Case Reports


Non-disjunction of an unusual X chromosome

Summary. Because of multiple abnormalities in her children, a young woman was investigated and found to have a 47,XXX chromosome constitution. Additional C group chromosomes without visible centromeric constrictions were found in a number of cells from the peripheral blood, and using C and Q banding techniques these chromosomes were identified as X chromosomes. Analysis of the banding karyotypes of 300 cells revealed that the acentric X chromosomes had the ability to replicate and that this replication was associated with non-disjunction leading to aneuploid cells. Even though cultured skin cells did not have acentric or extra chromosomes in addition to the triple-X, examination of buccal mucosa cells for the presence of X-bodies suggested that the phenomenon of non-disjunction was present in the epithelial cells of the patient. In addition to the X without a visible centromeric constriction, either acentric D or E chromosomes were found. The data suggest that a functional defect in the cells per se is responsible for the appearance of the acentric chromosomes.

Makino and Sasaki (1964) first described unusual C group chromosomes without visible centromeric constrictions in a case of myelocytic aleukaemic leukaemia. Mori et al (1969) reported similar chromosomes in a mother of an 18-trisomy baby and acentric C-like chromosomes were found by Bloom et al (1967) and by Honda and Sofuni (1969) in the cells of a normal female population. Furthermore, C and E group chromosomes with similar acentric morphology were found by Yoshida (1970) in a human diploid leucocyte cell line. From the size of these unusual C group chromosomes, it could be inferred that they were of the same origin; however, since no banding analysis of these chromosomes was made, uncertainty existed regarding their exact origins.

We have found similar acentric chromosomes in a triple-X mother who was investigated because of multiple abnormalities in her children. The present paper reports the detailed study of the chromosomes, including results with banding techniques.

Case Report

The proposita, a 30-year-old white woman, was ascertained through a Pediatric Clinic where her third child was being treated for minor infections and apparent malnutrition. She was found to be a somewhat ineffectual mother of low-normal intelligence though this has not been formally tested. She was severely myopic and her general appearance was unusual. Her face appeared asymmetrical and the lower jaw was prognathous. She was slender (wt. 50 kg and ht. 169 cm) and her extremities were very thin, with long fingers and toes, hypermobility of the knees, and high arched feet. There was striking dorsal kyphosis. Thus, some physical features resembled Marfan’s syndrome, but the cardiovascular system was normal.

Her first child was a premature girl who died 22 hours after birth. Though facial features suggestive of Down’s syndrome were recorded, no evidence of the syndrome was recorded at necropsy and no chromosome investigation was carried out. Her second child was a premature boy who had congenital heart disease, including tetralogy of Fallot with pulmonary stenosis. He died after open heart surgery when he was 2½ months old. The third child was also a premature boy who showed retarded motor development, but was shown to have a 46,XY normal male karyotype.

The proposita was married to a 27-year-old white man of low intelligence who had been raised in institutions because of parental inability to care for him. He was able to maintain his family by working as a hospital cleaner. Though he showed an abnormally prominent forehead, and a high arched palate, no more specific abnormalities were present. His karyotype was 46,XY normal male.
Results and discussion

The chromosome numbers in skin and blood cells are shown in Table I. The modal karyotype of the patient was 47,XXX in both the blood and skin cultures. In cells with more than 47 chromosomes, in addition to the extra X chromosome, all the extra chromosomes seen in the blood cultures belonged to the C group. No such extra chromosomes were found in 100 cells from the skin cultures. Usually, acentric C chromosomes were seen in cells from the blood cultures with more than 47 chromosomes. The Q banding pattern of the acentric chromosomes was identical to that of the X’s and more than one such chromosome was observed in some cells (Fig. 1). Even though these chromosomes did not have centromeric constrictions, C banding showed darkly stained spots on both sides of the chromatids (Fig. 2). The origin of the acentric chromosome was apparently the X. To investigate the genesis of the acentric X chromosomes, 300 cells were karyotyped. Of these, 17 cells had over 47 chromosomes, while 6 cells had missing chromosomes (Table II). All the extra chromosomes in the 17 cells were identified as

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<tr>
<th>TABLE I</th>
<th>CHROMOSOME NUMBERS OF CULTURED CELLS IN PRESENT CASE</th>
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<tbody>
<tr>
<td>Date</td>
<td>Chromosome No.</td>
</tr>
<tr>
<td>---------</td>
<td>----------------</td>
</tr>
<tr>
<td>Blood, 10 May '74</td>
<td>2 4 227 13 3 1</td>
</tr>
<tr>
<td>Blood, 3 July '74</td>
<td>1 6 100 3 1</td>
</tr>
<tr>
<td>Blood, 6 Nov. '74</td>
<td>4 95 1</td>
</tr>
<tr>
<td>Skin, 3 July '74</td>
<td>2 1 88 4</td>
</tr>
</tbody>
</table>

Materials and methods

Peripheral blood cultures from the proposita were set up on 10 May, 3 July, and 6 November 1974 (Table I) and the cultures were harvested after 3 days. Skin cells were cultured from one biopsy set up on 3 July 1974. A routine air-dry technique was applied to all of the chromosome preparations. Chromosomes were first examined with conventional Giemsa staining and subsequently with newer banding techniques. Q-banding was performed by the method of Caspersson, Zech, and Johansson (1970) and C-banding according to Sumner (1972).

![Fig. 1. Q banding karyotype of an aneuploid cell from the patient. Note 3 extra acentric like X chromosomes in addition to the 47,XXX chromosomes.](http://jmg.bmj.com/321/10.1136/jmg.13.4.320)
acentric X chromosomes or normal X chromosomes, even when more than one such extra chromosome was found in a cell. On the other hand, the missing chromosomes in 6 cells were No. 5, No. 14, No. 17, No. 20, No. 22, the X, and one unknown. There was no relation between these two groups. The results indicate that the acentric chromosomes can replicate and that this replication is associated with non-disjunction leading to cells with 49 or 50 chromosomes. In some cells, as mentioned above, the extra X chromosomes had centromeric constrictions. This suggests the capability for developing centromeric constriction in the acentric chromosomes in daughter cells. In addition, to the X without a centromeric constriction, small acentric chromosomes belonging either to D or E groups were found in one cell each, respectively. Therefore, the appearance of the acentric chromosomes seemed to be a functional defect of the cells per se, rather than of the X chromosomes.

The presence of an X chromatin body was ascertained in 300 cells from the buccal mucosa of the patient. Of these, 110 cells were without an X body, 187 cells with one or two X bodies, and 3 cells with three X bodies (Fig. 3). Thus, it appears that cells with extra, acentric X chromosomes did exist in the epithelial tissue of the patient in vivo, in addition to the extra, normal X, though neither acentric chromosomes nor extra chromosomes were found in the cultured skin cells. Probably, non-disjunction of the acentric X chromosomes occurred in this patient's epithelial cells.

To examine the DNA replicative pattern of the acentric X-chromosomes, cultures with tritium-labelled thymidine were set up with blood cells obtained from the patient at the last examination. Unfortunately, we could not obtain successful results, since only one acentric X chromosome was found in 100 cells in the control cultures without the isotope. However, shortly after the second

<table>
<thead>
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<th>TABLE II</th>
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<tr>
<td>MISSING OR ADDITIONAL CHROMOSOMES SEEN IN 300 KARYOTYPED CELLS</td>
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</table>

<table>
<thead>
<tr>
<th>No. of chromosomes</th>
<th>45</th>
<th>46</th>
<th>47</th>
<th>48</th>
<th>49</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cells</td>
<td>2</td>
<td>4</td>
<td>277</td>
<td>13</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Missing (−) or additional (+) chromosomes</th>
<th>− No. 17</th>
<th>− No. 20</th>
<th>− No. 5</th>
<th>None</th>
<th>All</th>
<th>+XX</th>
<th>+XXX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>− No. 14</td>
<td>− No. 22</td>
<td>− X</td>
<td>cells +</td>
<td>+XX</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Dual karyotype by conventional Giemsa staining (top) and by G banding (bottom) of an aneuploid cell from the patient. Note no visible centromeric constrictions (top) and darkly stained spots (bottom) on both sides of the chromatids of 3 unusual X chromosomes.

Fig. 3. Acetic orcein stained cells from the buccal mucosa of the patient, showing 2 and 3 X bodies in each cell.
examined of the chromosomes, the patient had been surgically sterilized under thiopentone sodium and nitrous oxide anaesthesia, and it is possible that this stress may have led to the disappearance from the blood of lymphocytes with the chromosomal abnormalities. Since these cells will probably reappear, we hope to repeat the autoradiographic studies in the future.

We are indebted to Dr Cynthia Clayton, Department of Pediatrics, State University of New York at Buffalo, for referring this family for investigation. We thank Professor Motomichi Sasaki, Associate Professor Michihiro C. Yoshida (Hokkaido University, Sapporo, Japan) and Dr Takeo Honda (Atomic Bomb Casualty Commission, Nagasaki, Japan) for information about the acentric like chromosomes, and Miss Christine Hanson for clerical assistance. The work was supported in part by Cont. C-40084 from the Birth Defects Institute of the New York State Health Department and by the Regional Genetic Program of the Lakes Area Regional Medical Program.

I. Hayata,* M. Oshimura,* Michelle J. Marinello,† R. M. Bannerman,*
*Roswell Park Memorial Institute
†Medical Genetic Unit, Department of Medicine, State University of New York at Buffalo, Buffalo, New York 14203, USA

References

Reciprocal translocation, 4q-; 21p+, giving rise to Down’s syndrome

Summary. A reciprocal translocation is described, t(4;21)(q27;p11), which occurs in a balanced carrier mother and her Down’s syndrome child, 47,XX,t(4q-;21p+),+21. A review is presented of Down’s syndrome associated with reciprocal translations involving chromosome No. 21.

The usual translocations involved in Down’s syndrome are Robertsonian translocations between chromosome No. 21 and other acrocentrics. However, a growing number of reciprocal translocations involving chromosome 21 have been discovered in individuals with Down’s syndrome, and the question of the possible role of such rearrangements in causing nondisjunction has arisen.

The purpose of this report is to describe a translocation between the long arm of a No. 4 chromosome and the short arm of chromosome 21, t(4q-;21p+), in a mother and her Down’s syndrome child, and to review the results from other Down’s syndrome kindreds where diverse reciprocal translocations involving G group chromosomes have been described.

Case report

The propositus was born in May 1973, the first child of American Indian parents. Both parents were healthy and the pregnancy and delivery were uneventful. The mother was a 29-year-old primagravida.

Examination at birth revealed epicanthal folds, a simian crease on the right hand, flat nasal bridge, and generalized hypotonia. Motor development was delayed; at 7 months of age the child was unable to sit but could roll over. Physical findings at age 13 months included coarse facies, with protruding tongue, mongoloid slant of the eyes, broad stubby hands, and hypotonia. Her height was 72 cm, weight 9 kg, and head circumference 43 cm (below the third centile). There were no Brushfield spots, no detectable heart abnormality, and the remainder of the examination was unremarkable.

Dermatoglyphic analysis showed a simian crease on the right hand. The palmar triradii were distally located on both hands with adl angles of 79° and 82°. There were interdigital loop IV patterns on both palms and, in addition, a loop III on the right palm. There was a hypotrichar loop on the left hand. Both fifth fingers had two creases. There were nine ulnar loops