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Aneusomy by Recombination

A possible example involving the E18 chromosome

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Several abnormalities involving the E18 chromosome are known including complete trisomy, partial trisomy and partial monosomies. An unusual patient with the apparent combinations of partial monosomy and partial trisomy for the E18 chromosome is reported here. It is proposed that the chromosome anomaly in this child represents an instance of " aneusomy by recombination ".

Case Report

B.D., the five year old daughter of Indian national parents, was evaluated at the Children's Diagnostic and Development Center of Georgetown University Hospital because of growth and developmental retardation.

B. was the product of an uncomplicated 42-week gestation with a weight of 3 120 gm. At the time of the patient's birth, the mother was 24 and the father 33. The infant's face was noted to be different from that of her two older siblings, the nose being slightly broad and flared. Growth was slow during infancy, weight being 5 400 gm at one year; and developmental milestones were also retarded. She sat unsupported at one year, pulled to a stand at 22 months, and walked alone at 27 months. She began saying single words at 2 years, imitated words at 3 years, and began speaking in simple sentences at 4½ years of age. She has always been quiet and wellbehaved and presents no behavior problem to the parents. External strabismus and a heart murmur were noted previously but not fully evaluated. The family history is negative for consanguinity, mental retardation, developmental delay, or metabolic diseases. The parents and two older siblings are healthy and above average in intelligence. Spontaneous abortions and stillbirths are denied.

Physical examination revealed a small, slender, poorly developed 5 year old girl with a weight of 12.68 Kg, and a height of 94.6 cm, both figures below the third percentile with the weight-age lower than the height-age. The head circumference was 48.2 cm, with the occiput being prominent. The face was symmetrical, the ears were moderately low-set, the nose was flared, and underdevelopment of the mid-face area was noted. A divergent

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alternating strabismus was present. The hairline was low on the forehead and neck, and midline hirsutism was present on the back. The palate was long and high-arched. The chest was symmetrical with moderate pectus excavatum, and the thoracic spine was mildly scoliotic toward the right. A grade II systolic murmur was heard diffusely over the precordium and in the back. Dimples were present on the dorsum of the hands over the metacarpal-phalangeal joints. The second and fourth toes overlay the third toes on both feet, and bilateral pes planus was present. There was hypermobility of both acromio-clavicular and sterno-clavicular joints allowing close approximation of the shoulders anteriorly.

Neurological examination revealed speech and motor coordination characteristic of a 3 or 4 year old child, but hypertonicity was not present. An EEG was abnormal with diffuse slowing and paroxysmal high voltage rhythmical activity. Developmental testing revealed fine motor performance in the two to three year level with slightly higher social adaptive functioning. Psychiatric examination revealed emotional immaturity and delayed development.

Laboratory studies included a normal blood count, urine analysis and blood urea nitrogen. The protein bound iodine was 21.7 ug% and 19.5 ug% on two occasions, the 24 hour I-131 uptake was 5% at two hours and 12% at 24 hours, and the T-3 uptake was 39.9%, findings best explained by iodine ingestion despite a negative history. Urine and blood amino acids were normal. A buccal smear was chromatin positive. Bone age by X-ray was 2 years. Cardiac catheterization confirmed the presence of an atrial septal defect most likely of the secundum type with stenosis of the main pulmonary trunk and right main pulmonary branch without pulmonary hypertension. The cardiac abnormality was not believed to be a cause of delayed growth or development.

Dermatoglyphic Findings

Examination revealed axial triradii in the t' position with displacement to the ulnar side, absence of hypothenar and thenar patterns, and distal loop in the third interdigital areas on both hands. On the left hand an ulnar loop was present on the thumb, a double loop on the index finger, an ulnar loop on the third, a simple whorl on the fourth, and concentric rings on the fifth finger. On the right hand, an ulnar loop was present on both the thumb and index finger, a double loop on the third, a simple whorl on the fourth, and an ulnar loop on the fifth finger. On the feet distal loops were present in both hallucal areas. Flexion creases were usual with no transverse palmar crease present.

Cytogenetic Findings

Leukocytes of the patient and her mother were examined. Other family members were not available for the interview or laboratory studies. Chromosome counts were performed on photographic enlargements of 50 metaphases obtained from two blood samples taken approximately two weeks apart.

Forty-six chromosomes were present in 46 metaphases, while three had 45 and one had 44 chromosomes. Twenty metaphases, 10 of each sample, were karyotyped. All karyotyped cells had an apparent XX sex chromosome constitution with all the chromosomes showing the usual morphology with the exception of one E group chromosome. One member of a homologous pair, believed to be E18, was smaller than its homolog in all cells examined.

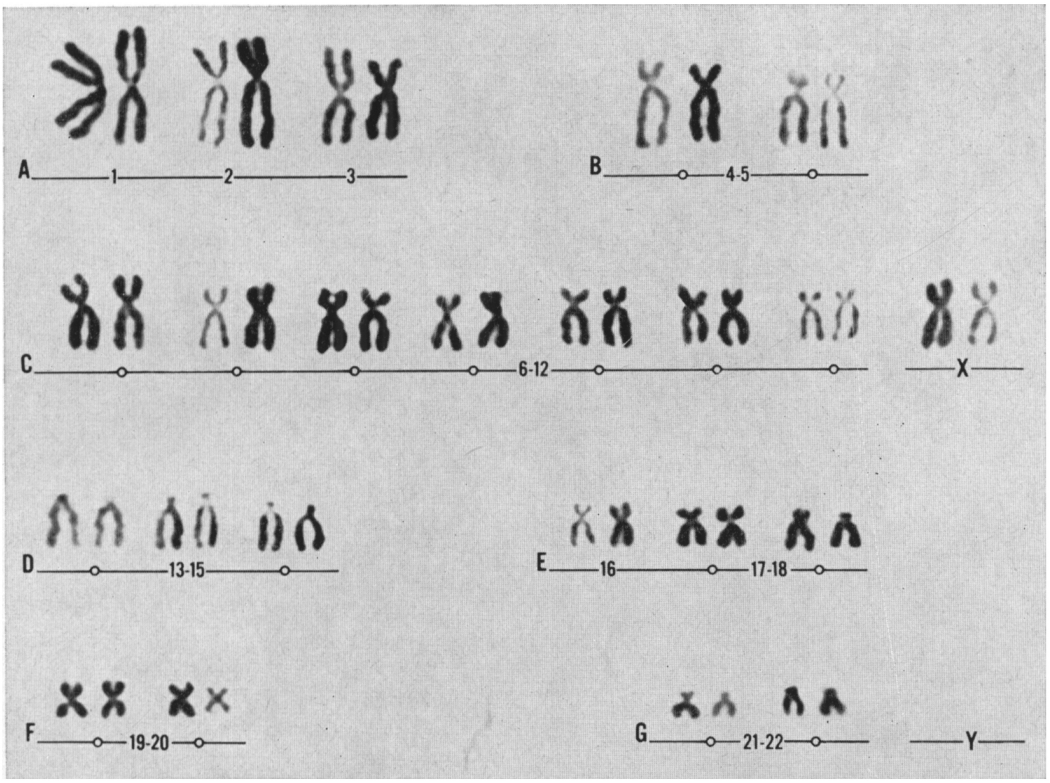

Fig. 1. Karyotype of the patient revealing abnormal E-18 chromosome.

It appeared that about 50% of the short arm was missing with an equal amount of genetic material missing from the long arm (Fig. 1). This finding was consistent in all good quality metaphases examined.

In the mother chromosome counts were made on 25 metaphases and karyotypes were prepared from 15 cells. No evidence was obtained for numerical or structural aberrations.

Discussion

The chromosomal finding in the present report can be explained in several ways. One of the simplest mechanisms would involve deletion of a segment of the short arm (Fig. 2*a*) or deletion of a segment of the long arm (Fig. 2*b*) followed by pericentric inversion. These rearrangements would require three breaks on the chromosome. A two-break mechanism, which would be a deletion of the terminal segments of both arms (Fig. 2*c*), is unlikely because this would probably result in a ring-chromosome formation. The next mechanism, in order of increasing complicacy, would involve three breaks followed by a shift of the interstitial segment from the

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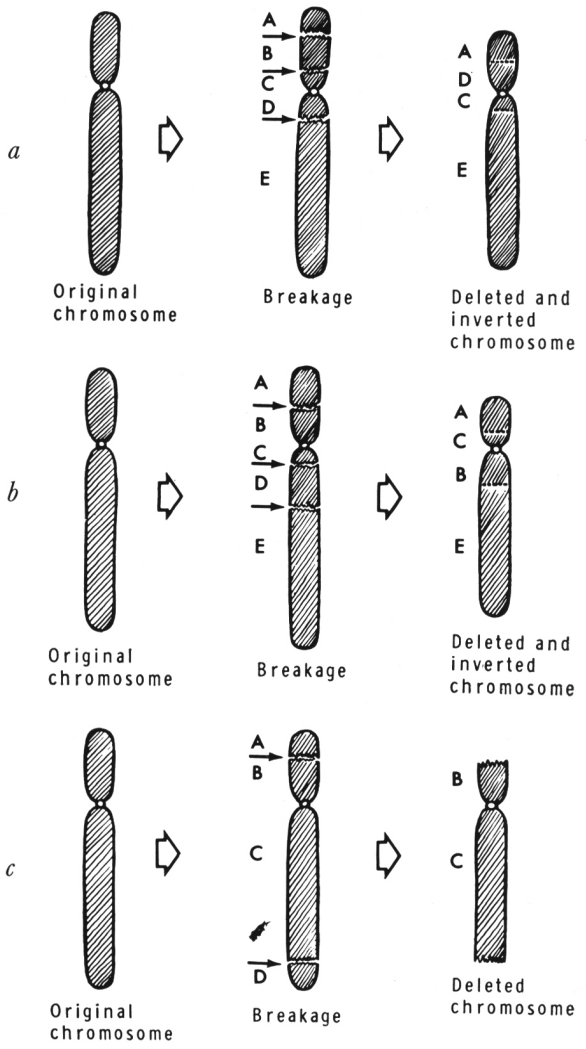

Fig. 2 (*a*, *b*, and *c*). Diagrammatic representations of some of the mechanisms by which simultaneous reduction in length of both arms of a chromosome might occur.

short arm to the long arm and attachment in inverted fashion (Fig. 3). During meiosis crossing-over within the shifted segment would result in the production of four different gametes with the smallest meiotic product resembling the abnormal chromosome of our patient. On the basis of the above mechanism, the abnormal chromosome is deficient for about one-third of the terminal segment of the long arm (marked segment E) and has an additional dose of a short terminal segment of the short arm, marked segment A. Thus our patient would be monosomic for a terminal segment of the long arm and trisomic for a terminal segment of the short arm.

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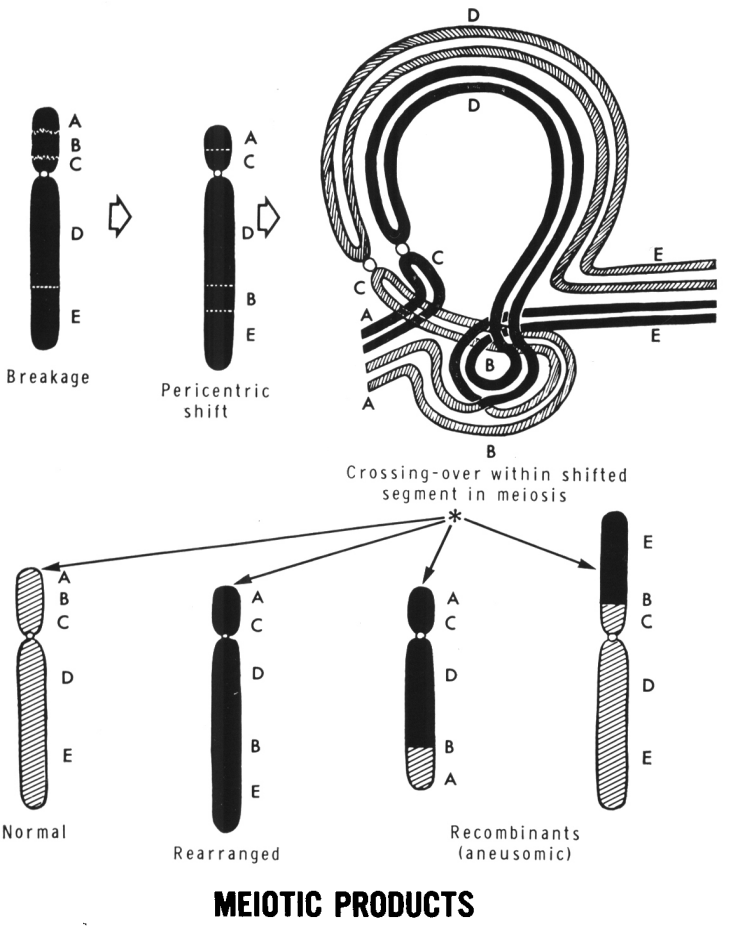

Fig. 3. Diagrammatic representation of the proposed mechanism of " aneusomy by recombination " during meiosis resulting in simultaneous reduction in the length of both arms of the chromosome.

One further mechanism that may be considered would involve reciprocal translocation. If a small segment of the short arm of one E18 chromosome is exchanged with an even smaller segment of the long arm of another E18 (or, in fact, any other larger chromosome) the short arm of one E18 would be noticeably smaller and the long arm of the other chromosome would be slightly longer. The size difference in the long arm, however, would not be expected to be noticeable by conventional cytogenetic technics. Also no genetic material would be deficient or in excess and one would have to assume that either (1) the presence of the clinical findings and the cytogenetic anomaly are coincidental and therefore not related, or (2) the clin-

ical findings are related to position effect (for which convincing evidence in man is lacking). Furthermore if one entertains this possibility the consistently observed size-differences in the long arms of the E18 chromosome pair would need further explanation.

In the child reported here the presence of mental retardation, short stature and low-set ears are compatible with long arm deletion, as are the congenital heart defect, mal-set toes, mid-face hypoplasia, and relatively high incidence of whorls (2-6, 8-12). The prominent occiput could be the result of partial short arm trisomy. The rest of the findings have been encountered in cases of long arm deletion and/or in E18 trisomy (Bartalos and Baramki, 1967). It is tempting to speculate that the absence of some commonly observed signs of partial long arm deletion in our patients could be due to the deletion of a relatively small segment as compared with other reported cases. This would imply that gene loci responsible for such traits are located closer to the centromere on the long arm. The missing signs to which this could apply include narrowing of the auditory canal, middle-ear defects, long and tapering fingers, nystagmus, carp-mouth, optic atrophy and umbilical hernia. It must be realized, however, that speculations of this kind are full with fallacies and, for the time being, must be regarded strictly as speculation.

The mechanism proposed here as the most likely explanation for the cytogenetic and clinical findings is referred to as " aneusomy by recombination " (Lejeune and Berger, 1965). This mechanism could have happened during meiosis in one of the parents or the unexamined father may be a carrier of a balanced rearrangement involving the E18 chromosome. The fact that in the family there is no history of spontaneous abortions, stillbirths, or similarly affected persons makes a paternal carrier state unlikely although not disproven. The most likely assumption is that the structural rearrangement occurred in the gametic cell line of one of the parents before the stage of homologous pairing.

Summary

A 5 year old female child is described with mental and growth retardation, prominent occiput, low-set ears, moderate mid-face hypoplasia, congenital heart defect, mal-set toes, and a relatively high frequency of whorls on the fingers. The abnormal E18 chromosome found is thought to represent a partial deletion of the long arm with trisomy for a small terminal segment of the short arm as the result of a pericentric shift followed by crossing-over within the inverted shifted segment. Thus this case may represent a further example of " aneusomy by recombination ".

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RIASSUNTO

Viene descritta una bambina di 5 anni con ritardo fisico e mentale, occipite prominente, orecchie basse, moderata ipoplasia mascellare, difetto cardiaco congenito, dita dei piedi male impiantate ed elevata frequenza di vortici sulle dita. Si ritiene che il cromosoma anomalo E18 riscontrato rappresenti una delezione parziale del braccio lungo con trisomia per un piccolo segmento terminale del braccio corto, come risultato di una deviazione pericentrica seguita da crossing-over nell'ambito del segmento invertito deviato. Anche questo caso può rappresentare un ulteriore esempio di « aneusomia per ricombinazione ».

RÉSUMÉ

Les auteurs décrivent une enfant, âgée de 5 ans, avec retard physique et mental, proéminence occipitale, oreilles basses, modérée hypoplasie maxillaire, vice cardiaque congénital, extroversion des orteils et haute fréquence de tourbillons sur les doigts. On pense que le chromosome anormal E18 trouvé représente une délétion partielle du bras long avec trisomie par un petit segment terminal du bras court, comme résultat d'une déviation péricentrique suivie par crossing-over dans le segment inverti dévié. Ce cas aussi peut représenter un exemple d'« anéusomie par recombinaison ».

ZUSAMMENFASSUNG

Beschreibung eines 5-jährigen, körperlich und geistig zurückgebliebenen Mädchens mit Occiput prominens, tiefstehenden Ohren, mässiger Hypoplasie der Maxilla, angeborenem Herzfehler, falschem Zehenansatz und erhöhter Anzahl Wirbel auf den Fingern. Man nimmt an, dass das anomal gefundene Chromosom E18 eine Teil-Deletion des langen Schen-

kels mit Trisomie eines kleinen Terminalsegment des kurzen Schenkels darstelle, als Ergebnis einer perizentrischen Deviation auf welche ein Crossing-over innerhalb des invertierten abgeleiteten Segments erfolgte. Auch dieser Fall kann ein weiteres Beispiel von « Aneusomie durch Rekombination » darstellen.

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