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Duplication 9q34 Syndrome

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SUMMARY

Phenotypic, karyotypic, and developmental homology between affected children of carriers of an inverted insertion (9) (q22.1q34.3q34.1) led to recognition of a new chromosome syndrome: dup 9q34. Individuals with dup 9q34 have slight psychomotor retardation, understand simple directions, and acquire a limited vocabulary. In childhood, many are hyperactive. Clinical features include low birth weight, normal birth length, and initial poor feeding and thriving. Musculo-skeletal systems are affected: there are joint contractures, long thin limbs, and striking arachnodactyly. There is abnormal implantation of the thumb, increased space between the first and second fingers, and excess digital creases. Marfan syndrome was a provisional diagnosis for several cases prior to cytogenetic analysis. Cardiovascular and ocular systems are minimally affected, erythema and heart murmurs occur, and ptosis and strabismus are frequent, but lens dislocation is not observed. Features at birth include: dolichocephaly, facial asymmetry, narrow horizontal palpebral fissures, microphthalmia, prominent nasal bridge, small mouth, thin upper lip with down-turned corners, and slight retrognathia. In older children, retrognathia is diminished and the nose becomes long and narrow.

The new culture and chromosome banding techniques enable sorting of cases with the distal dup 9q phenotype into two groups. The cases with a longer dup 9q are more likely to develop with life-threatening congenital anomalies. The cases with the shorter dup 9q34 have a less severe long-term prognosis and will benefit, together with their parents, from special education. Female carriers of the inv ins(9) (q22.1q34.3q34.1) have about a 31% risk in each pregnancy to conceive

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a fetus affected by the dup 9q34 syndrome. A comparable figure is not yet available for male carriers.

INTRODUCTION

The historic pattern of settlement along the coast of Newfoundland provides clusters of families sharing common ancestry, albeit unwittingly, and simplifies the process of tracking segregating chromosome rearrangements. Once the relationship between a specific phenotype and a specific chromosome duplication and/or deletion is known, additional affected cases in nearby communities are readily available [1]. Our study delineates the unique chromosome syndrome of duplication 9q34, as a subset of duplication 9q [2].

RESULTS

Case Reports

Case reports for seven affected children from four kindreds in which an inv ins(9) (q22.1q34.3q34.1) chromosome is segregating are presented in the APPENDIX.

Pedigree Data and Reproductive Histories

Kindreds 1, 2, 3, and 4 were each ascertained through a proband with congenital anomalies and developmental retardation (cases 1, 4, 5, and 7, fig. 1). Pedigree data and reproductive histories were obtained through interviews with available family members prior to karyotyping. The great-grandparents of each proband were born within a 50-mile radius of St. Anthony, Newfoundland. No common ancestral couple has yet been identified. Reproductive histories for 15 male and female carriers of the inv ins 9q34 total 50 pregnancies. There were six spontaneous abortions. Fourteen of 44 live births exhibited the dup 9q34 phenotype. Ten of these 14 were karyotyped. Each had inherited the recombinant chromosome dup 9q34. When probands' sibships are excluded, nine female carriers born since 1926 had 32 pregnancies resulting in three spontaneous abortions, 20 normal live births, and nine infants with the dup 9q34 phenotype. The maximum recurrence risk for female carriers is estimated as 31%. Comparable data are not yet available for male carriers.

Phenotypic Features

Table 1 lists clinical features for our seven cases with dup 9q34 and for six previously reported cases with overlapping duplications: dup 9q31qter [2, 4], dup 9q32qter [5–7], and probable dup 9q34qter ([8] and W. R. Breg, personal communication, 1982). One might predict that these cases would fall into three distinct phenotypic classes determined by the length of their partial duplication. Instead, each phenotype parallels the distal dup 9q syndrome first recognized by Turleau et al. [2]. Salient features include low birth weight, normal birth length,

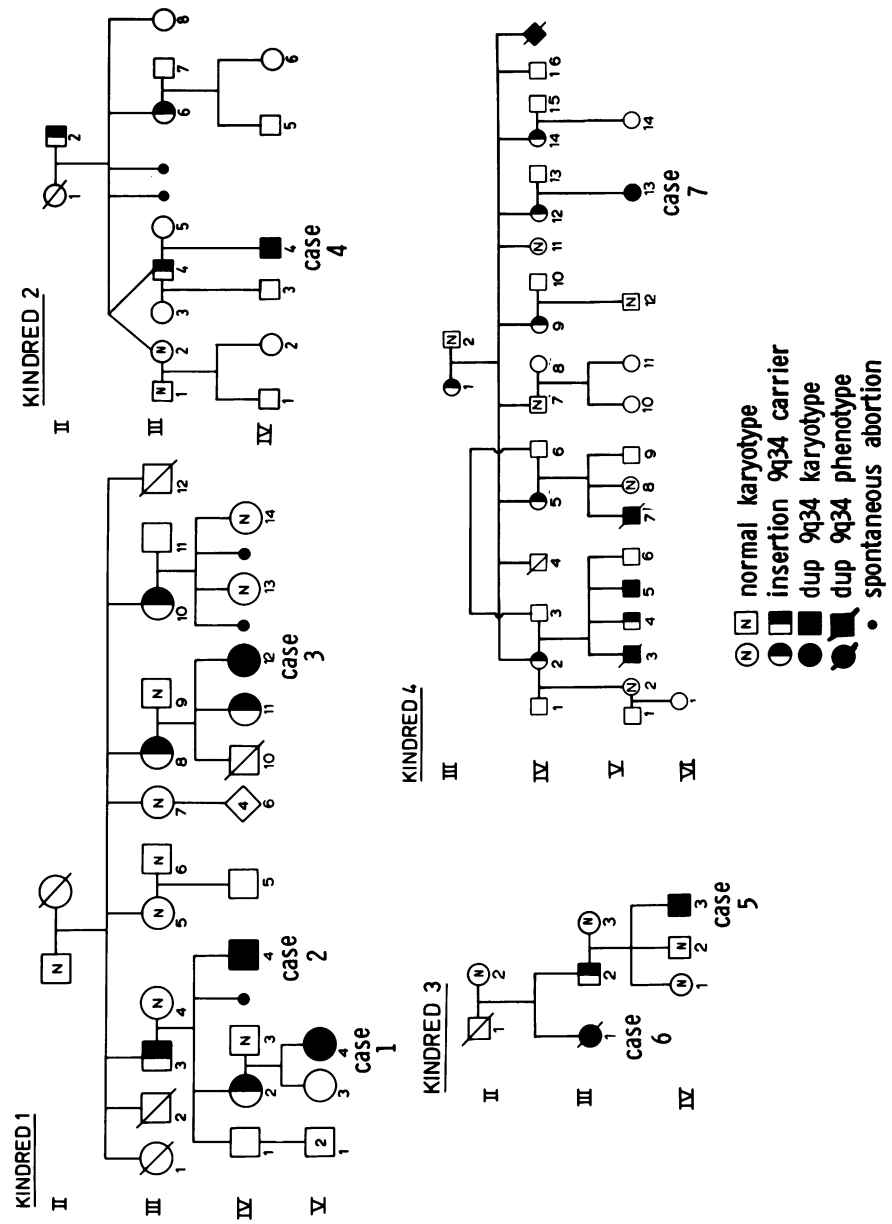


FIG. 1.—Partial pedigrees for the four kindreds in which the inv ins(9)(q22.1q34.3q34.1) chromosome is segregating. The presumed common ancestral couple is not yet identified. A sister of III_1 in kindred 4 also had five children with the dup 9q34 phenotype.

TABLE 1

CHARACTERISTICS OF DISTAL 9q DUPLICATION SYNDROME

Reference	[2]	[4]	[5]	[6]	[7]	[8]	PRESENT REPORT						
Case number	2						1	5	7	2	3	4	6
Duplicated segment: 9q	q31-qter		q32-qter			? q34-qter	q34						
Characteristic:													
Dolichocephaly	+	+	●	+	●	+	+	+	+	+	+	+	+
Dysplastic ears	+	0	+	+	+	+	+	+	+	+	+	+	+
Facial asymmetry	●	+	+	●	●	●	+	+	+	+	+	+	+
Palpebral fissures													
Narrow	+	+	+	●	+	0	+	+	+	0	0	0	●
Horizontal	+	0	●	●	●	●	+	+	+	+	+	+	●
Ptosis	●	●	●	●	●	+	0	0	+	+	+	+	●
Deep-set eyes	+	●	+	+	●	●	●	●	+	●	●	●	●
Microphthalmia	●	●	●	●	+	●	+	●	+	+	●	●	●
Exotropia	●	+	●	●	+	+	●	+	+	+	+	●	+
Prominent nasal bridge	+	+	+	+	+	+	+	+	+	+	+	+	+
Long narrow nose	●	●	●	●	●	+	0	0	0	+	+	+	+
Microstomia	+	+	●	+	+	●	+	+	+	+	●	●	●
Retrognathia	+	+	+	+	0	+	+	+	+	●	●	●	●
Arachnodactyly	+	+	+	+	+	+	+	+	+	+	+	+	+
Excess digital creases	●	+	●	+	palm	●	+	+	+	+	+	+	●
Abnormal implantation of digits	+	+	●	●	+	●	+	+	+	●	●	●	●
Flexion contractures	+	+	+	+	●	+	+	+	+	+	+	+	+
Dislocated (dysplastic) hip	0	0	(+)	0	+	0	0	0	0	0	0	+	●
Scoliosis	0	0	0	0	0	+	0	0	0	0	+	+	+
Torticollis	●	●	●	●	●	●	0	0	0	0	+	+	+
Amylotrophy	●	+	●	+	+	+	+	+	+	+	+	+	+
Heart murmur (in infancy)	0	+	●	●	●	0	+	0	0	+	0	(+)	+
Erythema	●	●	+	●	●	+	+	+	+	+	+	●	●
Severe congenital heart anomalies	0	+	+	0	+	0	0	0	0	0	0	0	0
Cryptorchidism	F	+	F	F	F	+	F	0	F	+	F	+	F
Renal anomalies	0	+	0	0	+	0	0	0	0	0	0	0	●

NOTE: + = present; 0 = absent; ● = not observed; F = female.

a long narrow habitus, dolichocephaly, and striking arachnodactyly. In infancy, facial dysmorphy includes: asymmetry, deep-set eyes, narrow horizontal palpebral fissures, receding chin with the upper maxillas overlaping the lower jaw, small mouth, and abnormally shaped ears. Five of the published cases also carry a minimal chromosome deletion [2, 4, 6–8], but the overall facial "gestalt" of the distal dup 9q syndrome clearly dominates (table 1, fig. 2).

Dysmorphology of the hands and feet of children with distal dup 9q is severe. In addition to arachnodactyly, the thumb and/or large toe may have abnormal implantation. A broader than usual space between the first and second fingers was noted for our cases 1, 5, and 7 (fig. 3). This, in combination with abnormal positioning of the thumb, interferes with their ability to grasp small objects. Congenital flexion contractures and limited joint movements were noted for all cases except the infant reported by Mattei et al. [7] (table 1). Camptodactyly is frequently present. Hips, knees, ankles, elbows, and other joints are also affected. The contractures generally diminish with age. A dup 9q31qter case was not walking at age 6 [2, 9]; however, our dup 9q34 cases and the case reported by Lucky and Gelehrter [8] were walking by the end of their second year. Initially, they have a characteristic broad-based, stiff-legged gait, taking short steps, and the body is tilted forward at the waist.

Cytogenetic Studies

Karyotypic results for members of the four kindreds are indicated on their pedigrees (fig. 1). Q-banding revealed all normal chromosomes with the exception of one marker chromosome 9 with longer than usual band 9q22. A marker 9 was carried by each affected child and by one of his or her normal parents. G-banding revealed a distinct difference in band sequence and total length between the inv ins(9)(q22.1q34.3q34.1) marker chromosome carried by each normal parent (fig. 4*A*), and the dup 9q34 marker chromosome carried by each affected child (fig. 4*B*). R-banding of the balanced paracentric insertion chromosome 9 showed about one-fourth of the dark-stained band 9q34.1 remained in its usual distal location (fig. 4*C*).

The balanced insertion 9q chromosome, inv ins(9)(q22.1q34.3q34.1), was carried by each mother of cases 1, 3, and 7, each father of cases 2, 4, and 5 (case 4, R. Worton, personal communication, 1976), the paternal grandfather of case 4, and the brother of case 6. The dup 9q34 chromosome, rec(9), dup q, inv ins(9)(q22.1q34.3q34.1), was inherited by cases 1–5 and 7 (case 4, R. Worton, personal communication, 1976). Case 6 was not karyotyped prior to her death in 1963.

One possible sequence in the origin of the balanced rearrangement is diagrammed in fig. 4*C*. After three breaks, at 9q22.1, 9q34.1, and 9q34.3, segment 9q34.1q 34.3 was removed from its normal distal location and either directly inserted, or inverted and inserted, in band 9q22.1, of the same chromosome 9 long arm. Comparison of G- and R-band patterns of the insertion chromosome 9 with the ISCN 550 and 850 band diagrams and with the R-banded karyotype by Dutrillaux and Viegas-Pequignot [3] led us to interpret the rearrangement as an inverted insertion. As a result of the inversion, band 9q34.2 was inserted closer to the

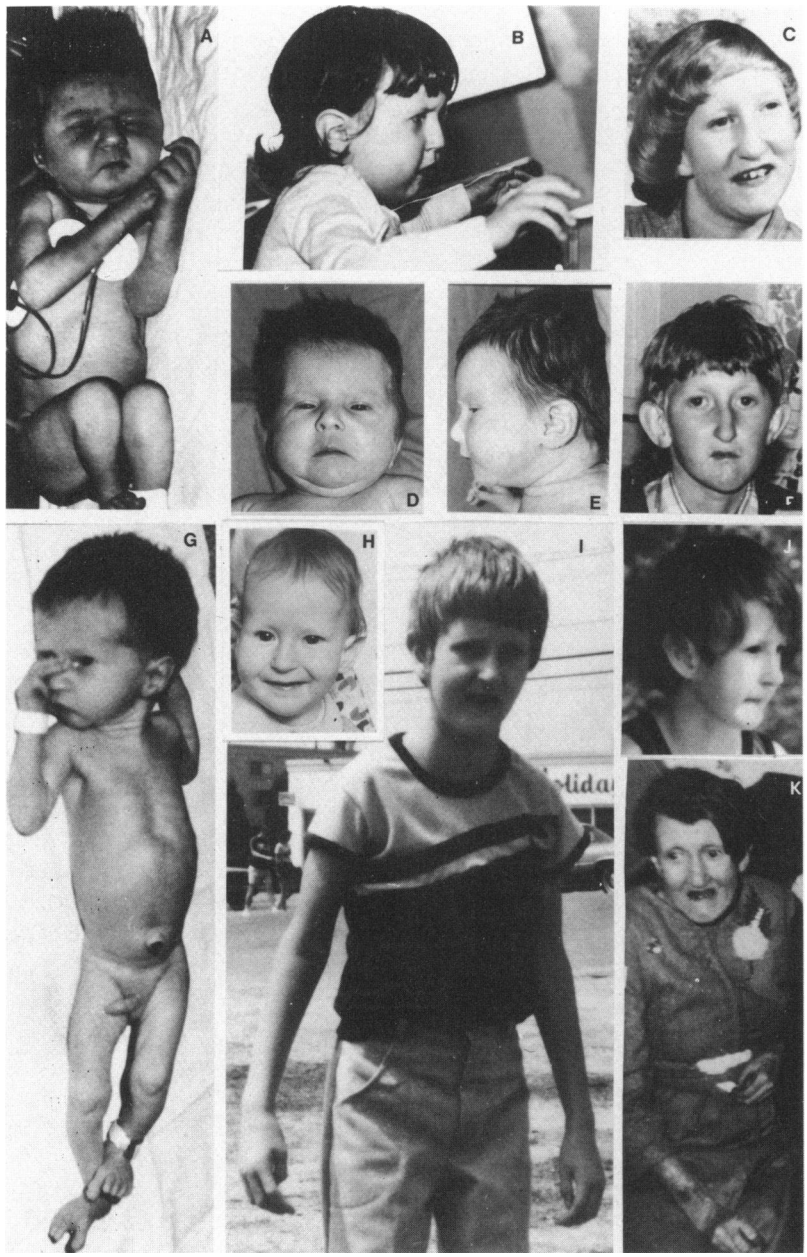


FIG. 2.—Duplication 9q34 syndrome. Case 7, *A*, 1 week; *B*, 14 months. Note arachnodactyly, small mouth, long nose, simple ear. *C*, Case 3, 15 years. Note: facial asymmetry, long narrow nose. *D* and *E*, Case 1, 1 week. Note: narrow horizontal palpebral fissures, retrognathia, large simple ears. Case 2, *F*, 11 years; *G*, 1 week. At 11 years, note: long narrow nose, hypoplastic nasae alae, small narrow mouth, large simple ears. At 1 week, note: arachnodactyly, implantation of toes. Case 4, *H*, 2 years; *I*, 6 years; *J*, 6 years. Note: facial asymmetry, posture. *K*, Case 6, 50 years. Note: amylotrophy, long nose, exotropia, arachnodactyly.

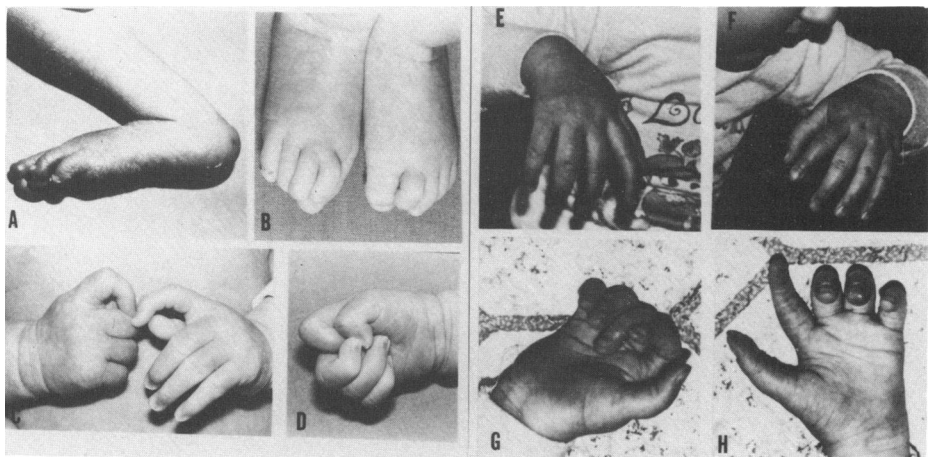


FIG. 3.—Duplication 9q34 syndrome, dysmorphy of hands and feet. *A*, Case 7, 1 week. Note: joint contracture and long narrow foot with overriding toes. *B–D*, Case 1, 1 week. Note: overriding toes, increased space between first and second fingers. *E–H*, Case 7, 22 months. Note: abnormal implantation of thumb, extra digital creases, tapering fingers.

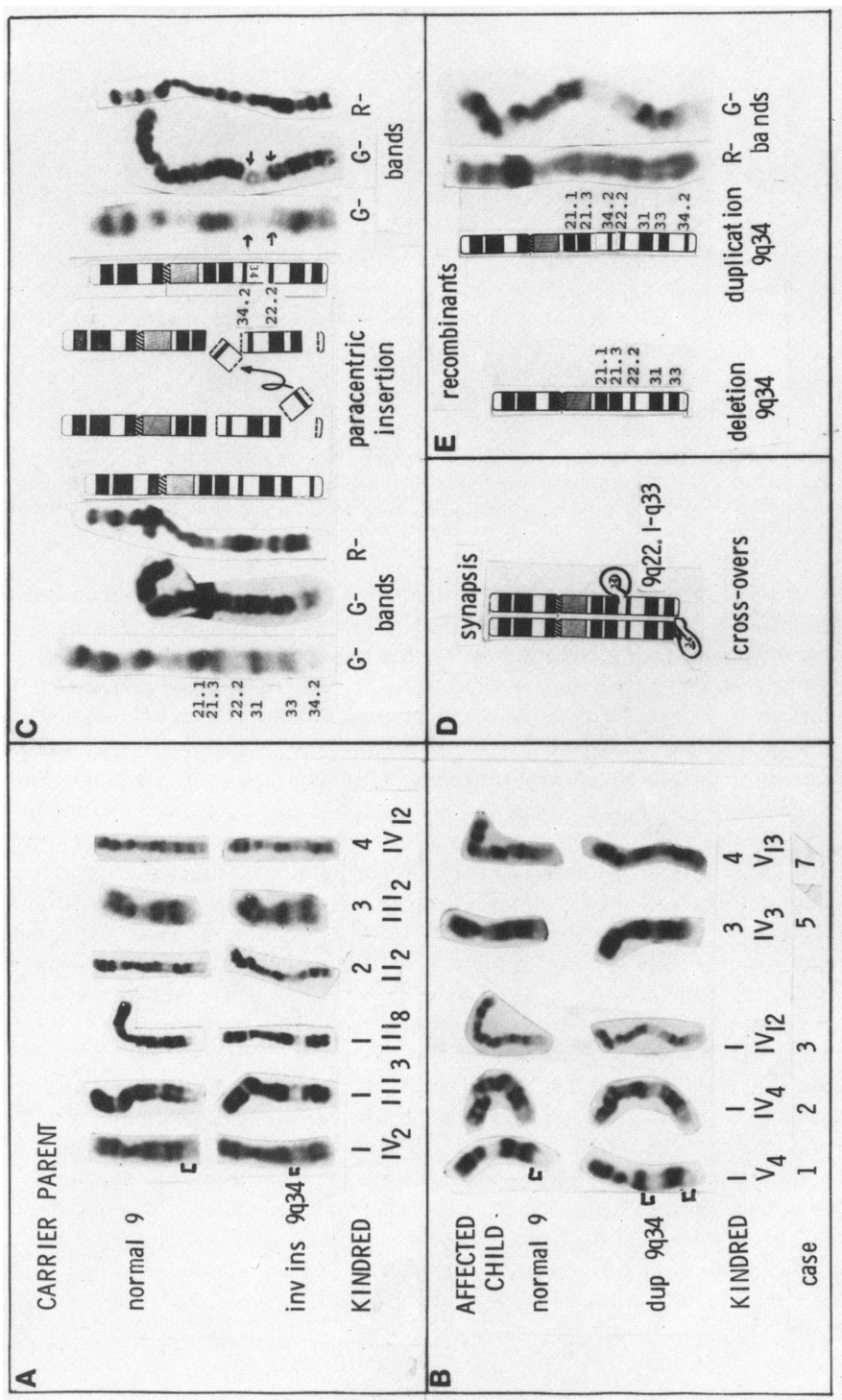
dark G-band 9q21.3 than to the dark G-band 9q22.2 (fig. 4*A* and *C*). In contrast, the band sequence for a recombinant duplication 9q34 chromosome derived from a direct insertion (9)(q22.1q34.1q34.3) is diagrammed in figure 4*E*, and compared with an R-banded and a G-banded dup 9q34.

DISCUSSION

The heterozygous carrier of an insertion 9q34 produces two nonhomologous unbalanced recombinant chromosome 9's (deletion 9q34 and duplication 9q34) after an uneven number of crossovers along the synapsed shifted chromosome segment 9q22.1-q34.1 (fig. 4*D* and *E*). Regardless of whether the paracentric insertion is direct, or inverted, the two recombinant duplication 9q34 chromosomes would differ only by the direction of the gene sequence in the inserted segment 9q34.1-q34.3. Each dup 9q34 duplicates the identical chromosome segment. Excluding possible position effects, there should be no difference in phenotype-karyotype correlation between children inheriting the recombinant dup 9q34 from the carrier of an ins 9q34, or from an inv ins 9q34 carrier. A second possible recombinant, del 9q34, was not carried by any of the children karyotyped. Together with the low frequency of spontaneous abortions, this suggests that gametes carrying the del 9q34 do not compete equally with gametes carrying the dup 9q34, the inv ins 9q34, or the normal chromosome 9.

Depending upon crossover location, other unique recombinants could segregate from an ins 9q34 or an inv ins 9q34. Recovery of a series of recombinants would provide additional data from which to accurately reconstruct the evolution of this specific rearranged chromosome 9.

Specific phenotypic differences between cases of distal dup 9q may be related to the age of the patient at time of examination, rather than to the length of the


A
CARRIER PARENT
normal 9
inv ins 9q34
KINDRED I I I 2 3 4
IV2 III3 III8 II2 III2 IV12
B
AFFECTED CHILD
normal 9
dup 9q34
KINDRED I I I 3 4
V4 IV4 IV12 IV3 V13
case 1 2 3 5 7
C
21.1 21.3 22.2 31 33 34.2
G- G- R- bands
34.2 22.2
paracentric insertion
G- G- R- bands
D
synapsis
9q22.1-q33
cross-overs
E recombinants
21.1 21.3 34.2 22.2 31 33 34.2
21.1 21.3 22.2 31 33
deletion 9q34
duplication 9q34
R- G- bands

duplication (table 1, fig. 2). For example, deep-set eyes and microphthalmia are often commented upon for infants, while divergent strabismus and ptosis are frequently obvious in older children. The mouth, noted as small at examination of some infants, appears near-normal in size in later photographs of the same cases. The chin, receding in infancy, becomes more prominent with age; and the nose, relatively broad at birth, is long and narrow with hypoplastic nasae alae for our older cases (fig. 2). Scoliosis may also be an age-related phenomenon. It was not mentioned for any of the infants with longer dup 9q but was noted for a 3½-year-old [8] and for our cases 3, 4, and 6 (table 1).

In contrast to the external phenotypic homology of cases with partial dup 9q, infants with longer duplications are more likely to develop with severe internal congenital anomalies, show greater psychomotor retardation, and probably have a shorter life expectancy than cases with shorter dup 9q34. Three of the infants with dup 9q31qter or dup 9q32qter were born with complex congenital heart defects [4, 5, 7]. Two had urogenital anomalies other than cryptorchidism [4, 7] and two died by age 5 months [4, 5]. On the other hand, children with dup 9q34 now range in age from 2 to 19 years. The affected aunt of our case 5 lived to age 51 during the early 1900s. We anticipate that dup 9q34 cases living within close reach of modern medical services will survive to middle age.

The long, narrow habitus, flexion contractures, and striking arachnodactyly exhibited by patients with distal dup 9q draw attention to similarities between Marfan syndrome [10], congenital contractural arachnodactyly (CCA) [11], and distal dup 9q. Marfan syndrome was a provisional diagnosis for our cases 2, 3, and 4, for the case reported by Lucky and Gelehrter [8], and for infant uncles of a new case of distal dup 9q (Z. Pyatt, personal communication, 1981). Dup 9q34 patients do not develop the ocular and cardiac malformations characteristic of Marfan syndrome, nor do they have the crumpled helix of the ear and oval head shape associated with CCA. Normal parental phenotypes together with hypotonia, unusual facies, psychomotor retardation, severe speech delay, and hyperactivity in the infant or child should lead to cytogenetic analysis (table 2). The correct diagnosis is essential not only for prognosis for the patient but also to ensure accurate estimation of the recurrence risk for the parents. Marfan syndrome and

FIG. 4.—*A*, Partial karyotypes for the carrier parents of cases 1–3, 5, and 7, and the paternal grandfather of case 4. Segment 9q34 is at the normal distal position on the normal 9, and inserted above band 9q22 on the inv ins 9q34. *B*, Partial karyotypes for cases 1–3, 5, and 7. Segment 9q34 is at the normal distal position on both the normal 9 and on the dup 9q34. In addition, there is a copy of 9q34.1-q34.3 inverted and inserted above band 9q22 on the dup 9q34. The insertion is easily overlooked in short metaphase chromosomes (i.e., the partial karyotype for case 5). *C*, A possible sequence in the evolution of the inv ins 9 is diagrammed. Examples of G- and R-banded normal chromosome 9's and G- and R-banded inv ins 9q34's are compared with the diagrams. *Arrows* indicate location of bands 9q34.2 and 9q22.2 on the inv ins 9. *D*, Diagram illustrating synapsis of segment 9q22.1-q34.1 on the normal chromosome 9 with the homologous shifted segment on the inv ins 9. An uneven number of crossovers in this segment will produce two distinct recombinant chromosomes: deletion 9q34 and duplication 9q34. Synapsis of the two segments 9q34 presumably occurs, but is ignored in this diagram for two reasons: (1) to concentrate on the origin of the dup 9q34, and (2) to demonstrate that the duplication will be identical regardless whether there was a direct or an inverted insertion of band 9q34 on the original ancestral chromosome. *E*, The band sequence for two dup 9q34 chromosomes is compared with the diagrams for the recombinants produced by a carrier of an ins(9)(q22.1q34.1q34.3).

TABLE 2

DUPLICATION 9q34 MIMICS MARFAN SYNDROME AND CONGENITAL CONTRACTURAL ARACHNODACTYLY (CCA)

Syndrome	Dup 9q34	Marfan	CCA
Reference	This report	[10]	[11]
Characteristic:			
Dolichostenomelia	+	+	+
Arachnodactyly	+	+	+
Kyphoscoliosis	+	Mild	+
Joint contractures present in infancy	+	Rare	+
Ectopia lentis	0	+	0
Mitral or aortic regurgitation, systolic click	0	+	0
Autosomal dominant	0	+	+
Crumpled helix of ear	0	0	+
Retrognathia in newborn	+	0	+
Cyanosis in newborn	+	0	0
Hypotonia in newborn	+	0	0
Psychomotor retardation	+	0	0
Severe speech delay but understands directions	+	0	0
Hyperactivity in childhood	+	0	0

NOTE: + = present; 0 = absent.

CCA are dominantly inherited and cannot be diagnosed prenatally. When a chromosome rearrangement is segregating in a kindred, the recurrence risk will be lower, and prenatal diagnosis is possible. Prior to our investigation of the inv ins(9)(q22.1q34.3q34.1) kindreds, it was deduced by members of one kindred that their familial retardation syndrome affected every third child. Case 1 was the second child born to one couple who acted on this folklore, arranging for tubal ligation immediately following delivery. Coincidentally, reproductive histories for nine carrier females (probands excluded) indicate a 31% recurrence risk of dup 9q34 in each pregnancy. This is higher than the reproductive risk for carriers of balanced interchromosomal rearrangments, and equals the risk observed for carriers of one other intrachromosomal balanced rearangement: inv(3)(p25q21) [1].

APPENDIX

CASE REPORTS

CASE 1 (221080, KINDRED 1, IV_4) (FIGS. 2 AND 3)

The karyotype of case 1 is 46,XXrec(9),dup q,inv ins(9)(q22.1q34.3q34.1) (fig. 4*B*). She was the last child born to a G2P2 mother, IV_2, karyotype 46,XX,inv ins(9)(q22.1q34.3q34.1) (fig. 4*A*), and father IV_3, karyotype 46,XY.

Pregnancy history was normal, gestation was 40 weeks, and delivery was normal vaginal. The Apgar score was 7 at 1 min and 9 at 5 min. The birth weight was 2,480 g (10%), length 49 cm (25%), and head circumference 33.5 cm (25%). She was 37 weeks gestation by the Ballard assessment. Initially, she was lethargic, with a weak cry, hypotonic, cyanotic, and slow to cry or suck. She was transferred to the Janeway Hospital for evaluation of peculiar facies, arachnodactyly, and a grade 2/6 systolic murmur.

On examination at 8 days, she was hypotonic, with a red flush to her skin, a full head of hair, open fontanelles, microphthalmia, hypertelorism, and normal fundi with good visual tracking. Her head was asymmetric, right ear smaller and low-set, nose short with left deviation of the nares, mouth small with down-turned corners, and palate normal (fig. 2). Her nipples were wide-spaced, abdomen normal, and labia minora was large, protruding outside the labia majora. Her fingers and toes were long and thin, with increased distance, and slight opposition between the first and second fingers. Three fingers were clasped over the index and thumb in a resting position (fig. 3*D*). There was abnormal implantation of the large toe (fig. 3*B*).

Chest X-ray showed possible right to left shunting with pulmonary plethora. EKG suggested some biventricular enlargement. Echocardiogram was normal. IVP and X-ray of the long bones was normal.

CASE 2 (050969, KINDRED 1, IV_4) (FIG. 2)

The karyotype for case 2 is 46,XY,rec(9),dup q,inv ins(9)(q22.1q34.3q34.1) (fig. 4*B*). He was the last child born to a G4P3A1 mother: III_4, karyotype 46,XX; and father: III_3, karyotype 46,XY,inv ins(9)(q22.1q34.3q34.1) (fig. 4*A*).

Pregnancy history was normal, delivery was at 36 weeks gestation, the infant was corded, and appearance was of 30–32 weeks gestation. Apgar score was 4 at 1 min. The birth weight was 1,930 g. He was hypotonic, cyanotic, and slow to breathe and had indrawn noisy respiration and poor sucking.

Physical examination at 4 days revealed small eyes, microglossia, high-arched palate, arachnodactyly, joint contractures of fingers and toes, lack of mesodermal tissue, and an unusual red flush to his skin. CNS, chest, and abdomen were normal. A diagnosis of Marfan syndrome, or of arthrogryposis, was considered. He came to attention at 2½ years of age with chronic constipation. Weight was 10 kg (below 3rd percentile); height, 86 cm (below 3rd percentile); and head circumference, 46.5 cm (below 3rd percentile). Chest circumference was 48.5 cm, and arm span, 86 cm. He had large protruding ears, prominent coronal suture, a long, narrow face, hooked nose, prominent cheeks, protruding maxilla, small mouth, no significant ocular findings, clear cornea and lens, blue sclera, and normal hearing (fig. 2). He had long tapering hands and feet, his fourth finger longer than his index finger bilaterally, and limited flexion of fingers and toes. There was pectus excavatum with some prominence of right side of chest, tight adduction of hips, genu varum, and bilateral pes planus. Testes were undescended.

At age 2½, he bruised easily. His skin was smooth and shiny; X-rays showed tortocollis with a convexity toward the left side. Curvature was maximum at C4-C5 level. The body of C4 appeared hypoplastic and fused in part with C3. Bone age was approximately 2 years. The skull appeared normal, and IVP was normal. Homocystinuria was ruled out.

At age 5, his height was 105 cm (10th percentile), and weight, 15 kg (3rd percentile). At age 9, his height was 134 cm (50th percentile); weight, 22 kg (below the 3rd percentile); and head circumference, 49 cm (2nd percentile).

He had difficulty swallowing until about age 5. During examination of his oral cavity at age 8, his tongue was noted as short and deviated to the right. On command he moved his tongue to the left, but not to the right. His musculature was flaccid, and he drooled. All his molars had been removed. When he opened his mouth, his lower lip became tight and tended to collapse inward. At age 6, he was partially toilet-trained in the day; at age 9, he still wet at night.

Psychomotor development is delayed. He rolled over at 5 months, and walked, falling frequently, at 22 months. At 2½ years, an unusual gait was noted. He took short steps, with pronated feet, buttocks protruding, and the whole lower extremities flexed at the

knee with each step. At 7 years, 10 months, he was still unsteady while running and hopping. By age 9, he was steadier on his feet. At age 8, he used his left hand for most tasks, and his right for writing. While holding a pencil, his fingers tended to collapse, and he had difficulty applying pressure to paper.

His speech development was slow. Between 11 and 22 months he said only two words: "Mom" and "Dad." He was over 3 years old before using sentences. When tested at age 8, he pronounced individual words fairly intelligibly, although often in error. Pronunciation of connected speech was difficult to understand. On the Goldman-Friscoe test of articulation, numerous sound substitutions and omissions were noted. His raw score on the Peabody picture vocabulary test was 3 years, 6 months. He could follow a chain of only two to three commands, and he had severe delay in receptive vocabulary skills. Overall, he functioned at about a 4-year-old level.

At age 9, the WISC test indicated functioning at less than 50. The Stanford-Binet IQ was 54, with a basal age of 4–6, and a ceiling age of 7. He was farsighted and used glasses. There was a question of strabismus, with amblyopia of the left eye, but he was uncooperative for examination. He tilted his head to the right when focusing on close objects. His frustration in communication is expressed by tantrums and head banging.

CASE 3 (130465, KINDRED 1, IV_{12}) (FIG. 2)

The karyotype for case 3 is 46,XX,rec(9),dup q, inv ins (9)(q22.1q34.3q34.1) (fig. 4*B*). She was the last child born to a G3P3 mother, III_8, karyotype 46,XX, and father III_9, karyotype 46,XY, inv ins(9)(q22.1q34.3q34.1) (fig. 4*A*). Their first son was not karyotyped, but was phenotypically normal. He died of malignant lymphoma at age 19.

Pregnancy history for the mother included intermittent spotting in the first 2 months, with normal vaginal delivery at 40 weeks gestation. Birth weight was 2,800 g (25%), and head circumference, 23 cm (10%).

Physical examination at birth revealed prominent torticollis toward the left, an asymmetric face, deformed nose deviated to the right, curvature in the cervical spine with convexity toward the left, and arachnodactyly. A preliminary diagnosis of Marfan syndrome was made. At 2½ years, she was re-evaluated. Features noted were: asymmetric head, the right hemicranium smaller than the left, prominent coronal sutures, increased torticollis with shortened and fixed clavicular origin of right sternomastoid muscle, slight prominence of left side of chest, poor movement of right arm, adduction contracture of the right hip, and flexion contracture of about 20° of both hips. The pupils' reaction to light was normal. The sclera were blue, hearing was normal, and there were no pathological reflexes. Her general health was good. She had atopic dermatitis during early childhood. At age 12, thin shiny skin was noted on hands, feet, and legs to midcalf, with bruises on legs suggestive of peripheral vascular disease.

Laboratory investigation at 2½ years showed normal BUN, blood sugar, urinalysis, CBC, and VDRL. X-ray was normal. EEG demonstrated poorly matured cortical activity, but no focal disturbance.

Psychomotor development is delayed. She sat a few minutes without support and crawled at 14 months, pulled to standing at 15 months, and walked at 24 months. She had a peculiar gait, with trunk inclined and knees flexed. By age 5, she walked and ran easily. At age 17, she rode a two-wheeled bicycle. At age 2, she said only "hi." She responded to commands but had no coordinated right/left-hand activity, was frustrated in motor coordination, hyperactive, and used head banging when thwarted. At age 8, she had a vocabulary of four to five words and used gesturing and one-word responses to communicate. She has been maintained on medication for hyperactivity since age 2½. She shows gradual improvement in behavior. She attends a TMR class and is learning Bliss symbolic language.

Her teacher remarks on her good long-term memory for the storing of objects in the schoolroom.

CASE 4 (180674, KINDRED 2, IV_4) (FIG. 2)

Karyotypes show marker chromosomes 9 with longer than normal band 9q22 carried by both case 4 (IV_4) and his father (III_4) (R. Worton, personal communication, 1976). The markers differ: the father carries an inv ins(9)(q22.1q34.3q34.1) and case 4 inherited a recombinant chromosome, dup q,inv ins(9)(q22,1q34.3q34.1). The karyotype for the paternal grandfather, II_2, is 46,XY,inv ins(9)(q22.1q34.3q34.1) (fig. 4*A*). Case 4 is the second child of his father. The first son is reported as normal.

There was spotting during the pregnancy. Gestation was 41 weeks, birth weight was 3,376 g (50%). The infant's left hip was dislocated during the breech birth. There was congenital dislocation of the right hip. He was slow to suck, and difficult to feed. A heart murmur detected at birth cleared spontaneously. At 27 months, he had two febrile seizures, controlled by medication.

He was re-examined at 34 months, after a third seizure. Physical examination revealed his weight at 15 kg (75%) and head circumference at 49 cm (97%). He was hypotonic, with poor muscle bulk. He had a prominent ridge over the coronal suture; closed anterior fontanelle; narrow, long, asymmetric facies with mild hypertelorism; normal conjugate eye movement; and a wide jaw. The right arm was held in a flexed corticate position, and there was cervical torticollis, an elongated, narrow chest, bilateral severe calcaneovalgus, and arachnodactyly. Testes were undescended. Heart sounds and deep tendon reflexes were normal, and hearing appeared normal. Laboratory tests at age 3 revealed normal chest X-ray, urinalysis, blood sugar, creatine, and spinal fluid.

Psychomotor development is delayed. An immobilization cast was used from age 5–14 months, he walked at age 18 months, and by age 3, he had full range of hip movement, used a below-knee brace, and had an unsteady, wide-based gait, keeping his head down. He understood simple directions, had a three-word vocabulary, and communicated with grunting noises and gestures. He cried without sound. At the time of this study, his major problems were: severe pronation of feet, overriding of toes, temper tantrums, head banging, and hyperactivity. Since age 5, he is in a TMR class and is learning sign language.

CASE 5 (281079, KINDRED 3, IV_3) (FIG. 2)

Case 5 is the last child born to a G3P3 mother: karyotype 46,XX; and father: karyotype 46,XY,inv ins(9)(q22.1q34.3q34.1) (fig. 4*A*). The karyotype for case 5 is 46,XY,rec(9),dup q,inv ins(9)(q22.1q34.3q34.1) (fig. 4*B*).

It was a normal pregnancy with vaginal delivery. At birth, the infant was tightly corded, with Apgar score 4 at 1 min, and 6 at 5 min. The birth weight was 3,300 g (50%); length, 53 cm (90%); and head circumference, 36.5 cm (90%). He was cyanotic and given oxygen. He had shallow respirations and no spontaneous movement.

On initial examination, he had a hoarse cry and persistent cyanosis. His head was asymmetric, with the right side of the forehead more prominent. His hair was grey-and-white streaked. The right cornea had a nebula at 5 o'clock with an adherent iris. The pupil peaked at 11 o'clock. Both pupils reacted briskly to light. Fundi were normal. There was a left preauricular appendage. The chest, heart sounds, and abdomen were normal. Both testicles were descended. There was a mild chordee. He had a right Erb's palsy and long fingers and toes. He could not straighten his fingers.

Psychomotor development is delayed. He sat alone at age 11 months. He walked with support at age 17 months. By the Denver developmental screening test, he was at the 12-

month level at age 17 months. At age 31 months, he is hyperactive, and is walking and running. He has had febrile convulsions.

CASE 6 (000012 KINDRED 3, III_2) (FIG. 2)

Case 6 was never karyotyped. Her mother is 46,XX; her father is no longer alive. The karyotype for her brother, the father of case 5, is 46,XY,inv ins(9)(q22.1q34.3q34.1) (fig. 4*A*). We presume from her phenotype and psychomotor development that she inherited the recombinant dup 9q34 from her father.

She was very thin, with long arms, legs, hands, and fingers. Strabismus, a pansystolic murmur, scoliosis, and torticollis were noted. Her skin was thin and shiny and bruised easily. She communicated with her family with signs and a few words but no sentences. She was anemic and died from multiple betoacidotic attacks associated with diabetes at age 51.

CASE 7 (050380, KINDRED 4, V_{13}) (FIG. 2)

Case 7 is the first child born to a single G1P1 mother. The karyotype for the mother is 46,XX,inv ins(9)(q22.1q34.3q34.1) (fig. 4*A*). The father has not been karyotyped. The karyotype for case 7 is 46,XX,rec(9),dup q,inv ins(9)(q22.1q34.3q34.1) (fig. 4*B*).

Pregnancy and delivery were normal. Apgar scores for the infant were 6 at 1 min and 9 at 5 min. Her birth weight was 2,900 g (25%), length was 52 cm (90%), and head circumference was 33.5 cm (25%). During her first week she had a hoarse cry, and was cyanotic. The maternal grandmother and aunts recognized their familial syndrome even before the diagnosis was made.

Physical examination revealed a hypotonic infant with small deep-set eyes, left intermittent estropia, low-set right ear, small mouth, high-arched palate, retrognathia, long slender arms and legs, long feet, long fingers and toes, and extra digital creases.

Chest and whole body X-ray were normal, except for flaring of distal ends of the radius and ulna on the left. X-rays at age 24 months showed congenital fusion of the posterior arches of C2 and C3.

Psychomotor development is delayed. At 6 months her weight was at the 50th percentile, length greater than 97th percentile, and head circumference at the 75th percentile. In her first months, she had severe seborrhea, pneumonia, and otitis media.

At age 24 months, she is at the 75th percentile in height and 50th percentile in weight. In walking she is unsteady, with stiff legs, and often falls. When sitting she holds her arms out and hands in the air (fig. 2*B*). She has apnoeic or blue spells that occur at home in the morning before she wakes up. She is found limp, cyanotic, with purplish hands and face, and the lips and tip of the nose are pale. No organic cause was identified when she was hospitalized for investigation. Her overall development at age 24 months is of a 12-month-old.

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