Jpn. J. Human Genet. **30**, 57–67, 1985

REPRODUCTIVE RISK OF PARACENTRIC INVERSION CARRIERS: REPORT OF TWO UNRELATED CASES WITH PARACENTRIC INVERSION OF THE LONG ARM OF CHROMOSOME 3

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Summary Two unrelated cases with a paracentric inversion involving the long arm of a chromosome 3 were described. One case was a 29-year-old female with habitual spontaneous abortions. The karyotype was 46,XX,inv(3)(q25q27). The other case was a two year one month-old girl with growth and psychomotor retardation and multiple minor anomalies. She was found to have a recombinant chromosome 3 resulting from a paternal paracentric inversion. The karyotype of the patient was 46,XX, rec(3),dup(q26.3),inv(3)(q12q29)pat. The review of previously reported cases showed a considerable risk for live-born recombinants derived from parental paracentric inversions and the analysis of reproductive histories of inversion carriers suggested a possible contribution of this type of chromosome abnormalities to the cause of spontaneous abortions.

INTRODUCTION

A paracentric inversion has generally been considered to be an exceedingly rare structural abnormality in human chromosomes, because no description was made in the consecutive cytogenetic newborn studies (Hook and Hammerton, 1977). Improvement of resolution in chromosome banding analysis, however, has accelerated the discovery of cases with paracentric inversions. The reliable estimate of the incidence of paracentric inversion in human population has recently been provided by Van Dyke *et al.* (1983). According to their data, which were obtained from three series of advanced maternal-age prenatal cytogenetic studies, 4 out of

Received January 19, 1985

8,158 individuals (1 in 2,040) were found to carry a paracentric inversion. A similar figure has been reported by Hook *et al.* (1984), who detected 6 cases with paracentric inversions in 24,951 fetuses (1 in 4,159). The overall incidence from these studies is 1 in 3,311 (10/33,109). Thus, the occurrence of paracentric inversions in humans is by far more frequent than was previously suspected.

On the other hand, Fryns and Van den Berghe (1980) found 7 cases with paracentric inversions in 14,500 patients (1 in 2,071) in whom chromosome analyses were carried out for diagnosis of abnormal phenotypes or genetic counseling. Surprisingly, the figure is similar to that of the prenatal studies, and the question of whether paracentric inversions are really related to abnormal phenotypes remains open.

In this paper, two unrelated cases with a paracentric inversion of the long arm of a chromosome 3 were presented. One case had multiple spontaneous abortions, while the other case with growth and psychomotor retardation and multiple minor anomalies was found to have a recombinant chromosome. Previously reported cases are reviewed with special respect to the reproductive risk of inversion carriers for liveborn recombinants and spontaneous abortions.

CASE REPORT

Case 1

The patient, a 29-year-old female of normal intelligence, and her husband were referred to us for chromosome analysis after three spontaneous abortions. There was no family history for miscarriages or congenital malformations. The patient had menarche at 13 years of age with subsequent regular menstruations. They were married when she was 24 years old. The first pregnancy resulted in mid-trimester abortion (at 5 month's gestation), and a fetus weighing 700 g was apparently normal. The second and third spontaneous abortions occurred at 2 months' and 5 months' gestation, respectively. She was 154 cm tall, weighing 50.5 kg. No overt malformations were present. However, hysterosalpingography revealed a bicornuate uterus (Fig. 1).

Case 2

The patient, a 2 year one month-old girl, was born to a healthy 26-year-old mother and an unrelated 31-year-old father. The parents and her three siblings had normal phenotypes. There was no family history for miscarriages, congenital anomalies, or mental retardation. The pregnancy was complicated by anemia in the early trimester and hyperemesis throughout the pregnancy. The delivery occurred at term in the vertex position with no asphyxia. At the patient's birth, the body weight was 2,550 g, and the length 45.0 cm. At age of two years one month, she was admitted to Department of Pediatrics, Kawasaki Medical School Hospital for evaluation of growth and psychomotor retardation.

Physical examination of the patient at admission showed that the body weight

was 6,950 g (less than third percentile), the height 73.6 cm (less than third percentile), and the head circumference 43.5 cm (less than third percentile). The child had peculiar craniofacial features (Fig. 2), including thin hair, frontal bossing, prominent nasal bridge, low-set and posteriorly rotated ears with prominent antihelices, small mouth, thin upper lip, and micrognathia with pointed chin. Anterior fontanel was still open (1.5 cm × 1.5 cm). Examinations of chest and abdomen were normal. There were no heart murmurs. Toes were short, with a cutaneous syndactyly between the second and third toes. Simian creases were present on the bilateral palms. She spoke only a few words, and developmental quotient was 80. Laboratory investigations including complete blood count, urinalysis, and blood chemistry gave normal results except for iron deficiency anemia. Bone age was appropriate for chronological age, and endocrinological studies were also normal. Intravenous

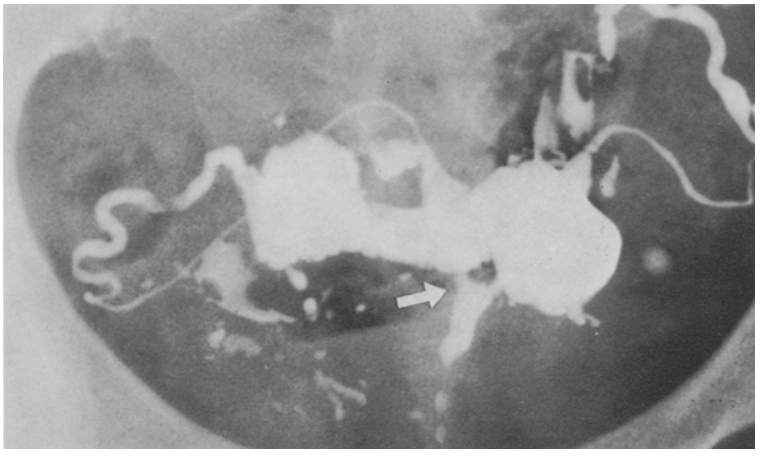

Fig. 1. Case 1. Hysterosalpingogram. An arrow indicates a bicornuate uterus.

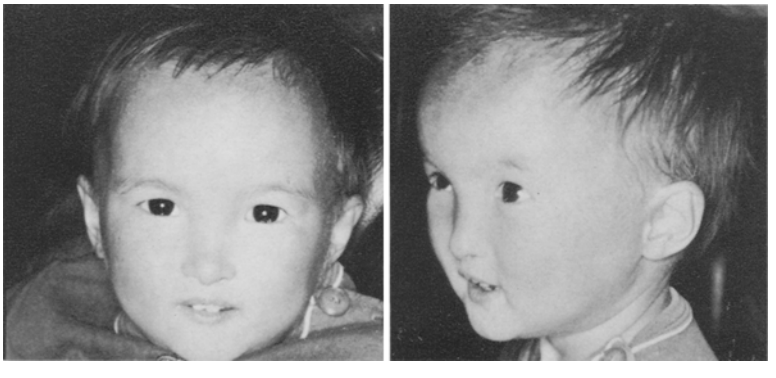

Fig. 2. Case 2. Frontal and lateral views.

pyelography and computed tomography of the head showed no abnormalities.

Her subsequent growth and speech development was slow. At age of 4 years 5 months, she died suddenly from acute myocarditis. Autopsy was not granted.

CYTOGENETIC FINDINGS

Peripheral blood lymphocytes were cultured with the conventional method. Chromosome analyses were carried out by use of GTG banding techniques.

The karyotype of case 1 showed a paracentric inversion involving the distal portion of the long arm of a chromosome 3, with the breakpoints apparently at q25 and q27 (Fig. 3). The karyotype was designated as 46,XX,inv(3)(q25q27). Chromosome analysis of her family members was unavailable.

The karyotype of metaphase cells from case 2 revealed a paracentric inversion involving the nearly whole part of the long arm of a chromosome 3. Chromosome analysis of the parents showed that the father was found to have an apparently same paracentric inversion as the case, with breakpoints at q12 and q29. Cytogenetic studies of prometaphase cells, however, demonstrated an additional small dark band on the inverted chromosome 3 of the child, which was not present on that of the father (Fig. 4). On the basis of the banding patterns, the additional band of the

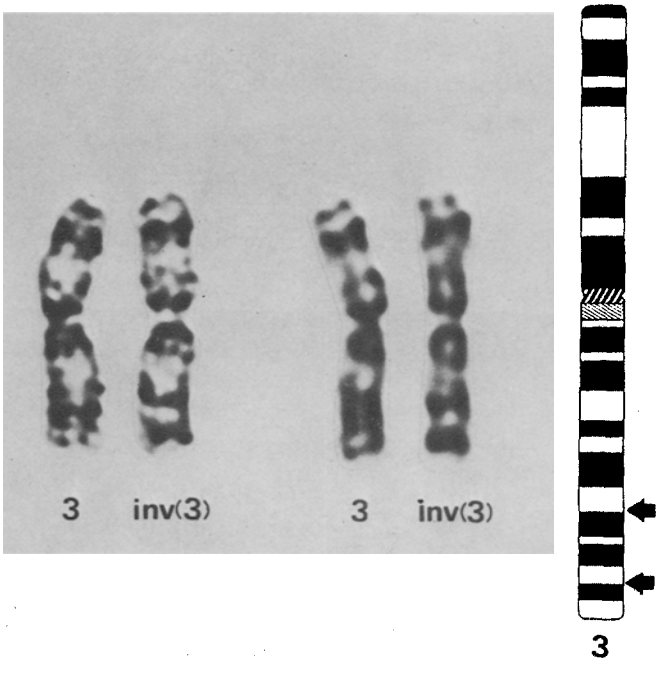

Fig. 3. Partial G-banded karyotypes of case 1. Arrows indicate breakpoints.

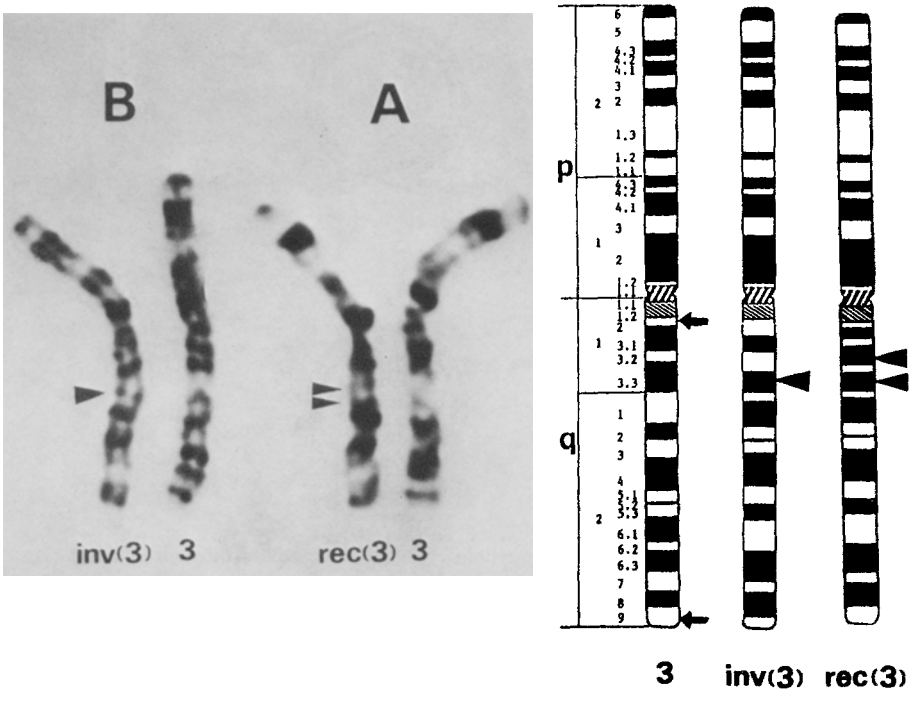

Fig. 4. Partial G-banded karyotypes of prometaphase cells from case 2 (A) and the father (B), corresponding to the level of 550 bands in a haploid set (ISCN, 1981). Arrows indicate breakpoints, and arrowheads a 3q26.3 segment, which was duplicated on the inverted chromosome 3 (rec 3) in case 2.

patient's chromosome 3 appeared to be 3q26.3. The duplication was assumed to result from an unusual recombination between the inverted chromosome 3 and normal homologue in meiosis of the father (Fig. 5). The chromosome formula of case 2 was designated as 46,XX,rec(3),dup(q26.3),inv(3)(q12q29)pat. The mother and three siblings had normal chromosomes.

DISCUSSION

Since the first description of a case with a paracentric inversion of the long arm of a chromosome 16 by Del Solar and Uchida (1974), 29 cases with paracentric inversions including ours have been published in the literature (Table 1). The inversions involved certain chromosomes more frequently: chromosome 3 in 8 instances (cases 3, 7, 11, 12, 19, 25, 28, and 29) and chromosome 7 in 6 (cases 2, 5, 15, 18, 20, and 24). It is interesting that the breakpoints on those chromosomes converge to the specific chromosome sites (3p13 and 3p25 in 4 cases, and 7q11 and 7q22 in 4 cases). Ascertainments of paracentric inversions among the reported cases

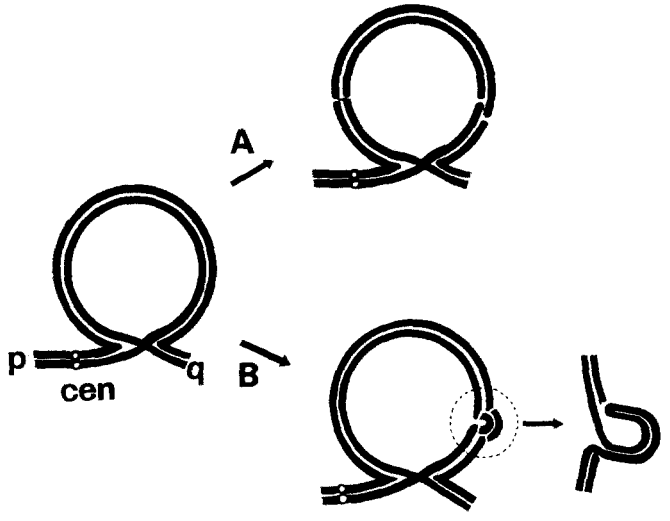

Fig. 5. Schematic representation of possible cytogenetic processes through which a tiny interstitial duplication in case 2 was produced in the meiotic inversion loop of the father. A: an even number of crossing-over with unequal one involving the duplicated segment, B: U-type exchange within the inversion loop.

were made through a progeny with a recombinant chromosome in 5 cases (cases 9, 18, 23, 27, and 29), some phenotypic abnormalities in 12 cases (cases 1, 3, 4, 5, 6, 7, 8, 10, 11, 17, 19, and 22), multiple spontaneous abortions in 4 cases (cases 14, 24, 25, and 28), or miscellaneous conditions in 8 cases (cases 2, 12, 13, 15, 16, 20, 21, and 26). The majority of the cases with inversions (23/29) are familial, and the remaining cases are *de novo* (2 cases) or undetermined (4 cases). Most of the index patients of the familial cases are associated with various congenital malformations or mental retardation, or both, although the same inversions are found in normal relatives. In six cases, an additional chromosome aberration is present (47,XXY in cases 4 and 17, 45,X in case 5, and partial trisomy 10q in case 3), or another obvious cause for the phenotypic abnormality is evident (the mother's use of many antiepileptic drugs during the pregnancy in case 19, and the close parental consanguinity in case 22). The association may be coincidental also in the three familial cases (cases 1, 6, and 7) as well as two *de novo* cases (cases 8 and 10) with phenotypic abnormalities. However, there is a possibility that altered phenotypes are caused by paracentric inversions through mechanisms analogous to those speculated in familial or *de novo* translocation cases with phenotypic abnormalities (Jacobs, 1974; Bühler, 1983).

Individuals carrying chromosome inversions are predisposed to have unbalanced gametes through 'aneusomic recombination.' An odd number of crossing-over within a pericentric inversion loop produces duplication-deficiency gametes,

while that within a paracentric inversion loop yields dicentric and acentric products which are unstable and probably nonviable. Nonetheless, 4 cases have been reported to have recombinant chromosomes derived from parental paracentric inversions: a dicentric recombinant (case 27), a disruption of recombinants resulting in different rearrangements (inverted duplication or terminal deletion) in different offspring (case 23), an interstitial deletion (case 9), and an interstitial duplication (case 18). As suggested by Mules and Stamberg (1984), the rearrangments seen in the latter two cases can be explained by unequal crossing-over due to the difficulty in pairing at the base of the inversion loop. Our case (case 29) is unique in that an interstitial duplication has occurred inside an inversion loop. Such a rearrangement requires not only unequal crossing-over at the base of the inversion loop but also an odd number of crossing-over within the inversion loop. In contrast to the previous cases with a recombinant chromosome, the nearly whole part of the chromosome arm was inverted in our case so that more than one crossing-overs were likely to take place within the inversion loop. The fact that the father was the inversion carrier also indicated a potential risk for a liveborn recombinant even to a male carrier. It should be noted that the two cases (cases 18 and 29) possessed a tiny interstitial duplication, which was difficult to detect by the conventional banding technique alone. This implies that a subtle 'aneusomic recombination' may be a possible cause for the altered phenotype in a case where an apparently same paracentric inversion as in a parent is present. In such cases, diligent chromosome examinations by using high-resolution banding methods are warranted.

It is expected that unstable dicentric or acentric recombinants derived from crossing-over in the meiotic paracentric inversion loop reduce gametic or embryonic viability. Four cases have been ascertained through multiple spontaneous abortions. In this context, the question of whether paracentric inversions are really associated with spontaneous abortions may arise. To test the hypothesis, we investigated the reproductive histories of inversion carriers and the ratio of paracentric inversions in systematic surveys of couples with recurrent spontaneous abortions. In the first place, the combined data in Table 1 showed that 45 inversion carriers were found to have a total of 144 recorded pregnancies, resulting in 30 spontaneous abortions (20.8%), 46 liveborn individuals with the same inversion as the parents (32.0%), 7 liveborn individuals with recombinant chromosomes (4.9%), 28 karyotypically normal individuals (19.4%), and 33 individuals with undetermined karyotypes (22.9%). The incidence of spontaneous abortions in inversion carriers is significantly higher than that in the general population (15%, Poland *et al.*, 1977) ($df=1$, $\chi^2=3.84$, $p<0.05$). However, the result is controversial, since the comparison neglected the racial differences in the ratio of spontaneous abortions. Second, if paracentric inversions are related causally to spontaneous abortions as pericentric inversions, the ratio of paracentric inversions to pericentric inversions in repeated aborters would be similar to that in the general population. The ratio from the recently reported systematic surveys of couples with recurrent spontaneous

Table 1. Reported cases

Case No.	Reference	Sex	Karyotype
1	Del Solar and Uchida (1974)	M	inv(16)(q11q22)mat
2	Shimba *et al.* (1976)	M	inv(7)(q22q31)
3	Bass *et al.* (1978)	F	inv(3)(q13q26)pat
4	Canki and Dutrillaux (1979)	M	inv(5)(q21q32)mat
5	*Ibid.*	F	inv(7)(q11.3q22.3)pat
6	De Roover *et al.* (1979)	F	inv(1)(p22p36)pat
7	Fryns and Van den Berghe (1979)	M	inv(3)(p13p25)mat
8	Riccardi and Holmquist (1979)	F	inv(13)(q12q22)
9	Sparkes *et al.* (1979)	F	rec(13), del(q14q22), inv(13)(q12q22)mat
10	Jaeken *et al.* (1980)	M	inv(14)(q13q24)
11	Fryns and Van den Berghe (1980)	M	inv(3)(p13p25)mat
12	*Ibid.*	M	inv(3)(p13p25)pat
13	*Ibid.*	M	inv(5)(q13q34)
14	*Ibid.*	F	inv(12)(q12q24)mosaic
15	Ridler and Sutton (1981)	F	inv(7)(q11q22)pat
16	Poulsen *et al.* (1981)	M	inv(12)(p12.3p13.1)pat
17	Singh (1981)	M	inv(13)(q15q24)mat
18	Hoo *et al.* (1982)	F	rec(7), dup(q11.22), inv(7)(q11q22)mat
19	Peters-Slough *et al.* (1982)	F	inv(3)(p13p25)mat
20	Orye and Van Bever (1983)	F	inv(7)(q11q22)pat
21	*Ibid.*	M	inv(11)(q13q23)mat
22	Romain *et al.* (1983)	M	inv(1)(p31.2p36.22)mat
23	Valcárcel *et al.* (1983)	F	rec(5), del(pterp14), inv(5)(pterp13)mat
24	Stetten and Rock (1983)	F	inv(7)(p15p22)mat
25	Djalali *et al.* (1984)	F	inv(3)(q21q25.1)pat
26	Venter *et al.* (1984)	F	inv(10)(q11q26)mat
27	Mules and Stamberg (1984)	M	rec(14), inv dup(q24.2→pter), inv(14)(q24.2q32.3)mat
28	Present case 1	F	inv(3)(q25q27)
29	Present case 2	F	rec(3), dup(q26.3), inv(3)(q12q29)pat

[a] In addition, there have been 26 unpublished cases with paracentric inversions (Yu *et al.*, 1976; Riccardi and Holmquist, 1979; Turleau *et al.*, 1979; Ridler and Sutton, 1981; Van Dyke *et al.*, 1983; Diedrich *et al.*, 1983; Hook *et al.*, 1984), and chromosomes involved are Nos. 3 (two cases), 4 (one case), 5 (three cases), 6 (six cases), 7 (three cases), 8 (three cases), 11 (three cases), 13 (one case), 14

with paracentric inversions.[a]

Phenotype	No. of pregnancy [b]	No. of spontaneous abortion [b]	Comments
Hypotonic newborn	5	0	
Normal	2	0	Systematic chromosome study
10q trisomy syndrome	6	0	
Klinefelter syndrome	2	0	
Turner syndrome	5	3	
Extreme mental retardation and multiple congenital anomalies	3	0	
Slight psychomotor retardation	8	0	
Mild mental retardation and multiple minor anomalies	—	—	*de novo*
13q− syndrome, retinoblastoma	1	0	
Extreme mental retardation and multiple congenital anomalies	—	—	*de novo*
Slight psychomotor retardation	1	0	
Normal	1	0	Prenatally detected
Normal	2	0	Father of a 21 trisomy girl
Normal	3	2	Multiple spontaneous abortions
Normal	7	3	Prenatally detected
Normal	3	0	
Klinefelter syndrome	—	—	
Multiple malformations	1	0	
Growth retardation	5	3	Three previous miscarriages
Normal	1	0	Acute leukemia
Normal	2	0	Hypoparathroidism
Mild mental retardation	22	3	
Cri-du-chat syndrome	13	4	Two sibs: 5p duplication
Normal	9	6	Multiple spontaneous abortions
Normal	4	2	Prenatally detected, two previous miscarriages
Normal	30	1	Prenatal test for advanced maternal age
Multiple congenital anomalies	1	0	
Normal	3	3	Multiple spontaneous abortion
Psychomotor retardation and multiple minor anomalies	4	0	

(two cases), 16 (one case), and X (one case). Most of these cases were prenatally diagnosed.
[b] Numbers of a total pregnancy and spontaneous abortion in available family member(s) with the same inversion as in the index case.

abortions (Turleau *et al.*, 1979; Antich *et al.*, 1980; Ward *et al.*, 1980; Simpson *et al.*, 1981; Husslein *et al.*, 1982; Michels *et al.*, 1982; Osztovics *et al.*, 1982; Diedrich *et al.*, 1983; FitzSimmons *et al.*, 1983; Fryns *et al.*, 1984) is 4 : 14, a figure similar to the ratio of 10 : 26 ascertained in the prenatal diagnosis (Van Dyke *et al.*, 1983; Hook *et al.*, 1984). These arguments lead us to suppose that paracentric inversions are associated with spontaneous abortions at least in some inversion carriers. In fact, the interpretation in our case (case 28) and case 24 is complicated by the presence of the uterine malformation. To confirm the causal relationship between paracentric inversions and spontaneous abortions, further case studies including complete gynecological evaluations are required.

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