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Duplication and Deletion 11q23-q24 Recombinants in Two Offspring of an Intrachromosomal Insertion ("Shift") Carrier

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Few examples of intrachromosomal insertions have been described. These usually result from deletion of a segment of chromosome material, with insertion of the deleted material elsewhere on the same chromosome. Previous insertional translocations have been identified through a proband who has either a deletion or a duplication of the inserted segment. We describe a family which has two probands, one with a duplication and one with a deletion of the inserted segment. The unbalanced chromosomes probably resulted from an uneven number of crossovers between the breakpoints in the chromosome 11 of the father, who carries a balanced intrachromosomal insertion of the segment 11q23.3-11q24.2 into the short arm of chromosome 11: 46,XY,ins(11)(p14.2q23.3q24.2). (Henry Ford Hosp Med J 1988;36:183-6)

Intrachromosomal insertions (shifts) are recognized as one cause of familial mental retardation and dysmorphism. These three-break rearrangements are among the rarest of known chromosome abnormalities. Intrachromosomal insertions result from three breaks in the same chromosome. Two breaks result in the extraction of a piece of material which is then inserted at the site of a third chromosomal break. If the third chromosomal break occurs in the same chromosome, it is called an intrachromosomal insertion, or a shift. An intrachromosomal insertion is called a direct insertion if the orientation of the material with respect to the centromere is unchanged; otherwise it is called an inverted insertion. Intrachromosomal insertions have been described in chromosomes 1, 2, 3, 5, 7, 9, 11, 13, 16, and X (1-13). In most cases, the material was inserted into the opposite arm.

The duplications and deletions that arise from insertions provide insight into phenotype mapping, whereby the role of specific chromosomal regions in the development and physical features of individuals is learned. The previously reported intrachromosomal insertion on chromosome 11 was identified through a patient who had an inverted duplication 11p11.3-11p14.1 inserted into 11q14.5; the mother carried the balanced form of the insertion (13). We report two siblings, one with a duplication and one with a deletion of 11q23.3-11q24.2, which resulted from two different recombinational events at meiosis in their father who carries an intrachromosomal insertion of this segment.

Case Reports

Case 1

This boy (Fig 1) was born July 6, 1977. He was a full-term infant born without complications to a 34-year-old, gravida 8, para 2, white mother and 55-year-old father. The mother denied prenatal teratogenic exposures including smoking, alcohol, illness, fever, and infection. At birth the boy weighed 2,520 g (5 lbs 10 oz) and had bilateral clubfeet, but no other abnormalities were noted.

At age 9 he was 126.4 cm (49.75 in) tall (tenth to 25th percentile), weighed 19.8 kg (44 lb) (< fifth percentile), with a head circumference of 49.5 cm (19.5 in) (second percentile). He had mild synophrys, downslanting palpebral fissures, bilateral epicanthal folds, anteverted nares,

Fig 1—Case 1, at age 9. This boy has the deletion of 11q23.3-q24.2. These photographs depict his bilateral ptosis, downslanting palpebral fissures, and micrognathia.

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Fig 2—Case 2, at age 13. This girl has the duplication of 11q23.3-q24.2. She has upslanting palpebral fissures, full lips, a broad nose, and mild micrognathia.

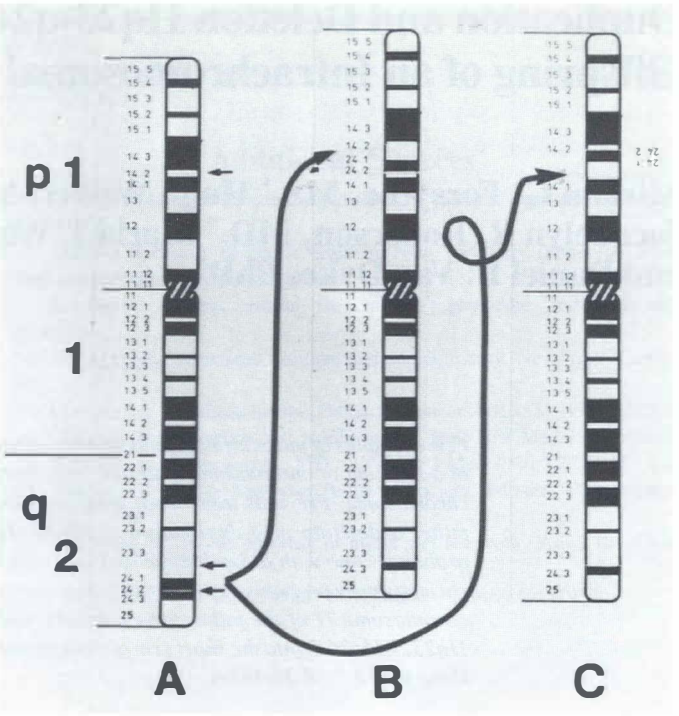

Fig 3—Idiogram (A) of chromosome 11 from ISCN (14) showing the three breakpoints (11p14.2, 11q23.3, and 11q24.2) involved in formation of the father's balanced insertion. The orientation of the insertion is uncertain. It could be inverted (B) with respect to the centromere, or direct (C). The difference in the banding pattern of an inverted or direct insertion of this material is apparently too subtle to distinguish with current techniques. From a clinical point of view, it may not matter whether or not the insertion is inverted.

thin upper lip, and micrognathia. His inner canthal distance was 3.5 cm (50th to 75th percentile) and outer canthal distance was 8.3 cm (97th percentile). His eyes and ears appeared normal, and his heart had a normal sinus rhythm, without murmurs. He had bilateral simian creases and short digits, with a single flexion crease on left digits 4 and 5 and right digits 2 and 4. There was a short fourth metacarpal in the left hand. A scar from umbilical hernia repair was present, and he had first-degree hypospadias with both testes descended. He had bilateral pes cavus with the right being much more severe than the left. Bilateral hallux valgus and a midfoot varus were evident on radiography. He had surgery to release plantar fascia on both feet. A bilateral coxa valga as well as an S-1 spina bifida were noted.

He has had seizures which have been controlled with phenobarbital. He was moderately to severely retarded and attended special education classes for the severely mentally impaired. His speech was limited with a vocabulary of five to ten words. His gross motor skills were adequate, although his fine motor skills were poor.

Case 2

Case 1's sister (Fig 2) was born January 5, 1975. Her birthweight was 2,604 g (5 lb 13 oz) after an uncomplicated full-term pregnancy. Teratogenic exposures were denied. At age 11 she was 142.2 cm (56 in) tall (25th percentile), weighed 42.1 kg (93.5 lb) (50th to 60th percentile), with a head circumference of 49.5 cm (19.5 in) (< second percentile). She had upslanting palpebral fissures with an outer canthal distance of 7.5 cm (25th percentile) and inner canthal distance of 3 cm (50th percentile). Her nose was broad, and her lips were full. Strabismus had been present at a younger age. She had a refractive error corrected with glasses. She had hyperextensible joints. Bilateral hindfoot varus deformities were evident on x-ray. Her skeletal age was advanced; at chronologic age 11 years 10 months, her bone age was 13 years 9 months. Minimal levoconvex scoliosis of the lower thoracic spine was present. Breast development and menstruation had begun at age 11.

Her gross motor skills were appropriate for her age, but her fine motor skills were poor. Although her speech was immature, she used full sentences. She could write her name, count, and name colors. She attended a special education program for the educable mentally impaired and was mildly to moderately retarded.

Pedigree

The family history was significant for pregnancy losses. These siblings were their parents' only liveborn children. A set of twins spontaneously aborted at two months gestation, and another pregnancy ended spontaneously in the first month of gestation. Their mother had three miscarriages with a different partner. Their father, currently 64 years old, has two healthy daughters, aged 32 and 23. The older daughter had a daughter in

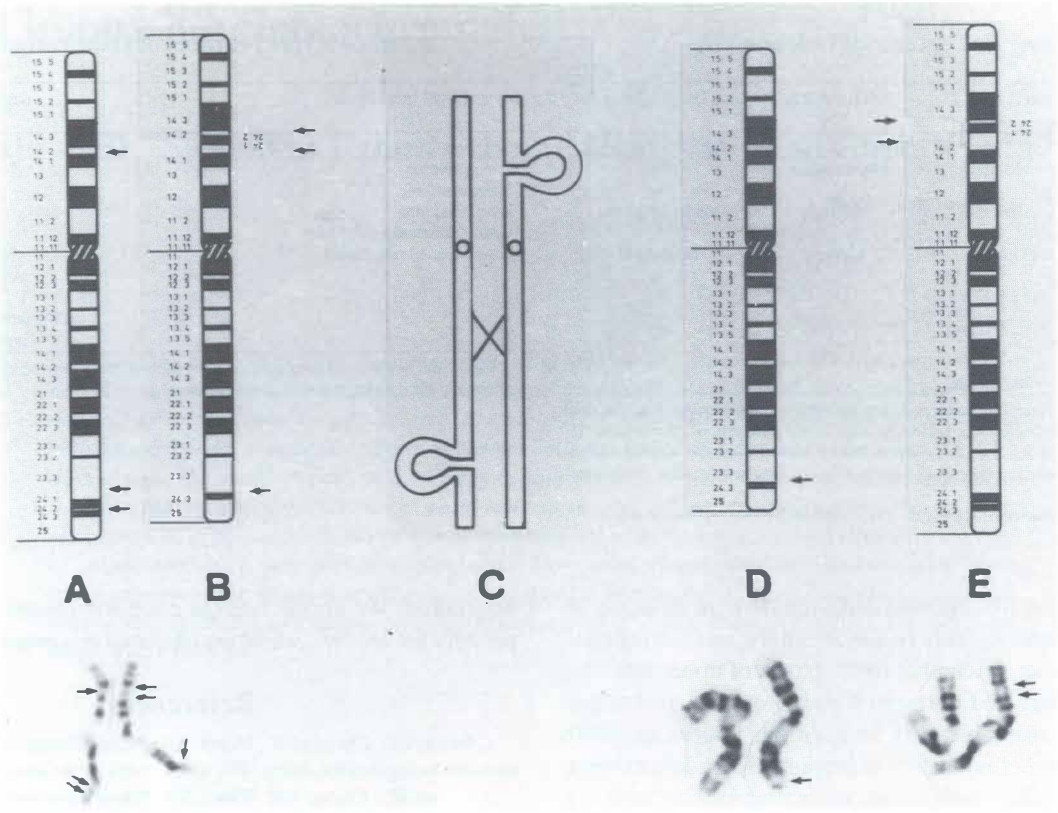

Fig 4—Idiogram and partial karyotype of the father's normal (A) and insertion (B) chromosome 11 and the deletion (D) and duplication (E) chromosome 11 of his children. In D and E, the normal chromosome is on the left. A single crossover between the normal and insertion chromosomes during meiosis in the father (C) would lead to the duplication and the deletion unbalanced gametes in equal proportion. The relative proportion of balanced to unbalanced gametes among all of the father's spermatozoa depends on the likelihood of a single (or any uneven number) crossover on chromosome 11 between the breakpoints in the short and long arms. Given the relatively large distance between 11p14.2 and 11q23.3, recombination should occur at a high frequency. The drawing (C) depicts no meiotic synapsis (asynapsis) of the insertion segments, but it is uncertain whether these segments synapse. Other more complex configurations have been proposed for synapsis of intrachromosomal insertions (5,6,9,11) at meiosis.

1983 who is reportedly normal. The probands' father's sister died at age 26 after an accident. She was apparently normal until her death. The probands' paternal grandparents died at ages 83 and 81.

Cytogenetic Findings

Peripheral lymphocytes were cultured, and G-banded metaphase slide preparations were obtained by standard methods for the two patients and their parents [Figs 3 (14) and 4]. The boy had a karyotype of 46,XY,del(11)(q23.3q24.2), and his sister had a karyotype of 46,XX,rec(11),dup q,ins(11) (p14.2q23.3q24.2). Their mother had a normal 46,XX pattern, while their father showed an apparently balanced intrachromosomal insertion which, after high-resolution analysis, was designated as 46,XY,ins(11)(p14.2q23.3q24.2). The boy has one chromosome 11 with a deletion of the region 11q23.3-11q24.2, whereas his sister has three copies of this region: one on the normal 11 inherited from her mother, and one on each arm of the recombinant chromosome inherited from her father. The paternal grandparents and the two half-sisters of the probands have not been karyotyped.

Discussion

A balanced intrachromosomal insertion can give rise to a deletion or duplication of the inserted material. In the family described, one child inherited a deletion of the inserted segment while the other inherited a duplication of the inserted segment (Fig 4).

These siblings exhibit phenotypic features similar to those of patients previously described who have a deletion or duplication of distal 11q, even though most others have a greater chromosomal imbalance (Tables 1 and 2). Two other patients with small deletions in 11q, one with del(11)(q23.3) and one with del(11)(q24.2), have similar characteristics described in individuals with larger deletions of 11q (15). The dysmorphic fea-

Table 1
Phenotypic Features of Deletion 11q

Deletion 11q (16)	del(11)(q23.2) (15)	del(11)(q24.2) (15)	del(11)(q23.3-q24.2) Case 1
Short stature	+	–	10th-25th Percentile
Microcephaly	Slight	Macrocephaly	+
Trigonocephaly	+	–	–
Mental retardation	Moderate	Severe	Moderate/severe
Anteverted nares	+	–	+
Palpebral fissures	Upward	Upward	Downward
Epicanthus	+	–	+
Ptosis	Slight	–	+
Mouth: large, carp-shaped	+	+	–
Short fingers, toes	+	+	+
Cardiac	Coarctation	–	–

Most of the common phenotypic features of patients with deletion 11q were also observed in the three patients with deletions of small segments of the long arm of chromosome 11. Case 1 and the patient with del(11)(q23.2) have similar phenotypic features whereas the patient with del(11)(q24.2) did not have short stature, trigonocephaly, epicanthal folds, anteverted nares, or ptosis.

(Note: + indicates characteristics present, and – indicates characteristics absent.)

Table 2
Phenotypic Features of Duplication 11q

dup(11)(q23-qter) syndrome (16)	dup(11)(q23.3q24.2) Case 2
Flat, broad nose	+
Long philtrum	–
Short mandible	–
Dysplastic hips	–
Heart malformations (43%)	–
Severe mental retardation	Mild to moderate
–	Advanced bone age
–	Full lips
–	Upslanting palpebral fissures
–	Hyperextensible joints

Case 2 did not have features considered typical of previously described patients with duplications of larger segments of chromosome 11q.

tures of the previously reported individuals with deletion of 11q22 or 23 to 11qter include trigonocephaly, upslanting palpebral fissures, inner epicanthal folds, ptosis of upper lids, depressed nasal bridge and anteverted nares, carp-shaped upper lip, and receding mandible (16). In addition, fingers are short and often flexed and clinodactyly is present. Heart defects were present in 50% of individuals. Other anomalies were present in a few individuals. Almost all were short and microcephalic. Mental retardation was severe to profound in all but one patient over 3 years old. The patients with larger deletions of 11q frequently had life-threatening cardiac malformations and approximately 25% died within the first months of life (16).

The characteristics of duplication of 11q23-qter (Table 2) include a flat, broad nose; long, prominent philtrum; short mandible; dysplastic hips; and heart malformations (16). Case 2 had only a few of these features, perhaps because most of the previously described patients had a duplication of a much larger segment of chromosome 11q.

Duplication of a specific region of the genome typically has a less dramatic effect on phenotype than does a deletion of the same segment. This is evident in the present family in which the girl, who has the duplication, is mildly to moderately retarded, whereas her brother is moderately to severely impaired. Her language ability is impaired, although markedly advanced when compared to her brother's. Her dysmorphic features are less distinct and less severe than those of her brother.

Duplication and deletion of the same segment often result in phenotypes that can be regarded as opposite, or exhibiting "type and countertype." In this family, the sister has upslanting palpebral fissures, a broad nose, full lips, and hyperextensible joints, whereas her brother has downslanting palpebral fissures, a narrow nose, thin lips, and clubfeet.

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