PARTIAL 18q TRISOMY AND 18p MONOSOMY RESULTING FROM A MATERNAL PERICENTRIC INVERSION, inv(18)(p11.2q21.3)

Takeshi ASANO,¹ Tatsuro IKEUCHI,² Tamiko SHINOHARA,³
Hisashi ENOKIDO,⁴ and Kiyoshi HASHIMOTO¹

¹Department of Pediatrics, Nippon Medical School,
1-1-5 Sendagi, Bunkyo-ku, Tokyo 113, Japan

²Department of Cytogenetics, Medical Research Institute, Tokyo Medical and
Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113, Japan

³Department of Human Cytogenetics, Japan Red Cross Medical Center,
4-1-22 Hiro-o, Shibuya-ku, Tokyo 150, Japan

⁴Department of Pediatrics, Shimodate Municipal Hospital,
1658 Tamado, Shimodate, Ibaraki 308, Japan

Summary A 7-year-old boy with dysmorphic features was found to have a recombinant chromosome 18, rec(18), resulting from meiotic recombination of a maternal pericentric inversion, inv(18) (p11.2q21.3), as defined by high-resolution banding. He was trisomic for the long arm (q21.3-qter) and monosomic for the short arm (p11.2-pter) of chromosome 18. His clinical features were compared with those in other rec(18) cases, and also those in monosomy 18p, trisomy 18qter and full trisomy 18 syndromes. The risk of recombinant formation for inv(18) carriers was also discussed.

Key Words chromosome 18, recombinant chromosome, partial monosomy 18p, partial trisomy 18q

INTRODUCTION

Clinical characterization for partial trisomy 18q and for partial monosomy 18p has been well established (de Grouchy and Turleau, 1977; Schinzel, 1984). However, combination of these chromosomal anomalies is very rare, and only 4 such cases resulting from recombination of parental pericentric inversions have been reported to date (Vianna-Morgante *et al.*, 1976; Turleau and de Grouchy, 1977; Kukulich *et al.*, 1978; Andrews *et al.*, 1982). We report here another case

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Reprint requests to: Takeshi Asano, M.D., Department of Pediatrics, Nippon Medical School First Hospital, 3-5-5 Iidabashi, Chiyoda-ku, Tokyo 102, Japan.

of recombinant chromosome 18 with duplication of the distal one-third of the long arm and deficiency of the terminal segment of the short arm, which arose from a maternal balanced pericentric inversion, inv(18) (p11.2q21.3). The patient's clinical manifestations and the risk of recombination for inversion carriers will be discussed in association with the chromosomal regions involved in the duplication and deficiency. A brief report on this patient has been presented preliminarily elsewhere (Shinohara *et al.*, 1985).

CASE REPORT

The proband, born after 39 weeks of gestation, was the second child of a 30-year-old mother and a 32-year-old father, who were both phenotypically normal. There was consanguinity in the mother's pedigree, *i.e.*, the mother's parents were cousins. The mother had a history of two spontaneous abortions and one stillbirth. The elder sister of the proband was phenotypically normal. The proband was born after an uneventful pregnancy and delivery, weighing 2,890 g. At birth, however, facial pallor was noted and he was transferred to an incubator. He complained of failure to thrive, and the intake was tube feeding. At 2 weeks, the body weight was 3,070 g, the length was 50 cm, and the clinical manifestations were as follows: hypotonia, dolichocephaly, slight frontal bossing, a prominent occiput, asymmetrical and narrow palpebral fissures, large and low-set ears, an upturned nose, a small mouth, a high-arched palate, micrognathia, microglossia

Fig. 1. Proband at 2 weeks of age (a) and at 7 years of age (b).

(Fig. 1a), camptodactyly of both the fifth fingers, typical overlapping of the two medial fingers by the index and fifth fingers in both hands, lack of a 12th rib on the right side, and micropenis. At age 3 months, he was able to control his head steadily and smile responsively. At 15 months of age, he was able to roll over and to sit without support, and his developmental quotient was 41. Results of routine laboratory tests, including EEG, brain CT scan, intravenous pyelography and echocardiography, were all within normal limits.

At the age of 7 years, his body weight was 14.9 kg (-3.4 S.D.) and his height was 100.5 cm (-3.9 S.D.). Microglossia and micropenis were still present (Fig. 1b). He was able to run, use a video-tape recorder, and speak a few words other than "mama" and "papa." He could not take solid food, however, and a nasogastric tube was still required.

DERMATOGLYPHIC STUDY

The propositus had 9 ulnar loops and one radial loop. The atd angles were 53.5° on the right palm and 60° on the left. There was a simian crease on the left hand and a Sydney line on the right hand. The total ridge count was 92 and c triradii were absent on both palms. The dermatoglyphics of his parents were normal.

Fig. 2. Pairs of high-resolution G-banded chromosomes 18 from the mother (a) and from the propositus (b).

Fig. 3. Schematic diagram of meiotic pairing of the normal and inverted chromosomes 18 in the mother (upper) and formation of the recombinant chromosomes following crossing-over within the inverted segment (lower).

CYTOGENETIC STUDY

Initial karyotype analyses of the patient using cultured lymphocytes and skin fibroblasts revealed a slightly elongated short arm of chromosome 18 along with an altered band profile. Chromosome studies of lymphocyte cultures from the parents showed that the mother had a pericentric inversion on chromosome 18, whereas the father's karyotype was normal. High-resolution G-banding by the ethidium bromide pretreatment method (Ikeuchi, 1984) was performed on cultured lymphocytes from the patient and his mother. The breakpoints in an $\text{inv}(18)$ chromosome of the mother were found to be at 18p11.2 and 18q21.3 (Fig. 2a). Thus, the mother's karyotype was identified as $46, \text{XX}, \text{inv}(18)(p11.2q21.3)$. A recombination event during meiosis in the mother would have given rise to the patient's recombinant chromosome 18 (Fig. 2b) if the crossing-over had occurred in the inverted segment, as shown in Fig. 3. The patient's karyotype was therefore designated $46, \text{XY}, \text{rec}(18), \text{dup } q, \text{inv}(18)(p11.2q21.3) \text{ mat}$, indicating the patient to be trisomic for the q21.3-qter and monosomic for the pter-p11.2 regions.

DISCUSSION

Our patient showed a recombinant chromosome with duplication of the distal region of the long arm (18q21.3-qter) and deficiency of the short arm (18p11.2-pter), which had originated from maternal balanced pericentric inversion of chromosome 18. In the literature, there have been only 7 reported cases of recombinant chromosome 18 due to parental inversions: 4 cases of long-arm duplication (associated with short-arm deficiency) (Vianna-Morgante *et al.*, 1976; Turleau and de

Table 1. Clinical manifestations in cases of rec(18) chromosome (trisomic for q21-qter and monosomic for p11-pter), and in 18p-, trisomy 18qter and full trisomy 18 syndromes.

	rec(18), dup q ^a				18p- ^b	Trisomy q21-qter ^c	Full 18 trisomy ^d
	1	2	3	4			
mental retardation	+	+	+		++	73% (8/11)	++
low birth weight (<2,500g)	-	+	-	-	+	45% (5/11)	++
early death	-	-	-	-	-	36% (4/11)	++
hypotonia	+	+	-	-	+	45% (5/11)	+
hypertonia	-	-	+	-	-	0% (0/11)	+
congenital heart disease	-	-	-		-	45% (5/11)	++
urological malformation	-				-	18% (2/11)	++
genital malformation	+	+		+	+	9% (1/11)	++
Cranial contour							
microcephaly	-	-	-	-	+	18% (2/11)	++
round face	-	-	-	-	++	27% (3/11)	-
prominent occiput	+		+		-	36% (4/11)	++
frontal bossing	+	+	-	-	-	36% (4/11)	-
Eye							
strabismus	-	-	-		+	18% (2/11)	-
narrow palpebral fissures	+	+	-		+	9% (1/11)	++
Ear							
low-set ear	+	-	+	+	+	45% (5/11)	++
deformed auricles	+	+	+	+	++	64% (7/11)	++
Nose							
bulbous nose	+	-	+	+	-	45% (5/11)	+
Oral							
micrognathia	+	+	+	+	+	73% (8/11)	++
microglossia	+				+	0% (0/11)	-
small mouth	+	-	-	-	-	18% (2/11)	++
carp mouth	-	-	-	-	++	0% (0/11)	-
high arched palate	+		+		-	45% (5/11)	++
Truncus							
pectus excavatum	-	-	+	-	+	36% (4/11)	-
Extremities							
overlapping fingers	+			-	-	18% (2/11)	++
clinodactyly	+	+	-	-	+	27% (3/11)	++
predominance of arch	-	+	+		-	36% (4/11)	++
prominent heels	-	+	-		-	18% (2/11)	++

^a 1, Present case; 2, Vianna-Morgante *et al.* (1976); 3, Kukulich *et al.* (1978); 4, Turleau & de Grouchy (1977). ^b Based on the articles by: Kunze *et al.*, 1972; Schinzel *et al.*, 1974; Faust *et al.*, 1976; de Grouchy & Turleau, 1977; and Schinzel, 1984. ^c The literature cited is shown in Table 2.

^d Based on articles by: de Grouchy & Turleau, 1977; Hodes *et al.*, 1978; Wilson *et al.*, 1990.

Grouchy, 1977; Kukolich *et al.*, 1978; Andrews *et al.*, 1982), as shown in the present case, and 3 cases of short-arm duplication (associated with long-arm deficiency) (Jacobs *et al.*, 1974; Vianna-Morgante *et al.*, 1976; Teyssier and Bajolle, 1980). Among the former, the case reported by Andrews *et al.* (1982) showed duplication of the longer segment (18q11-qter). As the duplicated and deleted segments in the other 3 cases were similar in size to those of our patient, their clinical pictures were compared as shown in Table 1.

These 4 cases are clinically similar, and share ceratin features: mental retardation, frontal bossing, deformed auricles, and micrognathia. Some minor inconsistent features seen among the 4 cases might be due in part to the slight differences in length of the unbalanced chromosome regions. The 4 patients with chromosome rec(18) showed the features seen in the 18p— syndrome (Kunze *et al.*, 1972; Schinzel *et al.*, 1974; Faust *et al.*, 1976; Schinzel, 1984), but most of them are also common in the full trisomy 18 and trisomy 18qter syndromes, as described below (Table 1). The rather unique features of 18p— syndrome, such as round face, strabismus, carp mouth and pectus excavatum, are not observed in cases of rec(18) chromosome. Thus, distal 18q trisomy seems to be epistatic in its expression over 18p monosomy. Alternatively, the above signs of 18p— syndrome might be due to monosomy of the more proximal restricted segment of the short arm of chromosome 18.

There have been a number of reported patients trisomic for only the distal region of 18q (18q21-qter), mostly derived from parental reciprocal translocation (Table 2), and these have been defined as the trisomy 18qter syndrome (Turleau and de Grouchy, 1977). As expected, their overall phenotypic spectrum is in some ways similar to that in the above 4 cases of chromosome rec(18) (Table 1).

Table 1 also presents the clinical pictures in full trisomy 18 syndrome, for comparison with those in the 4 rec(18) cases and in cases of trisomy 18qter syndrome. In general, the features of patients with distal 18q trisomy, whether derived from

Table 2. Full karyotypes of reported cases showing partial trisomy for the 18q21-qter region, which are cited in Table 1.

Karyotype	No. of cases	Authors
46,XX,—4,+der(4) t(4;18)(q35;q21)pat	2	Steele <i>et al.</i> , 1974
46,XX,—14,+der(14) t(14;18)(p13;q21.2)mat	1	Turleau & de Grouchy, 1977
46,XY,—21,+der(21) t(18;21)(q21;q22)mat	1	Niazi <i>et al.</i> , 1978
46,XX,—9,+der(9) t(9;18)(p24;q21)mat	1	Fryns <i>et al.</i> , 1979
46,XX,—6,+der(6) t(6;18)(p24 or p25;q21)pat	1	Fukuhara <i>et al.</i> , 1979
46,XY,—4,+der(4) t(4;18)(q35;q21.1)mat	1	Matsuoka <i>et al.</i> , 1981
46,XY,—9,+der(9) t(9;18)(p24;q21)mat	1	de Torres <i>et al.</i> , 1984
46,XY,—7,+der(7) rcp(7;18)(q36;q21)mat	1	Borovik <i>et al.</i> , 1987
46,XX,—9,+der(9) t(9;18)(p22;q21.3)mat	2	Tayel <i>et al.</i> , 1988

pericentric inversion or translocation, are clinically mild in comparison with those patients with full trisomy 18 syndrome. Several clinical signs, such as mental and growth retardation, auricular deformities and micrognathia, are seen commonly in both types of chromosome anomaly. However, some features characteristic of the full trisomy 18 are absent or very rare in cases of distal 18q trisomy. These include early death, microcephaly, congenital heart disease, urogenital malformation and abnormalities of the extremities.

The above findings imply that no critical region in the distal half of 18q is solely responsible for the typical phenotype of full trisomy 18 syndrome. Recently, in reviewing the phenotypes produced by various triplicated regions of chromosome 18, Wilson *et al.* (1990) suggested that no single specific region of chromosome 18 would be sufficient to produce the phenotype of complete trisomy syndrome, and that some "interaction" between different chromosome regions might be necessary for the full manifestation of complete trisomy 18. This complex situation seems to be analogous to the phenotypic expression of full trisomy 13 syndrome (Schinzel *et al.*, 1976), but in contrast to that of trisomy 21 (Down's) syndrome, which is due to trisomy of a well defined distal segment of 21q (Wahrman *et al.*, 1976; Korenberg *et al.*, 1990).

The general risk of producing recombinant offspring for carriers of pericentric inversion of chromosome 18 has been discussed in several articles (Vianna-Morgante *et al.*, 1976; Vigi *et al.*, 1977; Kukolich *et al.*, 1978; Teyssier and Bajolle, 1980; Andrews *et al.*, 1982). The probability of recombination would depend largely on the length of the inverted segment. In our present case, the length was about 60% of the total length of chromosome 18. Since the mean number of chiasmata for chromosome 18 has been estimated to be 1.92 (ISCN, 1985), the number of chiasmata within the inverted segment concerned would be about 1.2. If one or three chiasmata were to occur within this region, recombinants would result (Fig. 3). Thus, it is predicted that a carrier mother would be at high risk of producing chromosomally unbalanced progeny, and this may have been partly responsible for the reproductive failures of our patient's mother, which included two abortions and one stillbirth.

Based on all the pericentric inversions reported in the literature, ascertained through affected children, Sutherland *et al.* (1976) suggested that the risk figures for recombinant formation by inversion carriers are 5% for males and 10% for females. With regard to inversions of chromosome 18, the empirical risk has been estimated from the reported families to be 5–10% (Vigi *et al.*, 1977; Teyssier and Bajolle, 1980). Although the family data currently available are still limited, a more accurate estimate of the recombination risk is important in practice for genetic counselling, including prenatal diagnosis, in affected families.

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