Fertility in a male with trisomy 21

RICHARD SHERIDAN*, JUAN LLERENA JR*, SALLY MATKINS*, PAUL DEBENHAM†, ANDREW CAWOOD†, AND MARTIN BOBROW*

From *the Paediatric Research Unit, Division of Medical and Molecular Genetics, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, London SEI 9RT; and †Cellmark Diagnostics, ICI Chemical Industries plc, Blacklands Way, Abingdon, Oxfordshire OX14 1DY.

SUMMARY We review the published reports on reproduction in cases of non-mosaic trisomy 21 (Down's syndrome) and present the first fully documented case of a non-mosaic male with Down's syndrome fathering a pregnancy, a fact which has important implications in the light of caring for these people in the community.

The Down's syndrome female has ovaries containing a reduced number of small follicles, which have a greatly increased rate of atresia. Twenty-six non-mosaic trisomy 21 females, in 29 pregnancies, have produced 10 offspring with Down's syndrome, two spontaneously aborted fetuses whose status could not be evaluated, and 18 (including one monozygotic twin pair) chromosomally normal offspring. Of these, two are mentally retarded, four have other congenital malformations, and three were either spontaneously aborted or died of prematurity (table 1). Older published references describe a further seven women with nine offspring (table 2), although insufficient data are available to evaluate these.

Male Down's syndrome patients are often well masculinised, but are said to be infertile. Jagliello reported six adult male subjects showing normal serum testosterone levels in five of the six, normal testicular size in three, raised LH in five, and raised FSH in two patients. Benda commented that Down's syndrome males very often have small testes and that spermatogenesis was only rarely present. Stearns et al. showed a complete absence of sperm in four out of nine patients and only occasional spermatozoa in the other five.

Histology performed on Down's syndrome testes usually shows markedly decreased spermatogenesis. The inability of Down's syndrome males to reproduce may be related to their sexual impotence as well as to their inability to produce sufficient gametes.

Mosaic Down's syndrome can be associated with fertility in the male, as the germ cell line can contain normal cells. Thompson, describing case 10 (table 1), states that "there appears to have been reason to believe that the father was also a mongol, but this cannot be confirmed". Other than this very brief anecdotal aside, we can find no reference in published reports to a non-mosaic male with trisomy 21 who has fathered a child.

CASE REPORT

Our patient is a 29 year old man with trisomy 21, showing some of the classical features of Down's syndrome: low intelligence, short stature, low set ears, epicanthic folds, large tongue, and clinodactyly. His mother was aged 24 at the time of his birth and he is the oldest of five sons.

He lives in special local authority housing with three other mentally retarded adults. He developed a relationship with a girl, living in the same house, who is educationally subnormal with no specific medical diagnosis. She had been on oral contraception, but had recently stopped this. The couple were referred after eight weeks of amenorrhoea. A singleton pregnancy was confirmed by ultrasound scanning.

They had had unprotected sexual intercourse for three months before they were seen in the clinic and it therefore seems likely that she conceived the pregnancy during her first unprotected cycle.

The couple were counselled in the presence of their social worker. They were told that there was a significant risk of the baby being severely handicapped. They themselves decided that they would not want to bring up a handicapped child and that they wanted prenatal diagnosis.

All parties present agreed that the couple had understood the situation and that they had given informed consent.

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<table>
<thead>
<tr>
<th>No of</th>
<th>Refs</th>
<th>Karyotype of offspring where verified</th>
<th>Status of offspring</th>
<th>Presumptive father and mental status where known</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 3</td>
<td>46,XX</td>
<td>Normal female</td>
<td>Patient’s father</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>47,XX,+21</td>
<td>2 Down’s syndrome male</td>
<td>Mentally retarded; non-DS</td>
</tr>
<tr>
<td>3*</td>
<td>5–7</td>
<td>46,XY</td>
<td>3 Down’s syndrome female</td>
<td>Patient’s father suspected</td>
</tr>
<tr>
<td>4*</td>
<td>8 9</td>
<td>Slight MR, suspected CHD</td>
<td>4</td>
<td>Blind 60 year old epileptic (not MR) (normal 46,XY)</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>46,XY</td>
<td>5</td>
<td>Patient’s father</td>
</tr>
<tr>
<td>6*</td>
<td>11 12</td>
<td>46,XY</td>
<td>6</td>
<td>Normal male</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>46,XX</td>
<td>7</td>
<td>Normal male</td>
</tr>
<tr>
<td>8*</td>
<td>14 15</td>
<td>46,XY</td>
<td>8</td>
<td>8 Down’s syndrome male</td>
</tr>
<tr>
<td>9*</td>
<td>16 17</td>
<td>46,XY</td>
<td>9</td>
<td>Mother’s MR brother (46,XY)</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
<td>46,XY</td>
<td>10</td>
<td>Patient’s father (normal IQ)</td>
</tr>
<tr>
<td>11*</td>
<td>18 19</td>
<td>46,XY</td>
<td>11</td>
<td>Normal male</td>
</tr>
<tr>
<td>12*</td>
<td>20</td>
<td>46,XX</td>
<td>12</td>
<td>Slight MR.</td>
</tr>
<tr>
<td>13*</td>
<td>21</td>
<td>46,XX</td>
<td>13</td>
<td>Normal female (v slight microcephaly)</td>
</tr>
<tr>
<td>14*</td>
<td>22</td>
<td>46,XX</td>
<td>14</td>
<td>Normal female</td>
</tr>
<tr>
<td>15*</td>
<td>23</td>
<td>46,XX</td>
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<td>Normal female</td>
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<tr>
<td>16*</td>
<td>24</td>
<td>46,XX</td>
<td>16</td>
<td>Normal female</td>
</tr>
<tr>
<td>17*</td>
<td>24</td>
<td>46,XX</td>
<td>17</td>
<td>Normal female</td>
</tr>
<tr>
<td>18*</td>
<td>25</td>
<td>46,XX</td>
<td>18</td>
<td>Normal female</td>
</tr>
<tr>
<td>19*</td>
<td>26</td>
<td>46,XX</td>
<td>19</td>
<td>Normal female</td>
</tr>
<tr>
<td>20*</td>
<td>27</td>
<td>46,XX</td>
<td>20</td>
<td>Normal female</td>
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<tr>
<td>21*</td>
<td>28</td>
<td>46,XX</td>
<td>21</td>
<td>Normal female</td>
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<tr>
<td>22</td>
<td>29</td>
<td>47,XX,+21</td>
<td>22</td>
<td>Normal female</td>
</tr>
<tr>
<td>23*</td>
<td>30</td>
<td>46,XX</td>
<td>23</td>
<td>Normal female</td>
</tr>
<tr>
<td>24*</td>
<td>31</td>
<td>46,XY</td>
<td>24</td>
<td>Slight MR.</td>
</tr>
<tr>
<td>25*</td>
<td>32 33</td>
<td>46,XY</td>
<td>25</td>
<td>Normal male</td>
</tr>
<tr>
<td>26*</td>
<td>34</td>
<td>46,XY</td>
<td>26</td>
<td>Normal male</td>
</tr>
</tbody>
</table>

*A Mother’s karyotype verified cytogenetically.

A transcervical CVS was carried out. Unfortunately, some two weeks after the procedure, the woman experienced some bleeding, which settled on admission to hospital. However, the couple were sexually active throughout the post CVS period, and although this was found to exacerbate the bleeding, it was not possible to persuade them to cease. After further episodes of bleeding over the next six weeks, she lost the pregnancy some nine weeks after the CVS procedure.

Pathological examination (Dr M J Seller) showed a fetus of a physical size compatible with 16 to 17 weeks of gestation with no external or visceral anomalies.

Results and discussion

G banded chromosome analysis of the man showed a chromosome complement of 47,XY,+21 in 51 lymphocyte metaphases examined and in 101 meta-
phases from a skin biopsy. His partner had a normal female 46,XX chromosome complement. Chromosome analysis, after chorionic villus sampling (CVS), showed the fetus to have a normal male chromosome complement (46,XY).

In order to confirm paternity, DNA ‘fingerprint’ patterns were analysed from the CVS sample and both parents.

DNA was digested with 80 units of HinfI for four hours at 37°C, run at 2-5 V/cm in 0-7% agarose until a 2-3 kbp marker had run 20 cm, then transferred to nylon membranes (Hybond-N, Amersham), and probed with probes 33-6 and 33-15 (figure). The results from the two probes were combined to calculate the probability of the man with Down’s syndrome being the true father of this pregnancy.

The number of bands recorded in the mother was 53, the same as the putative father. The number analysed in the fetus was 55. Of these 55, the number of bands shared with the mother was 32, and the number shared exclusively with the putative father was 22. In addition, there was one unassigned band. Therefore, the DNA ‘fingerprint’ of the fetus contained 23 non-maternal bands in the region analysed. Of these, 22 were found to have the same ‘fingerprint’ as the putative father.

These results provide three possible hypotheses.

(1) Paternity is correct and the undefined band is a new mutation of one of the parental bands; the probability for this is calculated to be 0.1978.

(2) The putative father is a first degree relative of the true father; the probability for this is $2.989 \times 10^{-4}$.

(3) The putative father is unrelated to the true father, with a probability of $9.948 \times 10^{-13}$.

We decided, therefore, that the last hypothesis

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**TABLE 2 Very early reports of reproduction in Down’s syndrome.**

<table>
<thead>
<tr>
<th>No</th>
<th>Source</th>
<th>Ref</th>
<th>Karyotype where known</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pogue (1917)</td>
<td>7 35</td>
<td>Normal</td>
<td>(a) SA 4-5 months</td>
</tr>
<tr>
<td>2</td>
<td>Lind (1923)</td>
<td>7 36</td>
<td>NK</td>
<td>(b) Normal child, sex not known</td>
</tr>
<tr>
<td>3</td>
<td>Weygandt (1936)</td>
<td>7 37</td>
<td>NK</td>
<td>Caesarian section, status/sex NK</td>
</tr>
<tr>
<td>4</td>
<td>Allen and Baroff (1955)</td>
<td>6 38 39</td>
<td></td>
<td>Mother said to have had an abortive form of ‘mongolism’. Pictures suggest ‘mongolism’: fissured tongue, hyperextensible joints, low IQ. No further details of mother or child</td>
</tr>
<tr>
<td>5</td>
<td>Rosenberg (1924)</td>
<td>8 40</td>
<td>Normal</td>
<td>Describes 4 reports. Oster77 says that diagnosis was uncertain in 2, Forsmann and Thyssell8 say that only 1 was convincing</td>
</tr>
<tr>
<td>6</td>
<td>Holt (1949)</td>
<td>4</td>
<td>Non-mongol</td>
<td>Married ‘mongolian’ woman + 2 normal children</td>
</tr>
<tr>
<td>7</td>
<td>Orel (1926)</td>
<td>4 41</td>
<td>Non-mongol</td>
<td>No further details</td>
</tr>
</tbody>
</table>

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**FIGURE ‘DNA fingerprint’ gels from Down’s syndrome male (track M), his female partner (track F), and the chorion villus sample from their pregnancy (track C), using two different hypervariable probes 33-6 (a) and 33-15 (b).**
References


34. Bovicelli L, Orsini LP, Rizzo N, Montacuti V, Bacchetta M.

Correspondence to Professor M Bobrow, Paediatric Research Unit, 8th Floor, Guy’s Tower, Guy’s Hospital Medical School, London SE1 9RT.