A Family Apparently Showing Transmission of a Translocation Between Chromosome 3 and One of the 'X-6-12' or 'C' Group*

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The propositus (III.7 in the diagrammatic pedigree Fig. 1) was born in hospital on September 10, 1956 after an uneventful pregnancy lasting 39 weeks and a normal labour lasting 5 hours. Although nothing untoward was noticed at birth, within a few days it was noted that she was rather flaccid and seldom opened her eyes. Subsequently her mother was worried at her 'lifelessness' and suspected that she had mongolism. Between the ages of 3 months and 3½ years the child was investigated at 3 different hospitals, and at each the mother was told substantially the same, namely, that she was definitely not a mongol, but that she was not progressing as quickly as she should and was likely to be mentally retarded.

The child was able to sit unaided at about 21 months and walked without support at about 2 years and 3 months. Bladder control was established at about 3 years. At 4 years and 3 months she had an epileptic fit. Mild seizures recurred at decreasing intervals, and she has had only one fit in the last year.

Early in 1961 the family moved to the Oxford area and the child was seen by Dr Victoria Smallpeice. She has been under observation since then. In 1962 she began to attend a day school for severely retarded children at Borocourt Hospital.

At 7 years, she is a chubby child, 3 ft 9½ in. (115 cm.) in height which is more than one standard deviation below the mean for her age. Her head circumference is 21 in. (22 cm.) which is just over average for her age. Fig. 2 and 3 show her appearance. She has a dull, rather expressionless, face and an alternating strabismus. Her fundi are normal. Her neck is short with some webbing, and she has a high arched palate. There is genuvalgum, pes planus, and some increase in the carrying angle of both arms. She has short 'stubby' hands showing clinodactyly of both fifth fingers. However, this trait is shown also by her mother and her elder sister. Although the hands are short the fingers taper markedly, and there is limitation of full extension of the terminal interphalangeal joints, as can be seen in Fig. 3. Both hands show a single transverse palmar crease.

There is marked clinodactyly of both feet, the second, fourth, and fifth toes incurring towards the third. There is some dorsal scoliosis. Some of these features are evident in the photographs. The lower end of the sternum is depressed and the umbilicus is located rather high on the abdomen with a brown line running down to the pubis. On the right buttock is a flat café au lait spot. The external genitalia appear normal. The general muscle tone is poor and she has some hyperextensibility of joints. Cardiac examination reveals no abnormality and both femoral pulses are palpable. Toxoplasmosis skin tests and Wassermann reactions are negative. Skull and lumbar region radiography reveal no abnormality.

Mentally the child is severely retarded, scoring 43 on the Vineland Social Maturity Scale. She has, however, improved considerably since attending the day school and can speak short sentences and laboriously print her name. She enjoys going to school and is a contented happy child, which to some extent reflects an excellent home environment.

Dr C. Ounsted of the Park Hospital for Children, Oxford, kindly undertook an electroencephalographic investigation. He reports that neither the waking nor the sleeping record shows any specific anomaly.

Family History

A diagrammatic pedigree is set out in Fig. 1. The father and mother were aged 40 and 34 years respectively when the propositus was born. Both parents are of superior intelligence and have no physical stigmata.

There is no history that appears relevant on the father's side of the family. The last of 19 children in the family of the maternal grandmother of the child is said to have been a mongol. All that is known of II.4 is that

*Received February 17, 1964.
he is said to have been weakly at birth and to have died within a few days. II.5 is a tall man (6 ft 2 in.) (188 cm.) of more than average intelligence. He has extremely long hands measuring 8½ in. (22.2 cm.) from the distal wrist crease to the tip of the middle finger. He was married when aged 34 to a woman of the same age, and there have been no pregnancies in the ensuing eight years of the marriage. I.3, the mother’s father, is a healthy elderly man; his wife, I.4, is dead.

III.5, the eldest sister of the propositus, was born in May 1952 and has passed her ‘eleven-plus’ examination. She appears normal in every way as does her 3-year-old brother, III.8. III.6 was born in September 1954 and died in February 1955. She was recognized at birth to have a cardiac abnormality; when 2 months old she was admitted to hospital where an electrocardiogram showed right axis deviation and x-ray examination showed enlargement of both ventricles with widening of...
the upper mediastinum, mainly on the right side. She was regarded as having an anomaly of the great vessels, probably a coarctation of the aorta. There is no record on the hospital notes of any bodily anomaly. She died in another hospital at 18 months but there was no necropsy. III.8 was born in April 1960, but he has always appeared to be a normal child, and there are not obvious mental or physical anomalies. The mother had no abortions.

A note on the dermatoglyphs in the family by Dr Sarah Holt is given in the Appendix.

Karyotypes

The Denver Conference (1960) numbers are used in identification of chromosomes. For brevity, however, and following the lead of the recent London Conference on the Normal Human Karyotype (1963), the group of chromosomes numbers 6–12 inclusive and the X chromosome are referred to as group C.

On examination of chromosomes from skin fibroblasts and white blood cell preparations from the propositus, III.7, she was found to have a modal number of 46 chromosomes. Nos. 1 and 2 and 13 to 22 could be identified and paired or grouped without difficulty. There were, however, (a) five large sub-metacentric chromosomes instead of the expected four from Nos. 4 and 5 (the 'B' group); (b) only 15 of the intermediate size sub-metacentric group C chromosomes, instead of the expected 16 for a female child (Fig. 4).

Fig. 4a shows relevant chromosomes from additional fibroblast cells of the propositus III.7. These chromosomes are the five large sub-metacentric chromosomes mentioned above and a pair of normal No. 3 chromosomes.

Buccal smears appeared normal female with single Barr bodies in about 40% of cells.

Chromosomes from white blood cell preparations from the child's mother, II.6, are shown in Fig. 5. The modal chromosome number was 46. Chromosomes corresponding to Nos. 1 and 2 and 13 to 22 were readily identified and paired. As in her daughter, there were 5 instead of the expected 4 large sub-metacentric chromosomes like pairs 4 and 5. However, there were two differences from the karyotype of her daughter: (a) there was only one large metacentric chromosome like chromosome No. 3 which is usually so easily identified, and (b) there was a full complement for a female of 16 chromosomes which, by morphology, belonged to group C.

Fig. 5a shows relevant chromosomes from five additional leucocyte cells of the mother (II.6). They are (a) as in the propositus five large sub-metacentric chromosomes, (b) one unmistakable No. 3 chromosome, and (c) a chromosome with one pair of arms the same length as in a No. 3 and one pair of shorter arms.

There was no suggestion of mosaicism in the mother; the changes described could be identified in all well-spread metaphases. Buccal smears were those of a normal female with single Barr bodies in a majority of cells.

Karyotypes of the maternal uncle of the propositus, II.5, and of her elder sister, III.5, were normal in number and morphology for the appropriate sexes. However, that of her younger brother, III.8 (Fig. 6), was exactly similar to that of his mother except that being male he had one fewer group C chromosome and a small chromosome identified as a Y.

The most probable interpretation of the chromosome findings in the mother, taken in association with the fact that she appears normal phenotypically, is that there has been reciprocal interchange of unequal terminal portions of arms of a chromosome No. 3 and one of the group C chromosomes. As chromosome No. 3 has a median centromere, it is impossible to say which arm is involved, but it is the long arm of the group C chromosome that appears to have the attached portion of the No. 3 (Fig. 5 and 5a). It is impossible to judge the size of the small terminal portion of the group C chromosome which has been transferred to the No. 3 chromosome. If only a small acentric portion of the terminal section distal to a break was involved, it might be 'lost' without the deletion determining any ill phenotypic effects, particularly if, as appears to be the situation in some other organisms, the telomere region is inert. In such a situation the translocation would not be 'reciprocal'.

The above explanation, whether postulating that the telomere portion is lost or attached to No. 3, requires postulation of only two breaks and seems inherently more probable than an alternative one requiring three breaks, namely, that there have been two breaks in the arm of No. 3 and that the interstitial portion released was
inserted between the broken ends of a single break in the long arm of the group C chromosome.

Accepting the first explanation, namely, two-break single reciprocal interchange of terminal portions of two chromosomes, III.8, the son with a similar karyotype to that of his mother, presumably received both of his mother's abnormal chromosomes. The unaffected daughter, III.5, must have received normal No. 3 and normal group C chromosomes from her mother.

The propositus, III.7, would have received from her mother a group C chromosome with the relatively large portion of an arm of a No. 3 attached and a complete normal No. 3 (Fig. 4 and 4a). On this basis therefore she is (a) effectively trisomic for part of one arm of a No. 3 chromosome, and (b) deficient of a much smaller terminal portion of the group C chromosome which is involved.

**Blood Typing**

The Table below shows the blood types of members of the family whose karyotypes have been analysed. There does not appear to be any anomaly of an expected pattern of inheritance.

**Discussion**

The question as to which of the group C chromosomes is involved cannot be answered with complete...
Translocation between Chromosome 3 and 'X-6-12' or 'C' Group

![Karyotype of III.8.](image)

Confidence. Unfortunately, the Xg* blood type inheritance in the family does not enable us to know whether the mother, II.6, is homozygous or heterozygous for Xg*. If she could have been shown to be heterozygous, her husband is Xg* and all three children each of different karyotype are Xg**, involvement of the X chromosome could have been excluded. On the basis of over-all chromosome lengths and positions of centromeres the writers incline to the view that it is the No. 8 chromosome that is involved.

It is tempting to speculate whether the daughter in this family who died in infancy, III.6, probably having coarctation of the aorta, represents the complementary unbalanced karyotype which would have resulted from receiving a No. 3 with a piece missing, and the normal group C chromosomes from her mother. This would result in the child being heterozygous for a deficiency of the third chromosome.

The 'carrier' condition of the boy, III.8, was explained to the parents who understood the situation. They have decided that this will be explained to him when he grows up.

A considerable number of transmitted translocations involving acrocentric chromosomes have been reported in recent years, the most frequently reported being those associated with mongolism in appropriate karyotypes. Cases reported by Walker and Harris (1962) and by Mercer and Darakjian (1962) both involved attachments of complete or nearly complete large acrocentrics.

Edwards, Fraccaro, Davies, and Young (1962) reported transmitted anomalies of karyotype in two families. In one, the mother appeared to show a reciprocal exchange between partners of No. 4 and No. 5 chromosomes and one of the group C chromosomes: the authors favour No. 9 as being involved. In the other, a case analysed at the Population Genetics Research Unit, the father appeared to have a reciprocal exchange between No. 1 and No. 6 and a son had, as a result of receiving an unbalanced gamete, a duplication of a part of a No. 1 chromosome.

### TABLE

**BLOOD TYPES**

<table>
<thead>
<tr>
<th>Subject</th>
<th>ABO</th>
<th>MNS</th>
<th>P₁</th>
<th>Rh</th>
<th>Lu⁺</th>
<th>K</th>
<th>Le⁺</th>
<th>Le⁻</th>
<th>Fy⁺</th>
<th>Xg⁺</th>
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<tr>
<td>I.3</td>
<td>A₁</td>
<td>M, M₁</td>
<td>+</td>
<td>R₁ R₂</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>II.3</td>
<td>A₁</td>
<td>N, N₁</td>
<td>+</td>
<td>R₁ R₂</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>II.5</td>
<td>O</td>
<td>MNS</td>
<td>+</td>
<td>R₁ R₂</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>II.6</td>
<td>A₂</td>
<td>M⁺ M⁺</td>
<td>+</td>
<td>R₁ R₂</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>III.5</td>
<td>A₁</td>
<td>M⁺ N⁺</td>
<td>+</td>
<td>R₁ R₂</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>III.7</td>
<td>A₂</td>
<td>M⁺ N⁺</td>
<td>+</td>
<td>R₁ R₂</td>
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<td>+</td>
</tr>
<tr>
<td>III.8</td>
<td>A₁</td>
<td>MSN</td>
<td>+</td>
<td>R₁ R₂</td>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
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</table>
The family here described appears to be only the third reported where translocations have not involved acrocentric chromosomes. Two have been investigated at the Population Genetics Research Unit.

It will be interesting to see how many families with translocations, not involving acrocentrics, are reported in the future. They may not be as uncommon as is at present suggested, partly because severe affections of the child may result from genetic imbalances determined by structural changes that are close to the limits of optical recognition. It is perhaps noteworthy that, as in other complete or partial trisomies so far described, this child is severely retarded.

Summary

An account is given of a family identified by a mentally retarded girl. The chromosome anomalies described are interpreted as indicating that the mother is a balanced translocate having a reciprocal exchange of the long arm of a No. 3 chromosome and a terminal segment of one of X-6-12 or C group, probably No. 8. The affected propositus is heterozygous for the C group plus large portion of No. 3 compound chromosome and has two 'normal' No. 3 chromosomes, being thus effectively trisomic for part of the third chromosome. One female sib has a normal karyotype and a male sib appears to be a 'balanced' translocate like his mother.

We are indebted to Dr Victoria Smallpeice who first referred this child; to Dr J. F. P. Asbury, the family doctor, who made easy our approach to the family; to Dr Ruth Sanger, of the M.R.C. Blood Group Research Unit for the serological findings; to Dr C. E. Ford, of the M.R.C. Radiobiological Research Unit, who read the manuscript and made many helpful suggestions which we have followed in writing this paper; and to Dr C. Ounsted who advised us on interpretation of the electroencephalographic tracing.

References


Appendix

A Note on the Dermal Ridge Configurations

SARAH B. HOLT

From The Galton Laboratory, University College, London

FINGER RIDGE COUNTS

<table>
<thead>
<tr>
<th>Subject</th>
<th>Side</th>
<th>V</th>
<th>IV</th>
<th>Digits</th>
<th>III</th>
<th>II</th>
<th>I</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother (II.6)</td>
<td>Left</td>
<td>210/0</td>
<td>7/0</td>
<td>0/2</td>
<td>8/0</td>
<td>20/27</td>
<td></td>
<td>131</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>20/12</td>
<td>8/12</td>
<td>11/0</td>
<td>10/0</td>
<td>24/720</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daughter (III.7)</td>
<td>Left</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>1/0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>8/0</td>
<td></td>
</tr>
<tr>
<td>Son (III.8)</td>
<td>Left</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>6/12</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>5/13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother's brother (II.5)</td>
<td>Left</td>
<td>18/13</td>
<td>20/16</td>
<td>18/19</td>
<td>15/20</td>
<td>25/29</td>
<td></td>
<td>211</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>20/10</td>
<td>20/13</td>
<td>17/0</td>
<td>17/21</td>
<td>27/26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key to figures: 10/o indicates an ulnar loop, with a radial count of 10 ridges; 0/2 indicates a radial loop with an ulnar count of 2 ridges; 20/27 indicates a whorl with a count of 20 ridges on the radial side and 27 ridges on the ulnar side. When both radial and ulnar counts are zero, 0/0, the pattern is an arch. The larger number for each finger is used to obtain the total ridge count.
Translocation between Chromosome 3 and 'X-6-12' or 'C' Group

Commentary

The total finger ridge count of the mother (II.6) is near the population mean for females, 127 ridges. In contrast, both her children have low total counts, owing to the patterns on most of their fingers being arches (Fig. A). In the general population only 1.6% of females have total ridge counts under 10 ridges, while 1.6% of males have values under 30 ridges. The daughter (III.7) has ulnar loops on both thumbs and simple arches on her other fingers. This combination occurs in 0.5% of normal females. The son has a somewhat unusual type of whorl on both thumbs. The combination of whorls on the thumbs and arches on all other fingers does not occur in a series of 2,000 subjects from the general population.

The mother's brother (II.5) has large whorls on all save 1 of his fingers (Fig. A), resulting in a high total ridge count, well above the population mean for males, 145 ridges.

<table>
<thead>
<tr>
<th>Maximal and Angle on Palm</th>
<th>a-b Ridge Count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
</tr>
<tr>
<td>Mother (II.6)</td>
<td>41°</td>
</tr>
<tr>
<td>Daughter (III.7)</td>
<td>39°</td>
</tr>
<tr>
<td>Son (III.8)</td>
<td>50°</td>
</tr>
<tr>
<td>Mother's brother (II.5)</td>
<td>43°</td>
</tr>
</tbody>
</table>

The palms of the mother show no particularly unusual features. The arrangement of the main lines on the right hand is of a very common type. On the left hand one digital triradius, c, in the distal palm is absent (c is absent on one or both palms in nearly 13% of females in the population), and the axial triradius is duplicated, the distal, r', triradius forming a hypothenar loop.

There are transverse flexion creases on both the daughter's palms. On the left hand main lines C and D appear to join and such a configuration is uncommon.

Fig. A. Dermatoglyphic patterns on palms and fingers of members of the family. Top left, II.6, mother; top right, II.5, mother's brother; bottom left, III.7, daughter; bottom right, III.8, son.
There is duplication of triradius $d$ in the distal palm of the right hand of the son. The $t$ triradius is duplicated on both palms. The value of the maximal triradius $atd$ angle (sum both hands) is, consequently, higher than the mean for boys of his age-group in the general population, $92^\circ$. On both hands, the proximal triradius is associated with a loop pattern. Neither mother nor children have thenar patterns, but these occur on both hands of the mother's brother. On his right hand the axial triradius is duplicated and the distal, $r'$, triradius forms a hypothenar pattern similar to that on the left palm of the mother.

The soles of the daughter (Fig. B) show some unusual features. In the hallucal area of the left sole there is an $e$ triradius, but no pattern, and on the right an $f$ triradius also without pattern. Both $e$ and $f$ triradii without associated patterns in the hallucal area are uncommon in the general population. The distal radiants from triradius $d$ (on the fibular side of the sole) usually embrace the little toe. In this case on both feet the distal tibial radiant is extended and courses across the sole to terminate in the fourth interdigital interval. The proximal radiant continues to form the main line $D$, in the usual manner. Such an extension of the distal tibial radiant occurs in less than 1% of normal females. A somewhat similar configuration was present on the right sole of a grossly abnormal female child with a reciprocal translocation, probably between chromosomes Nos. 9 and 4 (Edwards et al., 1962).