marked contrast to the large stature commonly seen in XYY males, where, there is a duplication of each active factor carried on the Y chromosome.

We wish to thank Dr Byron Evans, Consultant Physician, University Hospital of Wales (Cardiff) H.M.C. for referring this patient to us.

HELEN LANGMAID and K. M. LAURENCE
Cytoprognetics Unit, Child Health Laboratories,
Department of Child Health, University Hospital of Wales, Heath Park, Cardiff

REFERENCES


A 48,XXXX female

Summary. A four-year-old mildly retarded girl with a 48,XXXX karyotype is described. Her phenotype is compared to previously reported cases.

The first tetra-X female was described by Carr, Barr, and Plunkett (1961). Since then only 16 other cases have been reported. The present paper reports a further case and the phenotype and origin of this abnormality are discussed.

Received 1 October 1973.

Case Report

The proposita was a Caucasian female born in August 1969 as the 2550 g product of an uneventful pregnancy and term delivery to a 25-year-old mother. Her mother, father, and the two older sisters were healthy and had normal intelligence and stature. During the first 6 months of life she had feeding difficulties, with frequent regurgitation and vomiting. Her growth and development were slow and at 32 months she was admitted to the Children's Centre in Winnipeg for investigation. Physical examination at that time showed a height of 85 cm, weight of 9.2 kg, and a head circumference of 43.5 cm, all of which were below the third percentile for her age. Facial features included prominent eyebrows growing together in the midline (synophrys), small epicanthic folds, and a small mandible (Fig. 1). She had a high arched palate. Her hands showed bilateral simian creases. Her gait was unsteady and she was mildly hypotonic. The remainder of her physical examination fell within normal limits. Laboratory tests showed her to have normal levels of calcium, phosphorus, alkaline phosphatase, BUN, glucose, and thyroxine. Radiology showed a bone age of 12 months and a reduced craniofacial ratio. Re-examination at 44 months did not reveal any other abnormalities and her measurements were still below the third percentile.

Developmental Assessment (E.L.). Evaluation at 45 months showed her to be functioning for the most
part between 2 and 2½ years. Her developmental quotient (DQ) was estimated to be 60. Speech production and comprehension were in keeping with her overall development, and after assessment in a sound field setting her hearing was considered to be grossly normal. Her gross motor skills showed the greatest delay, being at the 18 month level (less than 50% of normal).

Dermatoglyphics

Table I shows bilateral simian creases. The fingerprints showed six whorls and the total ridge was 104. Both axial triradii were distally placed but the atd angles were in the normal range. The b and c triradii were absent in both hands.

Chromosome Studies

Buccal smears showed 6% of the nuclei to have three, 18% two, and 23% one X-chromatin body. Chromosome preparations from short-term peripheral blood leucocyte cultures were stained conventionally with orcein and by Q-, G-, and C-banding. Orcein preparations showed a chromosome number of 48 with 18 chromosomes in the C group (Table II). Q- and G-banding showed the presence of four X-chromosomes (Fig. 2). A 16h+ chromosome was shown to be present by C-banding (Fig. 2). Cells with less than 48 chromosomes showed random chromosome loss and were interpreted as technical artefacts. One conventionally stained cell with 49 chromosomes was observed with an additional chromosome in the C group which could not be identified. In our view this was most likely a technical artefact but the possibility of a 49,XXXX cell could not be excluded. The karyotype was interpreted as 48,XXXX with no evidence of mosaicism. The karyotypes of the parents and sibs were all normal (Table II).

Discussion

Clinical data on 19 cases are presented in Table III. The mean total dermal ridge count determined from data on 10 patients is 84 ± 38* which is significantly lower than the mean for the general population of 127 ± 52 for females (t = 3.2, P < 0.01)

* Standard deviations follow the means in all cases.
FIG. 2. Top: Partial karyotype of the C group showing four X-chromosomes (Q- and G-banding). Bottom: Partial karyotype of the E group showing a 16h + chromosome (G- and C-banding).

(Holt, 1955/1956). This supports Penrose’s concept (1967) that extra heterochromatic X-chromosomes lead to a reduction in the total ridge count. The mean maternal age at birth of 15 patients is 28.0 ± 6.6 years; this is not significantly elevated over the population mean (27.0 years) for Canada (Vital Statistics Canada, 1969). Successive non-disjunction at both meiotic divisions in oogenesis is the most likely origin for this chromosome abnormality and has been shown by Xg groups to be operating in at least one patient with tetra-X chromosomes (De Grouchy et al, 1968) and in three patients with a 49,XXXXY chromosome complement (Race and Sanger, 1969); these findings therefore suggest that a maternal age effect may not account for the occurrence of non-disjunction in the majority of tetra-X females. Von Bergemann (1962) reported a 48,XXXX woman who gave birth to a 47,XX,+G child. She also reported a family in which a 47,XXX/48,XXXX woman gave birth to a child with the same chromosome complement and to another child with a 47,XX,+G karyotype; her mother also had a 47,XXX/48,XXXX karyotype and her sister was a 46,XX/47,XXX/48,XXXX mixoploid. These data on the 48,XXXX state may be compared to data on the 47,XXX condition, in which the mean maternal age is elevated over the mean for the population (Hamerton, 1971) and in which aneuploid states are rare among the offspring of affected patients (Barr et al, 1969) and may suggest the possibility of familial non-disjunction in the aetiology of the 48,XXXX state.

The clinical data (Table III) indicate the absence of a definite 48,XXXX phenotype. Mental retardation was noted in 16 patients; of the remaining three subjects one had normal intelligence (Blackston and Chen, 1972) while the IQ of two others fell into the sub-normal range (Di Cagno and Franceschini, 1968; Hanicka et al, 1969). The patient reported by Duncan, Nicholl, and Downes (1970) had an IQ of 94 in a nonverbal test; however, her verbal IQ was only 59. Since most of the patients were ascertained because of mental retardation, an association between the tetra-X state and mental retardation is at least questionable. A speech disorder has been reported in seven patients; in three instances the development of speech was more retarded than expected for the DQ (Carr et al, 1961; De Grouchy et al, 1968; Duncan et al, 1970). In four cases an articulation defect was reported (Di Cagno and Franceschini, 1968; Hanicka et al, 1969; Telfer et al, 1970; Blackston and Chen,
### Table III

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age at Examination (yr)</th>
<th>Maternal Age</th>
<th>Paternal Age</th>
<th>Height (cm)</th>
<th>Weight (Kg)</th>
<th>Total Ridge Count</th>
<th>IQ/DQ</th>
<th>Somatic Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carr et al (1961)</td>
<td>12.5</td>
<td>21</td>
<td>19</td>
<td>158.8</td>
<td>50.8</td>
<td>30</td>
<td></td>
<td>Strabismus</td>
</tr>
<tr>
<td>Carr et al (1961)</td>
<td>32</td>
<td>41</td>
<td>39</td>
<td>163.2</td>
<td>48.1</td>
<td>50</td>
<td></td>
<td>Enlarged thyroid</td>
</tr>
<tr>
<td>Von Bergemann (1962)</td>
<td>33</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>50</td>
<td></td>
<td>Enlarged thyroid</td>
</tr>
<tr>
<td>Davies (1963)</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>40</td>
<td></td>
<td>Bilateral congenital dislocated hip; large naevus left thigh and leg</td>
</tr>
<tr>
<td>Anderson et al (1968)</td>
<td>13</td>
<td>—</td>
<td>—</td>
<td>Tall</td>
<td>—</td>
<td>47–54</td>
<td></td>
<td>Tall stature; short fingers; enlarged end of radius and ulna</td>
</tr>
<tr>
<td>Di Cagno and Franceschini (1968)</td>
<td>4.6</td>
<td>25</td>
<td>31</td>
<td>103.5</td>
<td>16.6</td>
<td>125</td>
<td>80</td>
<td>Abnormal facies reminding Down's syndrome</td>
</tr>
<tr>
<td>Lejeune and Abony (1968)</td>
<td>14</td>
<td>31</td>
<td>38</td>
<td>156</td>
<td>60.0</td>
<td>Retarded</td>
<td>50</td>
<td>'Impression of Down's syndrome'</td>
</tr>
<tr>
<td>De Grouchy et al (1968)</td>
<td>6.5</td>
<td>26</td>
<td>27</td>
<td>125</td>
<td>25</td>
<td>139</td>
<td>51</td>
<td>Slight deafness; cataracts; myopia; irregular menses</td>
</tr>
<tr>
<td>Konishi and Yanagisawa (1968)</td>
<td>29</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>51</td>
<td></td>
<td>Hypertelorism; iridioschisis; webbed neck; clinodactyly of fifth digits</td>
</tr>
<tr>
<td>Hanicka et al (1969)</td>
<td>6</td>
<td>Young</td>
<td>Young</td>
<td>—</td>
<td>—</td>
<td>110</td>
<td>83</td>
<td>Myopia; strabismus; patent ductus arteriosus (?); infantile genitilia</td>
</tr>
<tr>
<td>Halikowski et al (1969)</td>
<td>12</td>
<td>22</td>
<td>27</td>
<td>—</td>
<td>—</td>
<td>30</td>
<td>65</td>
<td>Esotropia; nystagmus; abnormal EEG; radio-ulnar synostosis; underdeveloped breasts</td>
</tr>
<tr>
<td>Telfer et al (1970)</td>
<td>28</td>
<td>23</td>
<td>30</td>
<td>158.6</td>
<td>72.4</td>
<td>26</td>
<td>75</td>
<td>Microcephaly; abnormal ears; esotropia; abnormal EEG</td>
</tr>
<tr>
<td>Telfer et al (1970)</td>
<td>3.5</td>
<td>28</td>
<td>25</td>
<td>98.75</td>
<td>15.3</td>
<td>70</td>
<td>55</td>
<td>Clinodactyly of fifth digit; mandibular prognathism; slight kyphosis and lordosis</td>
</tr>
<tr>
<td>Duncan et al (1970)</td>
<td>10.5</td>
<td>43</td>
<td>60</td>
<td>—</td>
<td>—</td>
<td>95</td>
<td>59/94</td>
<td>Kyphosis; abnormal EEG; short terminal phalanges</td>
</tr>
<tr>
<td>Berkeley and Faed (1970)</td>
<td>33</td>
<td>31</td>
<td>26</td>
<td>—</td>
<td>—</td>
<td>87</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Park et al (1970)</td>
<td>16</td>
<td>23</td>
<td>27</td>
<td>180</td>
<td>79</td>
<td>—</td>
<td>70</td>
<td>Low stature; microcephaly; synophrys; small epicanthal folds; high arched palate; small mandible; bilateral simian creases; mild hypotonia</td>
</tr>
</tbody>
</table>

1972). In four other patients in whom speech development was recorded the level was found to be consistent with the reported DQ (Berkeley and Faed, 1970; Telfer et al, 1970; Larget-Piet et al, 1972; and the present report). In one patient surprising verbosity was reported (Carr et al, 1961). Further studies will be necessary to determine whether speech disorder forms part of the 48,XXXX phenotype or is merely secondary to mental retardation.
Addendum

Since submission of our manuscript for publication two additional cases of 48,XXXX have been published. Gardner, Veale, and Sands (1973) reported a 14-year-old girl ascertained by speech problems and epilepsy. Maternal and paternal ages were 31 and 28 years, respectively. Total ridge count was 132. Her full IQ was 58–68. Malformations noted were hypertelorism, epicanthal folds, bilateral radiolunar synostosis, clinodactyly, and camptodactyly of the fifth finger. Walbaum et al (1973) have reported a 21-month-old infant ascertained by features suggestive of Down’s syndrome. Maternal and paternal ages were 20 and 21 years, respectively. Total ridge count was 54. DQ was 85 with more marked retardation in speech development. Malformations reported were epicanthal folds, depressed nasal bridge and a right cataract.

These two case reports give further evidence suggestive that a speech impairment might represent a phenotypical manifestation of the 48,XXXX state.

We are grateful to Dr J. N. Briggs for allowing us to study his patient. The expert technical assistance of Mr F. Bauder, Miss V. Niewczas-Late, and Mrs M. Riffell is gratefully acknowledged. This work was supported by MRC operating grant No. 4458 and The Children’s Hospital Research Foundation, Winnipeg. G.R.D. acknowledges an MRC Postdoctoral Fellowship.

S. D. J. Peña, M. Ray, G. Douglas, E. Loadman, and J. L. Hamerton
Division of Medical Genetics, Health Sciences Children’s Centre, Winnipeg, Manitoba, Canada

References


A 48,XXXX female


doi: 10.1136/jmg.11.2.211

Updated information and services can be found at:
[http://jmg.bmj.com/content/11/2/211](http://jmg.bmj.com/content/11/2/211)

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)