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A Familial X-22 Translocation with an Extra X Chromosome

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INTRODUCTION

The occurrence of X-autosome translocations in man is rather infrequently observed. This type of rearrangement is of particular interest to geneticists because of the variety of late-labeling patterns which occur as a result of inactivation of the X chromosome and because of the role this inactivation may play with respect to clinical abnormalities.

We report in this paper a family in which the long arm of a no. 22 chromosome has been translocated to the long arm of an X chromosome. In addition to the translocation, some members of the kinship also possess an extra X chromosome.

FAMILY HISTORY

The four members of the sibship (fig. 1, table 1) were examined at the request of the mother (I-2) because of behavioral difficulties and retardation. The conflict over problems relating to these children has succeeded in totally alienating the children and their mother from the other members of the family. For this reason, analysis was limited to only the individuals listed.

The mother is 35 years of age. She is mentally alert, and both she and the father (I-1) are high school graduates. She suffers from chronic anemia and has had five spontaneous abortions, all occurring in the first trimester. She is now separated from her husband, who is 39 years of age and in good health. She has 11 sibs, none of whom have had birth defects or apparent behavioral abnormalities. Seven of the mother's 11 sibs have had a total of 26 children. There was one spontaneous abortion. One of the 11 sibs has given birth to six children, some of whom are reportedly "slow learners." Due to a lack of cooperation, it has not been possible to study these children.

Sib II-1

The oldest member of the sibship is a physically well developed 12-year-old Caucasian male with obvious hyperkinesis, intellectual deficiency, and delayed psychomotor development. His birth weight was 2.8 kg. The pregnancy and delivery were uneventful, although oxygen was required for resuscitation. He sat at 6 months, crawled at 8 months, walked at 20 months, was toilet trained at 2 years, and began using single words at 3 years of age.

He was struck with a farm tractor at 18 months, sustaining fractures of the lower femur and iliac crest. A seizure associated with fever occurred at 2 years of age. He sustained

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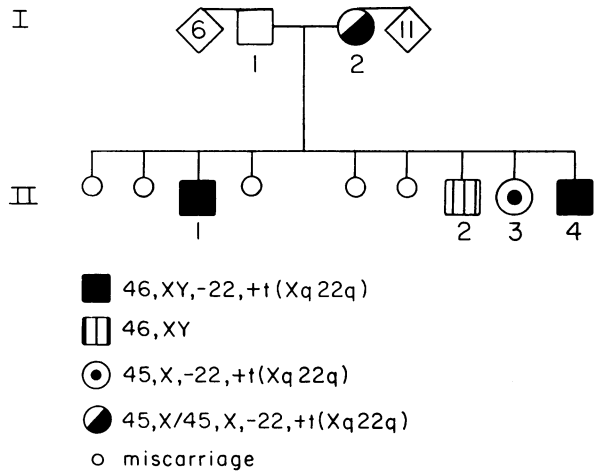

FIG. 1.—Family pedigree

TABLE 1

FAMILY DATA

Pedigree Identity	Birth Date	Karyotype	Clinical Summary
I-1	11/4/36	...	Alive and well
I-2	8/30/40	45,X/45,X,—22,+t(Xq22q)	Chronic anemia
II-1	4/17/62	46,XY,—22,+t(Xq22q)	IQ 76, hypotonia, positive Babinski, psychomotor retardation, hypogonadism (?), behavioral abnormalities
II-2	5/5/65	46,XY	Hypotonia, esotropia, IQ 128
II-3	5/15/66	45,X,—22,+t(Xq22q)	Hypotonia, motor incoordination, positive Babinski, IQ 68
II-4	9/30/69	46,XY,—22,+t(Xq22q)	Hypotonia, developmental delay, severe language delay, positive Babinski

a closed head injury in a fall at 6 years of age and as a result was disoriented for 2 hours and hospitalized for 3 days, although he did not lose consciousness nor was a fracture found on skull X-ray.

At 11½ years of age, his height was 158 cm (ninety-eighth percentile) and his weight was 47 kg (above the ninetieth percentile). No abnormalities of head size or shape and no organomegaly was detected. Heart sounds and blood pressure were normal. There were partial epicanthal folds, and the palate was high and arched. The penis was within normal size limits. The right testicle was 0.5 cm and soft; the left testicle was not palpable. Neurological examination was negative for cranial nerve abnormalities. There were bilateral Babinski reflexes and slight hypotonia. Coordination tests revealed finger-to-nose dysmetria and impaired fine movements. The patient was unable to hop on one foot. An electroencephalogram was questionably abnormal. Dermatoglyphic patterns were normal. Laboratory tests, including quantitative analysis for serum and urinary amino acids, were negative. There is a history of frequent upper respiratory infection.

He received 3 years of speech therapy and was enrolled in special education classes in public elementary school from 1967 to 1972. A full-scale IQ of 76 was obtained on the Wechsler Intelligence Scale for Children in 1971. In 1972 at age 10 years, the Peabody Picture Vocabulary Test yielded a recognition vocabulary age of 7 years and 1 month; his composite psycholinguistic language age, determined by the Illinois Test of Psycholinguistic Abilities, was 7 years and 5 months. Speech and language evaluation revealed articulation skills consistent with his age. Detailed psychological testing showed him to be distractable, easily frustrated, poorly socially oriented, and to exhibit poor achievement. Since September of 1972 he has been enrolled in a residential center for mildly retarded children with behavior problems.

Sib II-2

The second oldest member of the sibship had a normal and uneventful early development. When examined at 7 years of age, his height and weight were above the ninety-seventh percentile and his occipitofrontal circumference was 54.5 cm (ninety-eighth percentile). He had mild left esotropia and mild hypotonia. Deep-tendon reflexes were equal and active, and sensory testing was unremarkable. Muscular coordination was poor. The full-scale IQ on the Wechsler Intelligence Scale for Children was 123. Psychological testing was interpreted as indicative of a superior intelligence with perceptual difficulty.

Sib II-3

The only female member of the sibship was evaluated at 6 years of age because of poor academic achievement, withdrawn behavior, and poor speech. She was found to be a rather frail child who was reluctant to cooperate during the examination. Her height and weight were at the sixtieth percentile, and additional physical findings were likewise unremarkable. Neurological examination disclosed decreased muscle tone, normal tendon reflexes, left positive Babinski reflex, and poor coordination. The electroencephalogram was a normal wake tracing. During the examination, the child had two episodes of cessation of activity with staring and pupillary dilation which lasted 5–10 seconds. At age 5 a Stanford-Binet test yielded an IQ of 68.

Sib II-4

The youngest member of the sibship was seen for pediatric examination at 3 years of age. He was still using single words only and had exhibited delayed milestones: he sat at 9–12 months of age, walked at 16–18 months, and used single words at 2 years. His weight and height were between the ninetieth and ninety-seventh percentiles. His head circumference was at the fiftieth percentile. He appeared tired, and the left side of his head was more prominent than the right.

Partial epicanthal folds were noted; dermatoglyphic patterns were normal. The testes were approximately 0.5 × 1.0 cm and firm. Metabolic screening, including tests for amino acids, ketoacids, and mucopolysaccharides, was normal. His newborn examination had been normal with a 5-minute Apgar score of 10.

Neurological exam revealed hypotonia and a right Babinski sign. A normal electroencephalogram was obtained. The skull X-ray was normal.

Psychological testing at 3¾ years of age proved impossible because of very poor language development; no score was obtained on the Stanford-Binet for this reason. The Peabody Picture Vocabulary Test indicated an IQ of 80.

CYTOGENETIC RESULTS

Chromosome preparations were obtained from peripheral blood according to a modification of the method of Moorhead et al. [1]. Essentially all cells analyzed from cultures of the oldest sib (II-1) contained 46 chromosomes, although they

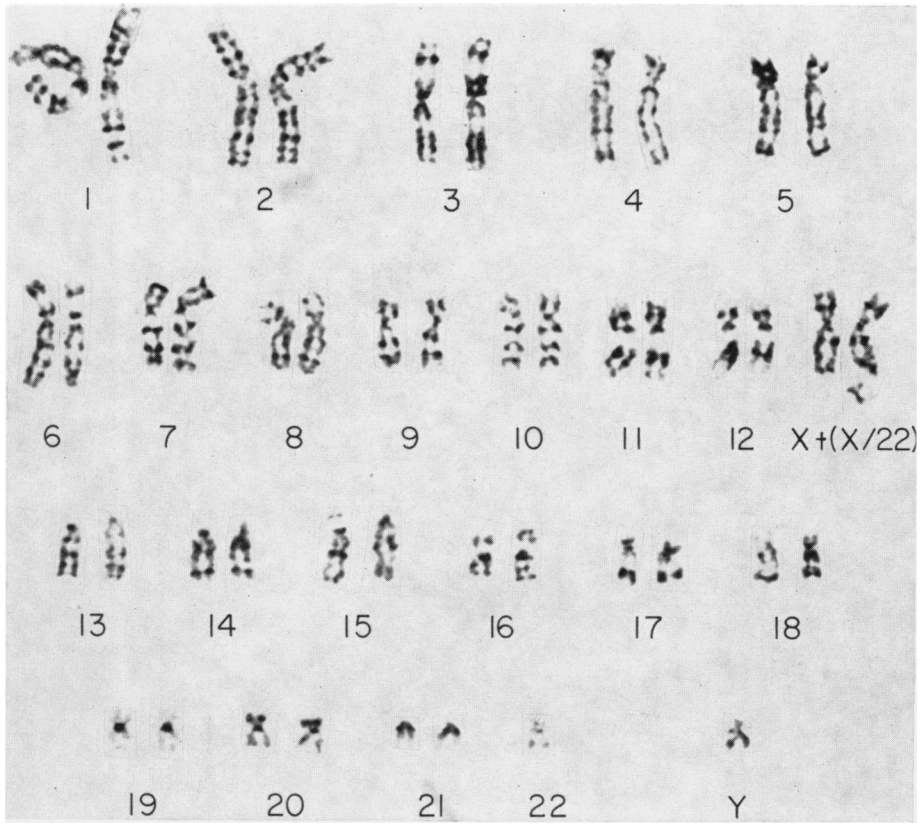

FIG. 2.—Giemsa banding in karyotype of oldest sib. Translocation involves long arm of chromosome no. 22 translocated to long arm of an X [46,X,—22,+t(Xq22q)].

lacked a G-group chromosome and had an additional B-group chromosome. Giemsa banding, following the method of Seabright [2], demonstrated that the extra B-group chromosome resulted from the translocation of essentially the entire long arm of chromosome 22 to the terminal portion of the long arm of an X chromosome (fig. 2). The G banding also showed that the cells contained a normal X and a Y chromosome in addition to the X involved in the translocation. The karyotypic designation is 46,XY,—22,+t(Xq22q) or, more specifically, 46,XY,—22,+t(X;22)(q28;q11). Fluorescence microscopy studies supported these findings.

A buccal smear showed 28% of the cells to have a well-defined sex chromatin body of normal size.

The karyotype of the youngest sib (II-4) was the same as that of the oldest. Autoradiographic studies were done on lymphocyte cultures following a procedure essentially like that of Schmid [3]. A total of 57 metaphases with informative labeling were selected for analysis. In all 57 cells, the X involved in the translocation was the late-replicating X chromosome. In 44 of these cells, only the X portion was

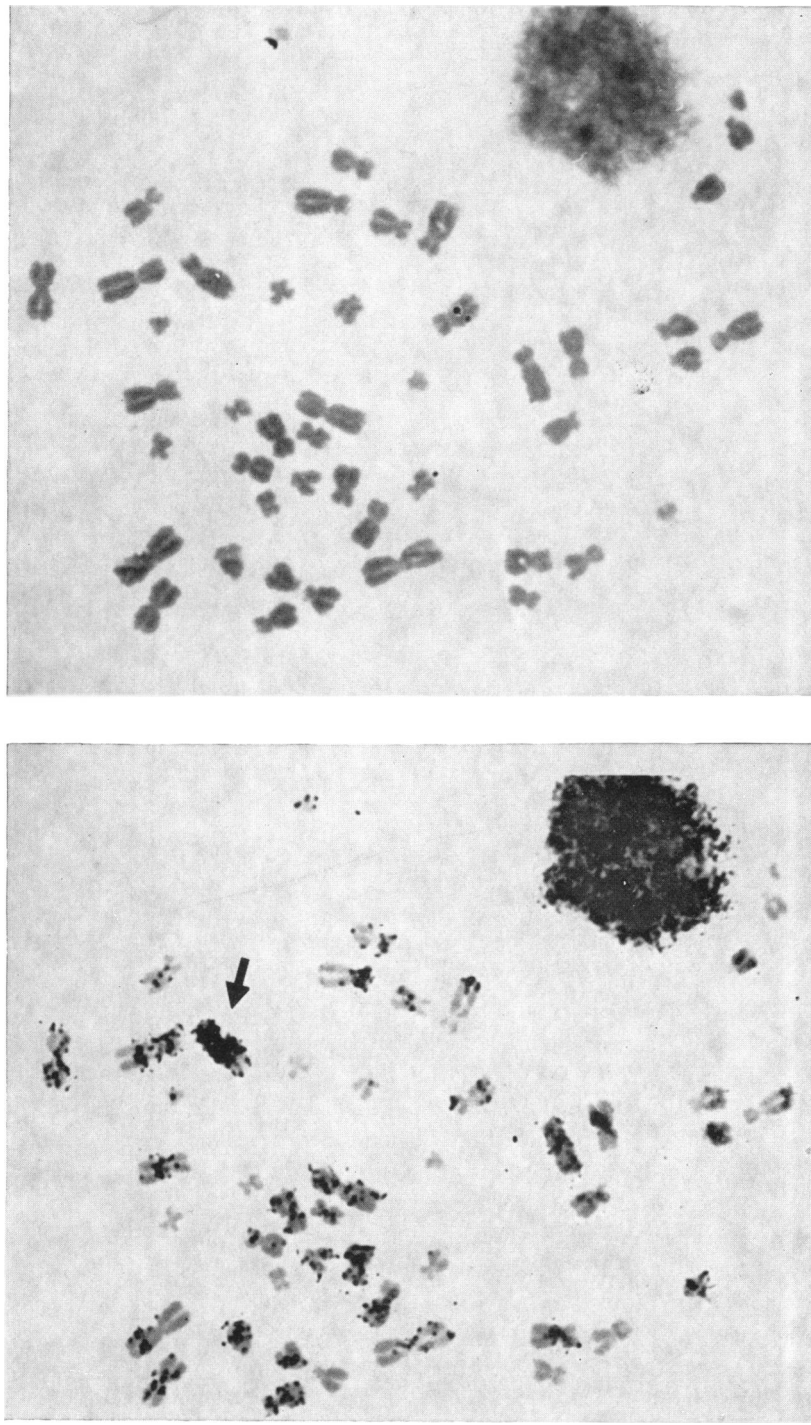

FIG. 3.—Labeling pattern in a cell from youngest sib showing late replication of X portion of translocation chromosome and early replication of autosomal portion.

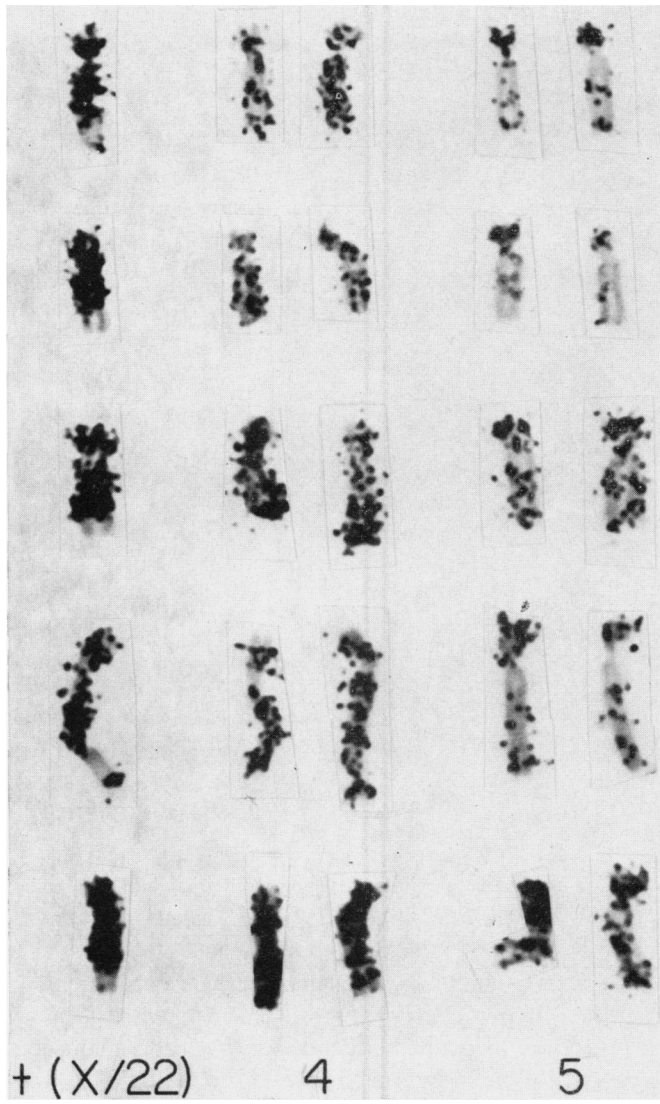

FIG. 4.—Labeling pattern of several B groups including translocation chromosome showing details of labeling of translocation chromosome observed in 77% of cells examined.

late replicating; the chromosome 22 portion was early replicating (figs. 3 and 4). Of the remaining 13 cells, the autosomal segment of the translocation chromosome was labeled in eight, although not as heavily as the X portion; and in five, the autosomal segment was so heavily labeled that the entire translocation chromosome could be considered late replicating (fig. 5). A similar autoradiographic pattern was observed in the oldest sib, although an extensive study was not performed.

The karyotype of the second oldest sib (II-2) was normal. The only female in

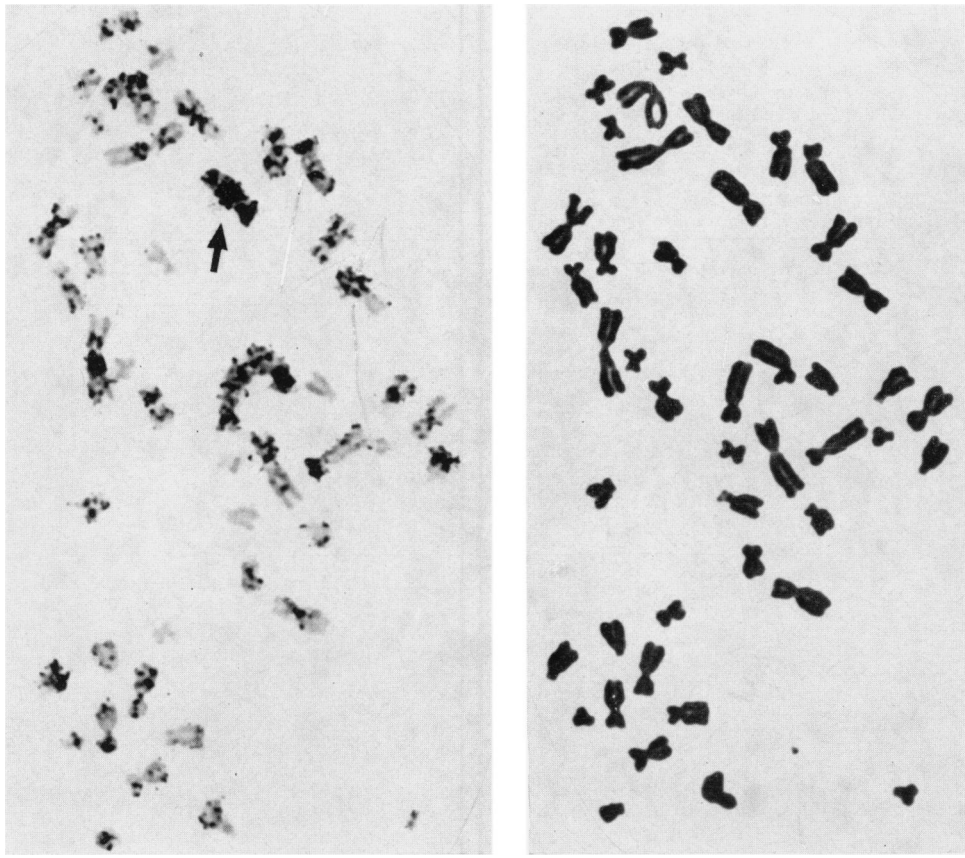

FIG. 5.—Late-labeling pattern in a cell from youngest sib showing late replication of entire translocation chromosome (observed in 5% of cells examined).

the sibship (II-3) was found to be a carrier for the translocation 45,X,—22,+t(Xq22q).

The mother (I-2) was found to be a mosaic with two cell lines. Of 114 cells analyzed from repeated lymphocyte cultures, 31 exhibited the carrier complement 45,X,—22,+t(Xq22q), while the remaining 83 were lacking an X (45,X). Eighty-four cells were also analyzed from multiple skin fibroblast cultures. All were apparently representative of a single cell line, that of the carrier state 45,X,—22,+t(Xq22q). Autoradiography was not performed on the mother or her carrier daughter. It is assumed that since these individuals are chromosomally "balanced," their normal X chromosome is late replicating, which is almost always true in such cases (see below).

DISCUSSION

Late-replicating behavior of the X-chromosome in man is markedly influenced

by structural changes. In rearrangements such as rings [4], deletions [5], and isochromosomes [6], the abnormal X rather than the normal X is invariably the late-replicating chromosome. However, when the X is involved in a translocation, a variety of late-replication patterns occur.

Although the number of cases of X-autosome translocations is still relatively small, certain generalizations are becoming more obvious. In most cases where the X chromosome material is translocated to an autosome the karyotype is "balanced," and the normal X is late replicating. This has been demonstrated in earlier reports, summarized by Cohen et al. [7], as well as in more recent reports [8, 9]. Summitt et al. [10] have reported such a balanced X-21 translocation in a mother whose normal X is late replicating. Her daughter, however, has an unbalanced karyotype, 46,XX,t(X;21), and the entire translocation chromosome is usually late replicating. Thus, although X-dosage compensation is maintained, the daughter is monosomic for the 21 chromosome involved in the translocation.

In cases where a portion of an autosome is translocated to an X chromosome, the X portion of the translocation chromosome is usually late replicating while the autosomal segment may be consistently late replicating (e.g., [11]) or early replicating (e.g., [7, 12]). In other instances, however, the normal X is late replicating exclusively [13], while in still others there is random inactivation of the normal and translocated X chromosomes [14].

The autoradiography in the present study showed that in most cells only the X portion of the translocated chromosome was late replicating, while in other cells either the autosomal segment was late replicating or it appeared as though the autosomal segment was partially late replicating. Studies in mice have shown variegated effects presumably due to inactivation of autosomal genes translocated to the X chromosome [15]. The variable degree of inactivation of these autosomal genes suggests only partial inactivation of the autosomal segment. Such partial inactivation may account for the patterns of replication seen in this study, patterns which vary from what appears to be complete early replication, to partial late replication, to complete late replication of the translocated autosomal segment. Such a varying degree of inactivation of the autosomal segment in the more severely affected sibs might account in part for their abnormalities, since some cells would then be monosomic for portions of the no. 22 chromosome. It is also possible that the deletion of the centromeric region and short arm of chromosome 22 is related to the clinical picture in the family, but the lack of clinical involvement of the mother tends to make this less tenable.

An alternative explanation for a part of the behavioral and learning difficulties in the two retarded male sibs is the possession of an extra X chromosome leading to features of Klinefelter's syndrome [16]. However, since all the sibs have some common abnormalities, both mental and physical, the extent of deleterious effect due to the additional X (or, as mentioned above, to partial monosomy for chromosome 22) is impossible to determine.

The presence of the extra X chromosome in the two male sibs is of interest as it relates to the process of disjunction. Since the mother is a "balanced" carrier, the

occurrence of the extra X chromosome in the two sibs probably arose by common segregation during oogenesis of both the normal and translocation X from a triradial configuration. This triradius would include the normal X, the translocation X, and the no. 22 chromosome. Subsequent fertilization of an egg containing both the normal and translocation X by a normal Y-bearing sperm would produce the chromosome complement observed in the two sibs. This type of segregation has been shown to occur in carriers "balanced" for a 13-15/21 translocation [17]. Fertilization of other genetically imbalanced eggs with monosomy or trisomy 22 would account for the numerous abortions experienced by the mother.

Also of interest is the mosaicism observed in the mother. This could have arisen from a normal fertilized egg by loss of an X chromosome during the initial cleavage followed by the X-22 translocation in the 46,XX cell at the subsequent cell division. The two resulting cell lines would have then had to contribute unequally to the primary embryonic germ cell derivatives in order to give the unusual mosaic pattern. Ridler et al. [18] have observed a similar mosaic dichotomy between skin and leukocyte chromosomes in a case of Down's syndrome.

SUMMARY

A family is described with a chromosomal rearrangement involving translocation of the long arm of a no. 22 chromosome to the long arm of an X [t(Xq22q)]. The carrier state 45,X,—22,+t(Xq22q) is present in the mother and her daughter, and two sons possess the translocation chromosome plus an extra X chromosome [46,XY,—22,+t(Xq22q)]. Autoradiographic analysis indicates that the X portion of the boys' translocation chromosome is late labeling, while the autosomal portion tends to be early replicating. These abnormalities are discussed in relation to clinical involvement.

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