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Fertility in a male with trisomy 21

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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.[1] 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. Jagiello[42] 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[43] commented that Down's syndrome males very often have small testes and that spermatogenesis was only rarely present. Stearns *et al*[44] 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.[45] 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.[46]

Mosaic Down's syndrome can be associated with fertility in the male, as the germ cell line can contain normal cells. Thompson,[18] 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.

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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.

TABLE 1 *Reproduction in non-mosaic Down's syndrome females.*

No of mother	*Refs*	*Karyotype of offspring where verified*	*Status of offspring*	*Presumptive father and mental status where known*
1	2 3		1 Normal female	Patient's father
2	4		2 Down's syndrome male	Mentally retarded; non-DS
3*	5–7	47,XX,+21	3 Down's syndrome female	Patient's father suspected
4*	8 9	46,XY	4 Slight MR, suspected CHD	Blind 60 year old epileptic (not MR) (normal 46,XY)
5	10		5 MR female; may represent 'partial trisomy 21'; low nasal bridge.	Patient's father suspected
6*	11 12	46,XY	6 Normal male	
7	13		7 Normal male	Mental debility?
8*	14 15		8 Down's syndrome male	Mother's MR brother (46,XY)
		47,XX,+21	9 Down's syndrome female	Mother's MR brother (46,XY)
9*	16 17	46,XY	10 Apparently normal MZ male twins stillborn at 5 months	Patient's father (normal IQ)
10	18		11 Normal male	Some suggestion that father was mongol; unsubstantiated
11*	18 19		12 Macerated female fetus SA at 28 wk; status NK	
			13 Down's syndrome male (TOP 20 wk)	
12*	20	46,XX	14 Normal female (v slight microcephaly)	
13*	21		15 3 month fetus, TOP post-SA. Status/sex not known	
		46,XX	16 Normal female	
14*	22	47,XX,+21	17 Down's syndrome female	
15*	23	47,XY,+21	18 Down's syndrome male	MR but ? owing to brain damage
16*	24	46,XX	19 Normal female	
17*	24	46,XX	20 Normal female	
18*	25	46,XY	21 Normal male	Normal male
19*	26	47,XX,+21	22 Down's syndrome female	Tubercular invalid of 50+
20*	27	46,XX	23 Normal female	Patient's husband (IQ=70)
21*	28	47,XY,+21	24 Down's syndrome male	Patient's husband; average IQ
22	29	46,XY+additional chromosome (3 different groups) in 4·4% of metaphases. ? Mosaic: could not be confirmed.	25 Normal male. Missing L 5th finger, bilateral syndactyly of 2nd/3rd toes. Dermatoglyphics felt to be compatible with DS but mental development normal. Mosaicism would account for observed stigmata	
23*	30	47,XX,+21	26 Down's syndrome female.	
24*	31	46,XY	27 Normal male except for hypospadias. Low set ears, apparent bilateral syndactyly 2nd/3rd toes, subluxation of right hip	Patient's father
25*	32 33	46,XY	28 Normal male karyotype; multiple malformations: cleft palate, unilateral genu recurvatum. Died at 1 wk	Patient's brother
26*	34	46,XY	29 Normal male, born prematurely at 30 wk. Died at 1 d	Patient's uncle

*Mother's karyotype verified cytogenetically.

A transcervical CVS was carried out.[47] 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-

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

No	*Source*	*Ref*	*Karyotype where known*	*Status*
1	Pogue (1917)	7 35		(a) SA 4–5 months
			Normal	(b) Normal child, sex not known
2	Lind (1923)	7 36	NK	Caesarian section, status/sex NK
3	Weygandt (1936)	7 37	NK	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
4	Allen and Baroff (1955)	6 38 39		Describes 4 reports. Oster[39] says that diagnosis was uncertain in 2, Forsmann and Thysell[8] say that only 1 was convincing
5	Rosenberg (1924)	8 40	Normal	Married 'mongolian' woman + 2 normal children
			Normal	No further details known; Forsmann and Thysell[8] say diagnosis should be disregarded because he had unconventional views regarding 'transitional types of DS'
6	Holt (1949)	4	Non-mongol	An undisputed mongol, with typical facies and hand formation
			Non-mongol	
7	Orel (1926)	4 41	Normal	No further details

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[48] were analysed from the CVS sample and both parents.

DNA was digested with 80 units of *Hinf*I 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[49] (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 $2{\cdot}989\times10^{-4}$.
(3) The putative father is unrelated to the true father, with a probability of $9{\cdot}948\times10^{-13}$.

We decided, therefore, that the last hypothesis

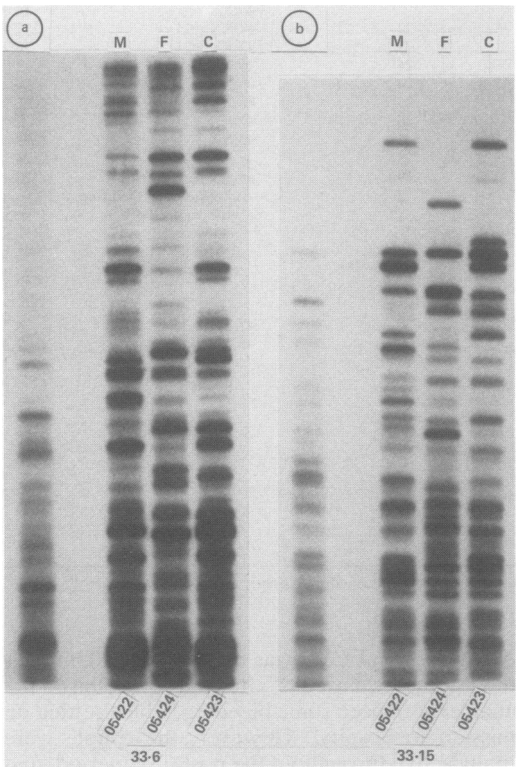

FIGURE *'DNA fingerprint' gels from Down's syndrome male (track M), his female partner (track F), and the chorion villus sample from their pregnancy (track C), using two different hypervariable probes 33·6 (a) and 33·15 (b).*

can be rejected. The relative likelihood of hypotheses 1 and 2 is 661·8 to 1.

It is exceedingly unlikely that any of the man's relatives could be the father, and we therefore concluded that our patient was indeed the father of this pregnancy.

Further evidence of paternity was provided in a comparison of the cytogenetic analysis of the CVS sample and chromosomes from the father's blood. The QFQ staining technique was used to compare the chromosomes of our patient and the fetus. These showed similar looking intermediate (size three) Y chromosomes and a brilliant basal segment on the short arm of chromosome 22 (p11.20-p12.00 with intensity five).[50]

This would appear to be the first documented example of a pregnancy fathered by a male with apparently non-mosaic trisomy 21. Paternal mosaicism cannot, by definition, be excluded, but with 152 cells analysed a 2% mosaicism can be excluded with 95% confidence.[51] It may well be that an undetected normal cell line is responsible for this man's fertility, but from a practical cytogenetic viewpoint this mosaicism could not have been predicted before the pregnancy, and caution should therefore be exercised in advising people responsible for the care of adults with this condition about possible fertility.

Conclusion

This observation emphasises the need to maintain adequate contraceptive cover, especially as more mentally handicapped adults are removed from supervised institutions and encouraged to live within the community.

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