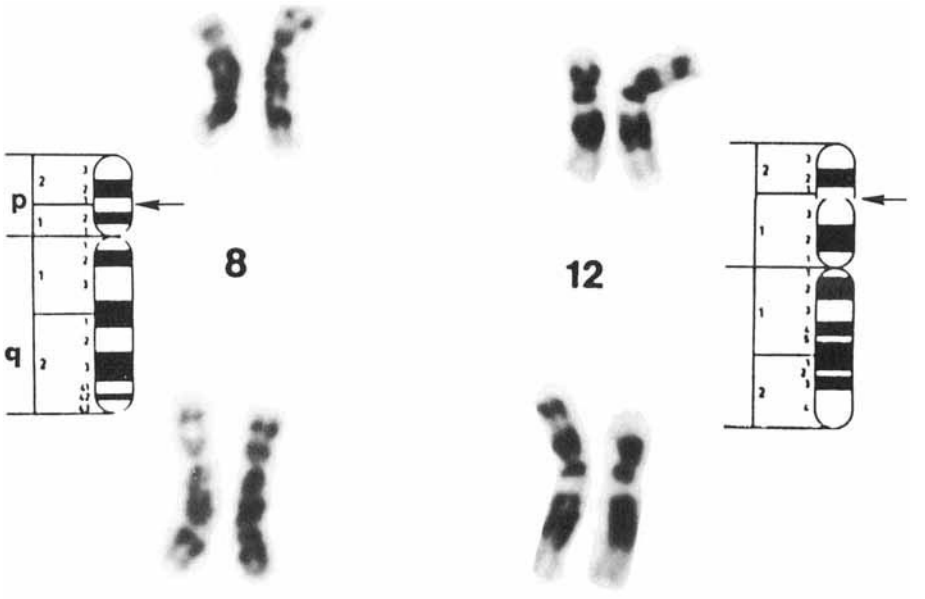

Fig. 3. Partial karyotypes of IV-5 (mother of the propositus, top) and V-2 (sister of the propositus, bottom). Arrows indicate the postulated position of the breakpoints in the chromosomal segments.

12pter→12p13. Their karyotype designation was 46,XX or 46,XY,der(12),t(8;12)(p12;p13) (Fig. 3). The other affected relatives were presumably similarly affected since the alternative cytogenetic abnormality, deletion 8p, is most likely inviable.

ENZYME ANALYSES

In the affected persons and a control group we assayed the activities of three enzymes (triosephosphate isomerase, E.C. 5.3.1.1.; lactate dehydrogenase-B, E.C. 1.1.1.27.; glyceraldehyde-3-phosphate dehydrogenase, E.C. 1.2.1.12.) whose structural loci are known

to be located on the distal band of the short arm of chromosome 12 [Serville et al, 1978; Rethoré et al, 1976; Bootsma and Ruddle, 1978; Law and Kao, 1979], and glutathione reductase, which has been mapped to the region p21 of chromosome 8 [de la Chapelle et al, 1976; Sinet et al, 1977; Magenis et al, 1978]; previously published methods [Beutler, 1975; Fielek and Mohrenweiser, 1979] were used. The level of activity of each enzyme was normal in each of the two groups. The absence of a dosage effect for glutathione reductase in the unbalanced carriers (affected patients mean values, 1,293 μmol/min/gm of hemoglobin versus controls, 1,317 μmol/min/gm of hemoglobin) indicates that the breakpoint on band 8p21 for this translocation is distal to the gene for glutathione reductase. Similarly activity measurements of the three enzymes mapping on 12p (TPI patients, 103,400 versus controls, 120,000 μmol/min/gm of hemoglobin; LDH-B, patients, 8,086 versus controls, 7,069 μmol/min/gm of hemoglobin; G3PD patients, 3,811 versus controls, 3,428 μmol/min/gm of hemoglobin) does not show loss of any activity, hence, the break must be distal to these loci on 12p.

DISCUSSION

Clinical findings in our patients are summarized in Table II and compared with those of previously reported cases [Yanagisawa and Hiraoka, 1971; Yanagisawa, 1973; Rosenthal et al, 1973; Chiyo et al, 1975; Taylor et al, 1977; Mattei et al, 1980]; another patient has been mentioned in an abstract [Cowell et al, 1978]. A distinct phenotype seems due to duplication 8p; namely, MR, strabismus, palatal abnormalities, malformed ears, congenital heart disease, brain abnormalities (including dilatation of the lateral ventricles and/or absence of the corpus callosum), hyperextensible interphalangeal and metacarpophalangeal joints, and flexion contractures. Dermatoglyphic abnormalities include an excess of arches or whorls, simplification of creases in the palms, and a narrow *atd* angle; the feet and soles may be abnormal and toenails hypoplastic. A shortened lifespan may be expected in these patients; early death seems related to the severity of the cardiac defects, associated malformations or possibly diminished resistance to infections (two of our patients died of pneumonia). Phenotypic variability in some of our patients regarding the severity of the heart disease, the dermatoglyphic findings, and the presence of associated malformations such as cleft lip and palate, and diaphragmatic hernias, falls within the range expected in duplication/deficiency syndromes.

This family is also useful for making inferences regarding the reproductive outcome of balanced carriers. The recurrence risk for the unbalanced genotypes among the offspring of carriers of chromosomal translocations has been estimated to be between 8% and 15% [Lejeune et al, 1970]. In our family, among 24 pregnancies observed in the matings of the balanced carriers, the following resulted: 1) seven abortuses (29%); 2) six mentally retarded individuals (25%); at least six translocation carriers (25%); at most, five cytogenetically normal individuals (20%). Assuming that the abortuses had an 8p deletion, the observed proportions of these four genotypes do not significantly differ from 25%. Previously reported pedigrees with the duplication 8p syndrome [Yanagisawa and Hiraoka, 1971] gave similar results. A similar outcome has been reported for a 4/12 translocation [Mortimer et al, 1980]. It follows, that segregation ratios may vary in the different forms of familial translocations and that selective mechanisms may act before or after fertilization to distort the theoretical ratios in some of them [Jacobs et al, 1970]. We suggest that, whenever possible, counselling of balanced carriers should be based on the observed segregation ratios within their families.

TABLE II. Duplication 8p – Clinical Findings

Author	Yanagisawa, 1973; Yanagisawa and Hiraoka, 1971	Rosenthal et al, 1973	Chiyo et al, 1975	Taylor et al, 1977	Mattei et al, 1980	This report 1980
Patients	3	1	1	1	3	6
Gestation	?,?,?	Term (t)	t	43 weeks	t,t,36 w	t,t,t,t,t,t
Maternal age	21–23	26	27	32	29,30,40	20–25
Paternal age	26–27	29	32	40	23,30,56	23–27
Sex	M,M,M	M	M	F	F,F,M	M,M,M/F,F,F
Birth weight (gm)	?,?,2,600	3,200	3,150	4,400	3,150;2,350;2,700	Normal
Mental motor delay	+,+,+	+	+	+	+,+,+	+,+,+/+,+,+
Seizures	?,?,?	+	–	–	?,?,?	–,–,–/–,–,–
Brain abnormalities	?,?,?	?	+	?	+,+,+	?,?,+/?,?,–
Short stature	?,?,?	?	+	–	–,+,?	?,?,+/?,+,+
Hypertelorism	+,+,–	?	+	–	+,+,+	?,?,+/+,+,+
Antimongoloid slant	–,–,+	+	+	+[a]	–,+,–	?,?,+/+,+,+
Strabismus	+,+,+	?	+	±	–,?,?	?,?,+/+,+,+
Nasal bridge depressed	+,+,+	+	+	–	+,+,+	?,?,+/+,+,+
Dental malocclusion	?,?,?	?	?	+[a]	?,?,?	?,?,+/?,+,+
Palate, highly arched	+,+,+	+	+	?	?,?,?	?,?,+/?,+,+
Palate/lip, cleft	–,–,–	–	–	–	–,–,–	–,–,+/–,–,–

Mandible, prominent	?,?,?	?	+	+[a]	+,+,+	?,?,+/+,+,+
Mouth, large	±,±,±[a]	±[a]	±[a]	±[a]	+,+,+	?,?,+/+,+,+
Ears, malformed	+,+,+	+	+	+	+,+,+	?,?,+/?,+,+
Heart defects	+,+,–	–	–	–	+,–,–	?,?,–/?,+,+
Diaphragmatic hernias	–,–,–	–	–	–	–,–,–	–,–,+/–,–,–
Penis, small	+,+,+	–	+		,,?	?,?,+/
Cryptorchidism	–,+,+	–	–		, ,–	?,?,+/
Joints, abnormal	+,+,+	?	?	+	?,?,?	?,+,+/+,+,+
Toenails, hypoplastic	+,+,+	+	+	?	?,?,?	?,?,+/?,+,+
Simian crease	+,+,–	?	+	–	?,?,+	?,?,–/?,+,+
Sydney line	–,–,?	?	–	–	?,?,–	?,?,+/?,–,–
Single creases, fingers	+,+,–	?	+	–	?,?,?	?,?,–/?,–,–
Dermatoglyphics unusual	+,+,+	+	+	+	+,+,+	?,?,+/?,+,+
Familial translocation	8p/21	8p/22q	8p/13q	–	–,?,?	8p21→pter
Duplication	8p??→pter	8p??→pter	8p11→pter	8p12→p23	8p11→p 232	8p21→pter
Deletion	21p–	22q–	13q34→qter	–	–,–,8p233→2 & 14q12→pter	12p13→pter
Age of death	?	?	?	?	?,?,?	47,38, / , ,
Present age	?	?	?	?	?,?,?	5/43,24,11

Findings in our patients are indicated according to age (the oldest first) and sex (M, males/F, females).
? = Unknown or not reported; + = present; – = absent; ± = questionably present.
[a]Observed from published photograph.

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