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A Dicentric Recombinant 9 Derived from a Paracentric Inversion: Phenotype, Cytogenetics, and Molecular Analysis of Centromeres

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Summary

A 4-year-old girl with multiple malformations and severe developmental delay has been shown to have a karyotype of 46,XX,−9,+rec(9),dup p,inv(9) (q22.1q34.3)mat, with duplication 9pter-q22.1 and deficiency 9q34.3-qter. This case confirms that a stable recombinant chromosome can result from a paracentric inversion. The recombinant was derived by two crossovers, one within the inversion loop and a second outside the inversion loop, between 9q21 and the beginning of the mieotic inversion at 9q22.1. In 87 cells the rec(9) had one Cd-positive primary constriction. In 13 cells the rec(9) had two primary constrictions; in 12 of these cells there was one Cd-positive centromere, and in one of these cells both primary constrictions were Cd-positive. Nuclear projections were observed in 10% of fibroblast interphase cells harvested in situ, suggesting that there was some spindle-fiber activity of the "latent" centromere. In situ hybridization with a centromere-specific probe (p82H) and a satellite III probe (L6) revealed no differences between the two C-band regions of the rec(9) and the normal 9 or inverted 9 chromosomes.

Introduction

G-banded chromosome studies have shown that paracentric inversions are present in 1/2,000–1/3,500 persons (Fryns and Van den Berghe 1980; Van Dyke et al. 1983; Hook et al. 1984). Here we describe a dysmorphic individual with a stable dicentric recombinant chromosome inherited from her paracentric inversion–carrier mother.

Case Report

The patient (R87-30) was born in 1983 to a 32-year-old, $G_4P_2Ab_2$ Caucasian mother and a 35-year-old Caucasian father. Pregnancy had been complicated only by questionable oligohydramnios. There was no exposure to known teratogens. The infant was delivered vaginally at 42 wk gestation. Her birth weight was 2,730 g, her length was 51 cm, and her APGAR scores were 4 and 5 at 1 and 5 min. Multiple malformations (fig. 1) included slightly enlarged fontanelles, low-set and posteriorly rotated ears, anisocoria (left pupil larger than right), incomplete coloboma of the left iris, significant myopia, variable estropia, micrognathia, thin lower lip, high-arched palate, umbilical hernia, and hypoplastic fingernails.

She was hospitalized for congestive heart failure at 5 and 9 mo of age. Cardiac catheterization at 11 mo revealed a patent foramen ovale, patent ductus arteriosus, atrial septal defect with left-to-right shunt, mild-moderate pulmonary artery hypertension, and anomalous origin of the right subclavian artery. There was mildly decreased cardiac contractility, probably secondary to cor pulmonale. She responded to treatment with digoxin and spironolactone. The digoxin was discontinued at 18 mo of age, without further deterioration of cardiac function.

Chest roentgenograms at 1 day of age revealed a transient right pneumothorax, with normal-appearing lung parenchyma. Subequent X-rays revealed patches of at-

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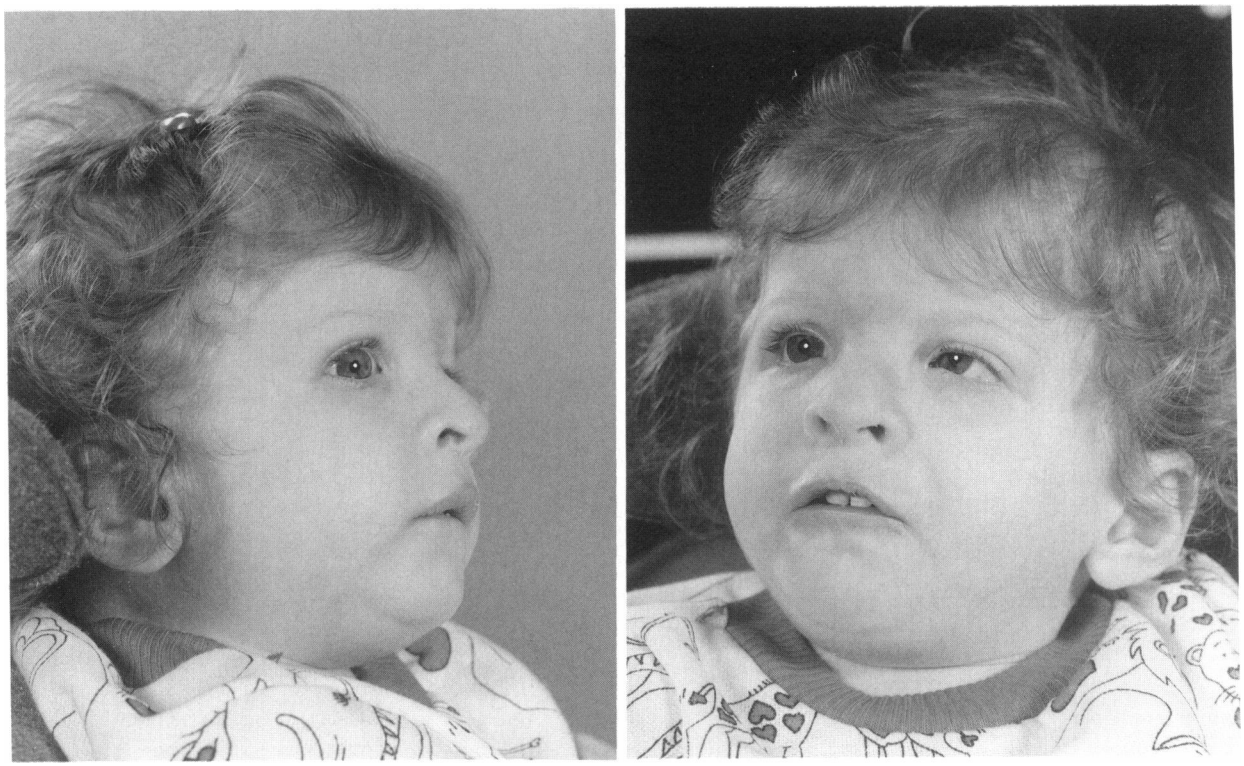

Figure 1 Proband at 3 years

electasis and chronic scarring in all lung fields. Scattered inspiratory rales were most prominent at the bases.

Alkalosis was first noted at age 16 mo. Blood gases revealed pH 7.45, P_{CO_2} 53 mmHg, and bicarbonate 35 mEq/L, representing a partially compensated metabolic alkalosis. She has been successfully treated with acetazolamide.

Cytoscopy revealed an absent tigone region of the bladder. Computerized tomography demonstrated that the left kidney was of normal size but had areas of cortical thinning that may have been secondary to pylonephritis. There is a virtual absence of the left renal pelvis, with multiple dilated calyces draining directly into the ureter. The left kidney contains multiple radio-opaque intraparenchymal calculi. The right kidney is very atrophic and contains a single radio-opaque calculus.

Neuromuscular development has been severely delayed. At age 25 mo, her fine motor skills were at the 3–4-mo level. All extremities were mildly hypertonic, and deep tendon reflexes were slightly brisk. Computerized tomography revealed dysgenesis of the corpus callosum.

In the neonatal period she was found to have hyperextensibile joints and bilateral hip dislocations. She has subsequently been found to have femoral coxa valga, subluxation of the left knee, dislocation of the right radial head, and mild generalized osteopenia.

She had persistent difficulty in swallowing, with occasional aspiration of liquids that is probably due to mild glossopharyngeal incoordination. Contrast studies have demonstrated normal esophageal motility with severe gastroesophageal reflux. She underwent Nissen-Hill fundoplication and gastrostomy tube placement at 4 mo of age, without subsequent regurgitation.

Her birth weight was in the tenth percentile, and her length was between the 50th and 75th percentiles. She has steadily scored below the fifth percentile for weight, length, and head circumference, despite a diet providing 120 cal/kg/day. Thyroid studies and somatomedin-C have been within normal limits.

Cytogenetic Studies

Peripheral blood lymphocytes and skin fibroblasts were cultured according to conventional methods. The metaphases were Giemsa stained, G-banded by the tryp-

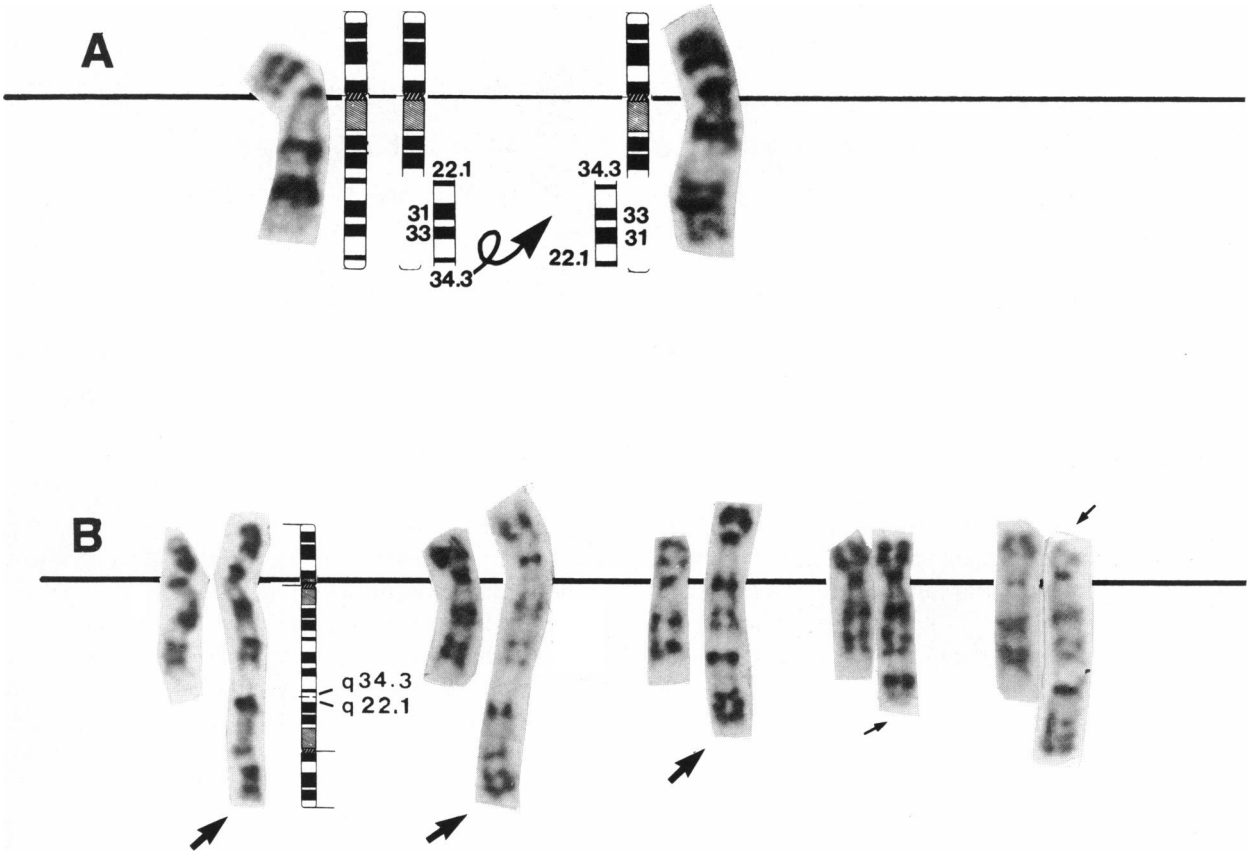

Figure 2 Chromosome 9 pairs from the mother (*A*) and the proband (*B*). *A*, The mother had one structurally normal chromosome 9 (*left*) and one chromosome 9 with a paracentric inversion (*right*): inv(9)(q22.1q34.3). The idiogram (ISCN 1981) depicts the regions involved in the paracentric inversion. *B*, Three normal (*left*) and recombinant (*right*) pairs of chromosome 9 from the proband's peripheral lymphocytes are shown at left (large arrow indicates recombinant 9). The two pairs of 9's shown at the extreme right were observed in fibroblast metaphase cells; the recombinant 9 in these pairs appeared to be dicentric with GTG- or C-banding, but part of one of the 9pter-9p11 segments was deleted (small arrow).

sin technique (GTG), C-banded, or centromere dot (Cd) stained (Maraschio et al. 1980). The father's karyotype is normal. The mother, grandmother, and three maternal aunts carry a paracentric inversion (figs. 2, 3): 46,XX,inv(9)(q22.1q34.3). The proband's mother had two miscarriages, and the proband's maternal grandmother reportedly had nine miscarriages. The karyotype of the proband is 46,XX,rec(9)dup p,inv(9)(q22.1q34.3). The structure of the recombinant chromosome is 9pter-9q34.3::9q22.1-9pter. The recombinant chromosome is dicentric with duplication 9pter-q22.1 and deficiency 9q34.3-qter. Of 50 fibroblast metaphase cells (Camden Repository GM9064) from the proband, 37 had the intact recombinant 9, but in 13 cells the recombinant 9 had varying amounts of 9p deleted (fig. 2*B*). In more than 300 lymphocyte metaphase cells, only the intact recombinant chromosome 9 was observed.

In the mother's structurally normal chromosome 9, the entire block of C-band-positive material was confirmed to the proximal q arm, whereas her chromosome 9 with the paracentric inversion contained C-band-positive material on both sides of the centromere (fig. 4*A*). In the recombinant 9, the centromere with a C-band block on both sides always had a primary constriction and hence was the active centromere (fig. 4*B*). Both centromeres of the recombinant 9 had a primary constriction in 18% of the Giemsa-stained lymphocyte metaphases. The rec(9) had one primary constriction with one pair of Cd's in 87 of 100 Cd-stained metaphases (fig. 4*C*). In the remaining 13 metaphases the rec(9) appeared to have two primary constrictions,

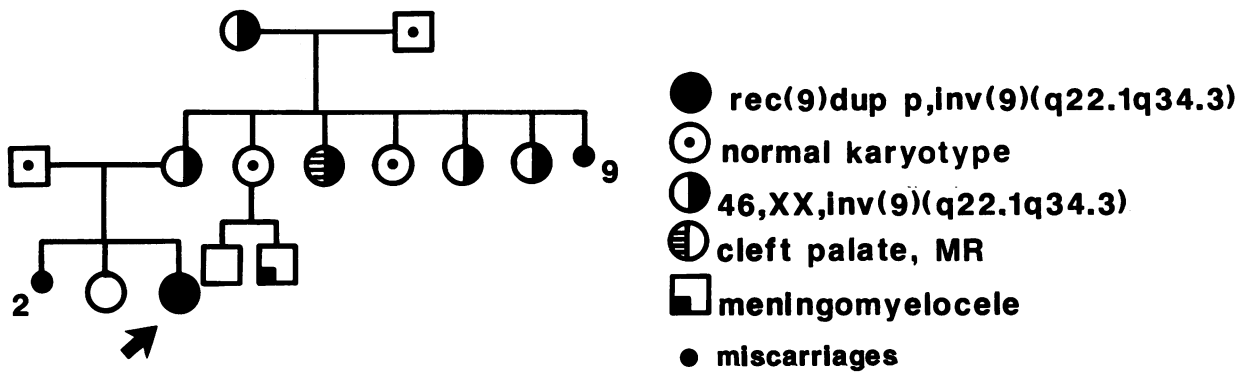

Figure 3 Pedigree of the paracentric-inversion family, showing that the maternal grandmother, mother, and three maternal aunts of the proband are inversion carriers.

but in only one of these 13 cells was there a pair of Cd's at both primary constrictions. Thus, both centromeres had the potential to form a Cd-positive primary constriction.

The centromere with the C-band block restricted to the long arm was present in the mother's normal 9q, and the variant centromere region, with C-band blocks in both arms, was present in the mother's paracentric inversion 9. However, in the proband's recombinant chromosome this orientation was unexpectedly reversed: the "normal" 9qh was adjacent to the inverted 9 segment, whereas the variant heterochromatic block was adjacent to the noninverted long-arm segment. Thus, there must have been two meiotic crossover events. One crossover within the inversion loop created the dicentric recombinant chromosome. The second crossover, outside the inversion loop, between bands 9q21 and the beginning of the meiotic inversion loop at 9q22.1, resulted in the exchange of centromere regions (fig. 5).

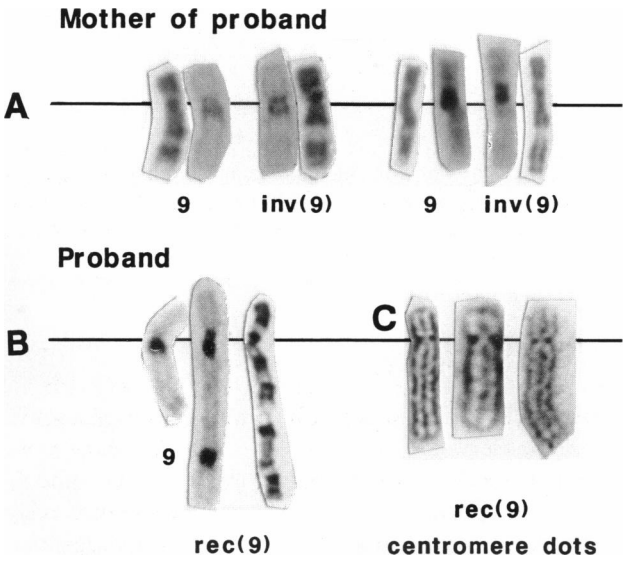

Figure 4 *A*, Two pairs of sequential G- to C-banded chromosomes 9 from the mother. The normal chromosome 9 (at the left of each set) has a heterochromatic region in proximal 9q. The inverted 9 (at right) has a small heterochromatic block in each arm. *B*, In the patient the recombinant had one primary constriction in most cells. A C-banded chromosome 9 pair from the proband (*left*) stained to show the heterochromatic blocks. The primary constriction in the C-banded recombinant 9 had a small heterochromatic block on each side of the centromere, and the other centromere had a larger C-band region in the q arm. *C*, Rec(9) chromosomes from three metaphase cells, stained by the centromere-dot technique, show one pair of centromere dots at the primary constriction but not in the region of the suppressed centromere.

Fibroblast cells from the proband and a normal female control were grown in individual tissue culture chamber slides (Lab Tek, Miles, IN) for 2–3 days and were stained in situ with 5% Giemsa. Nuclear projections or blebs were observed in 10% of 500 cells from the proband (fig. 6), and no anaphase bridge configurations were observed. Nuclear projections were not observed in the control.

Molecular Studies

For in situ hybridization studies, metaphase chromosomes were prepared as usual from leukocyte cultures, except that 3.7 or 7.4 $\times$ 10^{-7} M 5-azacytidine was added for the final 7 h of culture to inhibit condensation of the heterochromatic region on chromosome 9 (Schmid et al. 1983). Slides were stained with quinacrine mustard, and metaphases with an elongated number 9, inv(9), or rec(9) chromosome were photographed. The slides were treated with boiled RNase (100 mg/ml

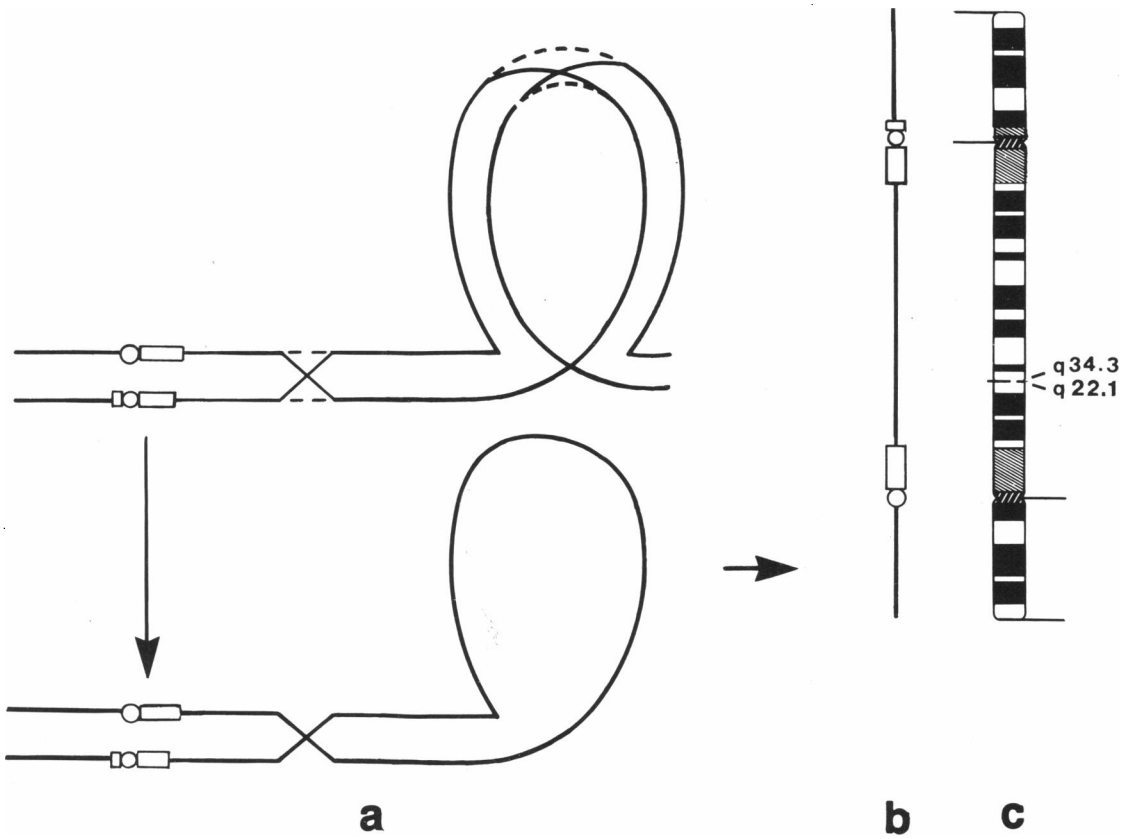

Figure 5 Paracentric-inversion loop in the mother (*a*), depicted as having two points of recombination. The exchange within the inversion loop resulted in formation of a dicentric recombinant (*b*, line diagram; *c*, idiogram). The crossover depicted in the long arm adjacent to the C-band-positive region resulted in exchange of the C-band in 9q, which was present in the normal 9, but the double C-band variant, which was present in the paracentric inversion 9, as described in the text. Crossing-over occurs at the four-strand stage (meiosis I prophase), but, for the sake of simplicity, only the two strands involved in the actual crossover events are drawn here.

in 2 × SSC) for 1 h at 37 C, rinsed with 2 × SSC, and passed through an alcohol series. Chromosomes were denatured by heating the slides in 70% formamide–2 × SSC for 2 min at 70 C. The slides were plunged into cold 70% EtOH, passed through an alcohol series, and air-dried.

Probe p82H detects sequences present at every human centromere (Mitchell et al. 1985), and probe L6 detects adjacent sequences in the heterochromatic region of number 9 (Mitchell et al. 1986). Each probe was nick-translated (Rigby et al. 1977) using four 3H-dNTPs: probe p82H, specific activity 2.4 × 10^7 cpm/μg; probe L6, specific activity 3.9 × 10^7 cpm/μg. Each labeled probe was dissolved in 300 μl 50% formamide–2 × SSC–10% dextran sulfate and denatured for 10 min at 70 C; 25 μl was placed on each slide under a 24 × 50-mm coverslip, and hybridization was carried out for 16 h at 37 C (Harper and Saunders 1981). Slides were rinsed repeatedly in 50% formamide–2 × SSC and 2 × SSC at 39 C or 68 C. The slides were coated with Ilford K2 emulsion and exposed at 4 C for 7–28 days, developed in D19, and stained with Giemsa. The previously photographed cells were relocated, and the number and location of the grains were scored on photographic prints.

Probe p82H hybridized to the centromeric region of every chromosome, including number 9. It also hybridized to the distal end of the heterochromatic region on 9q, although grains sometimes overlay the entire heterochromatin region. This was true for the number 9's in both mother and child, for the inv(9) in the mother, and for the rec(9) in the proband (fig. 7). In 10 cells scored from the mother, the distribution of grains was the same over the 9 and inv(9) chromosome. In most

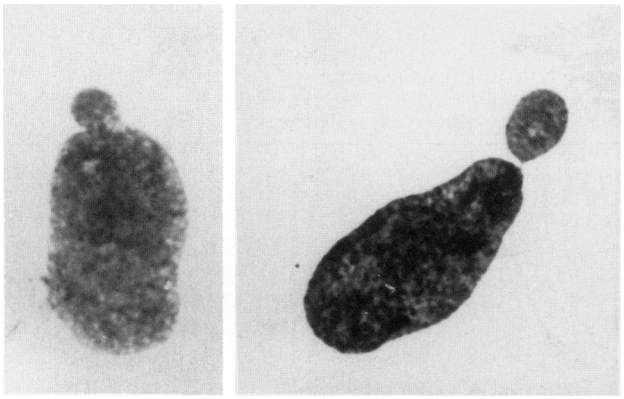

Figure 6 Nuclear projections in fibroblast cells of the proband, appearing as distinct blebs along the intact nuclear outline.

of the 52 cells scored from the proband, p82H hybridized to both centromeric regions of the rec(9). In 12 of the 52 cells grains were present at only one of the centromeres: eight in the region of the presumed active centromere and four in the region of the presumed suppressed centromere. Probe L6 hybridized to the heterochromatic region of 9 (fig. 7), as well as to the short arms of the acrocentric chromosomes. Grains were observed over the entire heterochromatic region in each of the three types of number 9.

Discussion

The proband's dicentric recombinant chromosome 9, with deficiency 9q34.3-qter and duplication 9pter-9q22.1, resulted from a crossing-over event within the paracentric-inversion loop in maternal meiosis (fig. 4). Our case is apparently only the second in which the classical dicentric product of crossing-over was actually recovered in a live-born progeny (Swanson et al. 1981, pp. 375–380). Mules and Stamberg (1984) described an infant who survived <1 day, who had a dicentric recombinant 14 which was derived by crossing-over within the maternal meiotic paracentric-inversion loop. Both the rec(14) and the rec(9) were relatively stable in both lymphocyte and fibroblasts cells. The five other reported recombinants from paracentric inversions (table 1) were monocentric-duplication or -deletion chromosomes that may have been formed by unequal crossover at the base of the inversion loop, by breakage and U-type reunion within the loop, by deletion of the inverted segment, or by formation of a classical dicentric recombinant with further rearrangement to stabilize it (Sparkes et al. 1979; Hoo et al., 1982; Valcarel et al. 1983; Kasai et al. 1985).

In the present case, a second crossover occurred outside the inversion loop, between 9q21 and the beginning of the meiotic inversion loop at 9q22.1. It would have been invisible cytogenetically but was detectable because the mother had a structurally normal number 9 with a common C-band pattern, in addition to the number 9 with the paracentric inversion and a C-band variant.

Schinzel (1983) has documented 12 patients with duplication of 9pter-9q2. The phenotype of our patient did not differ substantially from that of patients

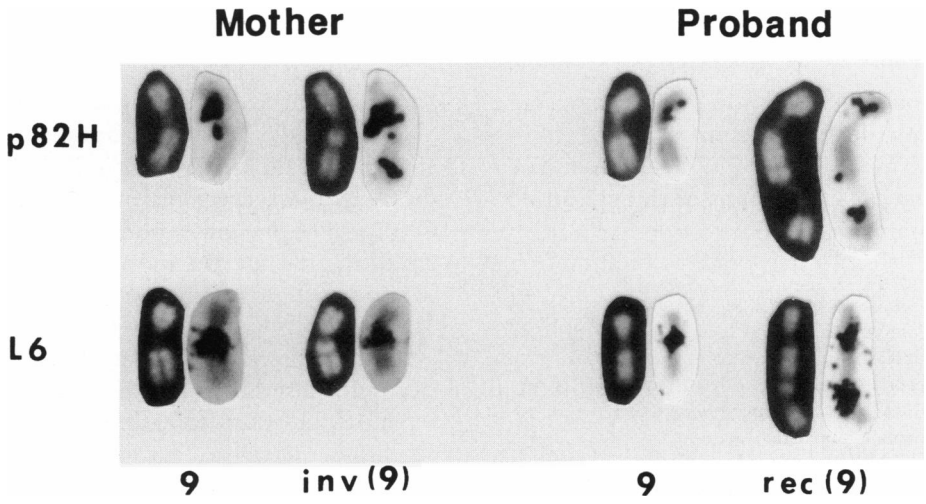

Figure 7 Partial karyotypes from the mother (9 and inv(9); *left*) and the proband (9 and rec(9); *right*). The chromosomes were identified by Q-banding, then hybridized in situ to either tritium-labeled p82H (which hybridizes to the centromere of 9) or L6 (which hybridizes to the heterochromatic region of 9).

Table 1

Dicentric and Monocentric Recombinants Derived from Paracentric Inversions

Recombinant	Reference
Dicentric:	
46,XY,rec(14),dup p,inv(14)(q24.2q32.3)mat	Mules and Stamberg 1984
46,XX,rec(9),dup p,inv(9)(q22.1q34.3)mat	Present study
Monocentric:	
46,XX,rec(13),del(q14q22),inv(13)(q12q22)mat	Sparkes et al. 1979
46,XX,rec(7),dup(q11.22),inv(7)(q11q22)mat	Hoo et al. 1982
46,XX,rec(5),dup(5)(p13),inv(5)(pter-p13)mat	Valcarcel et al. 1983
46,XX,rec(5),dup(5)(p13),inv(5)(pter-p13)mat	Valcarcel et al. 1983
46,XX,rec(3),dup(q26.3),inv(3)(q12q29)pat	Kasai et al. 1985
46,XX,rec(8),dup(p12.2p23.3),inv(8)(p12.2p23.3)mat	Our unreported case B87-171

with duplication of 9pter-9q2, nor from that of patients with duplication of only the short arm of chromosome 9. There are also clinical similarities between the present case and trisomy 9 (table 2).

Groupe de Cytogénéticiens Français (1986) reported normal reproductive fitness for paracentric-inversion carriers, without decreased male-carrier fertility. Although this may be true in general, it is apparently not the case for the inversion carriers in the present family, since 11 of 19 pregnancies ended in miscarriage (9/15 in the grandmother and 2/4 in the mother). Furthermore, the eight known cases of a recombinant chromosome (table 1) demonstrate that there is some risk to a paracentric-inversion carrier for bearing progeny who have an unbalanced recombinant. This risk probably varies depending on the sex of the carrier and on the specific inversion in question.

The dicentric constitution of the recombinant was maintained in lymphocytes as well as in fibroblasts. Anaphase bridges, acentric fragments, or monocentric variants of the recombinant were not found. Nuclear projections are often present in cells that have a dicentric chromosome with one active and one "latent" centromere (Fraccaro et al. 1978). The finding of nuclear projections in the present case, as well as the presence of only one primary constriction in the majority of cells, suggests that the centromere not exhibiting a primary constriction is "suppressed" or "latent." Likewise, in most cells the rec(9) had only one primary constriction at the "variant" C-band and had one pair of Cd's. Simi-

Table 2

Clinical Abnormalities Present in Proband That Are Associated with Both Duplication 9p and Mosaic Trisomy 9

Clinical Findings	Proband	Dup(9)p	Trisomy 9 and Mosaic Trisomy 9
Small head	+	+	+
Myopia	+	+	
Coloboma of the iris	+	+	
Micrognathia	+		+
Epicanthus	+	+	
Broad-based nose	+	+	
Ears low set and posteriorly rotated	+		+
Nails hypoplastic	+	+	+
Cutaneous syndactyly of fingers three and four	+	+	
Dislocation of hips and knees	+	+	+
Talipes calcaneo-valgi	+	+	
Heart defect	+	+	+

SOURCE.—Schinzel (1983).

lar preferential activity of one centromere was observed in a tdic(9;9) (q22;q22) (Wisniewski et al. 1983) that exhibited one primary constriction in 96% of cells. In that case the two 9qh regions differed in size, and the larger of the two was always seen adjacent to the active centromere. Most other examples of preferential centromere activity in dicentrics have been less dramatic (Niebuhr 1972; Daniel 1979; Dewald et al. 1979; Ing and Smith 1983; Uehara and Kida 1986), and in some cases neither centromere appeared to be suppressed (Funderburk et al. 1977; Mascarello et al. 1983).

In exceptional cases a centromere may be rendered inactive as a result of a loss of centromeric or heterochromatic material. Nakagome et al. (1986) described two dicentric X chromosomes in which the active centromere stained C-, Cd-, and DAPI-positive, whereas the inactive centromere did not stain by any of these methods. Presumably the inactive centromere of the dicentric lost a block of chromatin that included the centromere region. In a dicentric 13/20 translocation, stability was reportedly achieved by suppression of the chromosome 20 centromere in one variant and by deletion of the centromere of chromosome 13 in another variant of the dicentric (Vianna-Morgante and Rosenberg 1986).

The question of loss of centromeric material and paracentromeric heterochromatin was addressed at the molecular level in our patient, and the in situ hybridization of p82H and L6 probes was similar in the normal and recombinant 9 chromosome. Neither p82H- nor L6-hybridizable sequences were relocated as a result of the inversion. Probes p82H and L6 hybridized to both centromeric regions of the dicentric 9, demonstrating that suppression of centromeric function in the recombinant was not accompanied by deletion of these hybridizable sequences.

While the results do not shed light on the points of exchange that occurred outside the inversion loop, they do support the interpretation that the paracentric-inversion breakpoint is distal to the heterochromatic region.

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