survived. A comparison of features observed in all seven patients is reviewed below (table). The most prominent features in all, or nearly all, cases include microcephaly (6/7) dolichocephaly (3/7), micrognathia (5/7), epicanthic folds (5/7), low set or malformed ears (6/7), and ptosis (7/7). Visceral anomalies seen in the current case were renal cysts with hypoplasia of the bladder and ureters, fused adrenal glands, and anomalous mesenteric attachment. The radiological finding of hypoplastic clavicles has been seen in trisomy 17 and 18. Microscopic renal cystic disease has been found in between 1 per 1000 and 5 per 100 paediatric necropsies, and is often associated with multiple malformations, most commonly oesophageal atresia or other anomalies of the gastrointestinal tract, or chromosomal abnormalities. Cortical cysts have been reported in association with trisomies 13, 18, and 21, and Turner’s syndrome. It is interesting to note the association here, as in other established genetic syndromes, of ear abnormalities with malformations of the urinary tract.

Each of the external features described in patients with 3p- syndrome is seen in other chromosomal anomalies, most often in the better known syndromes involving alterations of chromosomes 4, 5, 13, 14, 15, 18, and 21, as well as in patients damaged antenatally by drugs, infection, or other external causes. Consistent association of visceral anomalies with these characteristics cannot be evaluated on the basis of a single case. However, the constellation of growth and mental retardation, microcephaly, dolichocephaly, micrognathia, epicanthic folds, low set or malformed ears, ptosis, and postaxial polydactyly may constitute a recognisable clinical syndrome.

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References

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Down’s syndrome with a recombinant tandem duplication of chromosome 21 derived from a maternal ring

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SUMMARY An account is given of the cytogenetic investigations of a girl with Down’s syndrome found to have a dicentric duplication of chromosome 21. This tandem type of rearrangement was interpreted as a recombinant derived from a single meiotic crossover between a maternal ring 21 and its normal homologue. A population of cells was also found in which breakage of the dicentric resulted in a chromosome 21 with a small terminal deletion. The mother and the proband’s younger brother, who was also a ring 21 heterozygote, were both clinically normal.

A high proportion of those who possess a ring chromosome manifest clinical abnormalities owing to the deletion of material from the ends of the affected chromosome, and possibly also to the
inherent instability of the ring which leads to dynamic mosaicism. Nevertheless, there are cases recording phenotypically normal or minimally affected carriers of an autosomal ring chromosome and in some instances familial transmission has been described.1–3

As far as ring chromosome 21 is concerned, a number of reported cases have occurred in severely affected subjects with certain clinical features in common (reviewed by Ferrante et al4), and other cases have been associated with a Down’s syndrome phenotype.5

Not all ring 21 heterozygotes follow these patterns of abnormality, however,6 and in this report we describe a phenotypically normal female heterozygote whose first child, with many clinical features of Down’s syndrome, was found to carry a dicentric duplication of chromosome 21 probably resulting from a meiotic crossover between the ring and its normal homologue.

It is believed that the phenomenon of recombination in a ring chromosome heterozygote has not been described previously in man, although recombinant products of pericentric inversions6 and complex rearrangements have been reported.7

Case report

The proband was born in 1977, the first child of unrelated parents, a 25 year old mother and a 30 year old father. Labour was induced at 38 weeks’ gestation owing to fetal distress and forceps delivery was necessary. She was 2.56 kg at birth and was noted to have mongoloid facies, clinodactyly, and hypotonia. Down’s syndrome was suspected and chromosome studies revealed the abnormal karyotype described below which was considered to be consistent with the clinical features.

She became an active and responsive baby and the health visitor’s reports up to 2½ years of age indicate that she was not markedly delayed in her milestones. She attended a normal infants school from 4½ years of age, but as she showed developmental delays in various areas, she repeated her year in the reception class. She made considerable progress there, although her attainments were poor compared with her classmates, and at 5½ years the Stanford-Binet test indicated intellectual functioning within the below average range. She was beginning to read but her concentration span was poor and she was receiving speech therapy.

Her mother, who is mentally and physically normal, despite carrying a ring chromosome 21, has had three other pregnancies, two of which ended in spontaneous abortion at 8 and 12 weeks, the third resulting in the birth of a clinically normal son in whom the ring 21 was diagnosed antenatally. He is now 2 years of age and developing normally.

Cytogenetic investigations

The proband

Chromosome studies were first carried out on cultures of blood taken at birth. Trypsin G banding showed a tandem rearrangement interpreted as a direct duplication8 involving the majority of the long arm of chromosome 21 (fig 1a, b). This was later confirmed by BrdU/R banding (fig 1c) and the karyotypic abnormality was considered to be consistent with the clinical diagnosis of Down’s syndrome.

C banding showed the abnormal chromosome to have two regions of constitutive heterochromatin, one sub-terminal at the centromeric constriction and the other interstitial in the middle of the long arm (fig 1d). Silver staining revealed small sub-terminal

![Figure 1](http://jmg.bmj.com/)

**FIG 1** The chromosome abnormality in the proband. (a, b) G banding demonstrates the direct (tandem) duplication of chromosome 21. The normal 21 is to the left. (c) R banding after BrdU incorporation. Note the secondary constriction in the region of the interstitial satellite stalks. (d) C banding shows two regions of constitutive heterochromatin. (e) Silver staining shows two NOR regions. (f) Non-banded preparation shows the secondary constriction (arrowed).
FIG 2  Homologues of chromosome 21 from the proband showing the deletion which is believed to have originated by breakage of the dicentric duplication chromosome. (a) G banding. (b) R banding after BrdU incorporation. The normal homologue is to the left.

FIG 3  The maternal ring 21. (a) Non-banded preparation. (b) G banding, double sized ring. (c) Silver stain/phase contrast to show nucleolar organiser. (d) Silver stain/phase contrast showing ring in satellite association with two D group chromosomes.

and interstitial NOR regions in a proportion of cells (fig 1e), and in non-banded preparations a secondary constriction was sometimes visible in the mid region of the long arm (fig 1f), where its position suggested that it represented the interstitial satellite stalks (NOR region).

These investigations indicated that the abnormal chromosome was structurally dicentric, with suppression of the median centromeric region and breakpoints distal to the NOR in the short arm (p13) and close to the tip of the long arm (q22:2 or 22:3).

In four out of 50 cells from the cultures grown at birth the dicentric duplication chromosome was absent, and in its place was a 21 which apparently had a terminal deletion of the tip of the long arm (band q22:3) (fig 2). This chromosome was believed to represent the proximal part of the dicentric
duplicated chromosome which became broken at anaphase owing to incomplete suppression of the interstitial centromere. The proportion of cells containing the deleted 21 was found to be higher in blood cultures analysed at 2, 4, and 6 years of age (table), eventually becoming the predominant cell line. It was impossible to ascertain whether the deletion was identical in all cells, having originated from a single breakage event, or whether breakage occurred on different occasions giving rise to different populations of cells with indiscernibly different deletions. There was no evidence of a C band or a silver staining region on the distal end of the deleted 21.

A skin biopsy was obtained at 4 years of age, and 134 metaphases examined from fibroblast cultures over 26 passages revealed no instability of the dicentric duplication chromosome.

Following the ISCN (1978) guidelines the karyotype may be written as 46,XX,−21,+dup(21) (p13→q22)/46,XX,−21,+del(21)(q22).

THE MOTHER

Extensive examination of metaphases from blood cultures showed a ring chromosome 21 in every cell, typically with a 'figure of eight' configuration (fig 3a). In a proportion of metaphases (which varied considerably from culture to culture) a double sized, presumably dicentric, ring was present (fig 3b) and occasionally cells with two double sized rings were seen. Owing to the small size of the ring, it was not possible to identify the breakpoints accurately by G banding. C banding was uninformative but silver staining revealed the presence of an active NOR region (fig 3c) and the ring chromosome was frequently observed to engage in satellite association with acrocentric chromosomes (fig 3d).

The breakpoint in the short arm was considered, therefore, to be distal to the NOR region, that is, in band p13. In view of the carrier's normal phenotype it was believed that minimal deletion of long arm material had occurred and the karyotype was interpreted as 46,XX,−21,+r(21)(p13→q22·3).

OTHER FAMILY MEMBERS

Chromosome analysis of metaphases from an amniotic fluid specimen taken from the mother at 16 weeks' gestation revealed a male karyotype with the ring chromosome 21. As in the mother, both monocentric and dicentric rings were seen. The karyotype was confirmed on a culture of blood obtained at the birth of the normal male child. The father and maternal grandparents of the proband all had normal karyotypes.

THE RELATIONSHIP BETWEEN THE KARYOTYPE OF THE PROBAND AND HER MOTHER

The most straightforward explanation for the origin of the dicentric duplication chromosome 21 is that it arose by a single meiotic crossover between the

![Diagram](http://jmg.bmj.com/)

**Fig 4** Diagram to show the origin of the dicentric duplication chromosome 21 by a single meiotic crossover between the ring 21 and its normal homologue. The ring chromosome material is shaded. S represents the satellite stalks (NORs) in the ring. The nullisomic first polar body and the disomic second polar body may be regarded as having the potential to form gametes.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Age at investigation (yr)</th>
<th>No of cells examined</th>
<th>Dicentric duplication</th>
<th>Deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>0</td>
<td>50</td>
<td>46</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>50</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>50</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>50</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>Skin</td>
<td>4</td>
<td>134</td>
<td>134</td>
<td>0</td>
</tr>
</tbody>
</table>
maternal ring 21 and its normal homologue, as shown in fig 4. Given this interpretation it is possible to describe the recombinant karyotype as 46,XX,−21, +rec(21)dic,r(21)(p13q22−3)mat, although it should be stressed that the ISCN\(^8\) makes no specific provision for this particular event and the shorthand form does not account for the subsequent deletion. The dicentric duplication chromosome can also be generated by various types of multiple crossover (see discussion).

**Discussion**

The detection of recombination in a ring chromosome heterozygote is believed to be extremely rare, firstly because only a very small minority of heterozygotes are clinically normal enough to achieve reproductive status, and secondly because the dicentric duplication chromosome generated by recombination is inherently unstable.

The history of abnormality and miscarriage in the heterozygote in the present report is not unexpected. A significant proportion of gametes produced must be unbalanced as, at meiosis, only a two strand double crossover between the ring and the normal homologue reliably produces balanced gametes. A single crossover results in a significant proportion of unbalanced gametes, not only the dicentric duplication type which we have demonstrated, but also nullisomic and disomic types (fig 4). Three and four strand double crossovers also generate high proportions of the same abnormal gametes and one type of three strand double results in a single tricentric product. Crossing over between the normal 21 and a dicentric ring also produces a variety of unbalanced and unstable forms.

The cell line containing the deleted 21, originating by breakage of the dicentric duplication chromosome, indicates incomplete suppression of the interstitial centromere at least during some stage of early development if not throughout life. The apparent progressive selection by which the deleted 21 cell line eventually became predominant in blood cultures is interesting and it is tempting to speculate on whether this cell line had a better genetic balance than the dicentric duplication cell line. Had the same phenomenon occurred in other tissues, it might possibly have been reflected in the child’s relatively good progress, but this may not be so, however, as no such evidence of chromosomal instability was found in the fibroblast culture. Also, the instability of the ring chromosome in the two heterozygotes, which led to considerable genetic imbalance in mosaic form, had no detectable clinical effect.

The phenomenon of centromeric suppression through which a dicentric chromosome becomes stabilised (a pseudodicentric\(^8\)) is now familiar and a number of dicentric 21s associated with Down’s syndrome have been reported.\(^9−12\) These, however, are isodicentric (mirror image) structures unlike the dicentric duplication chromosome described here, but it should be noted that in all of those reports the dicentric 21 was referred to confusingly as a ‘tandem translocation’.

We thank Dr R D G Creery for referring this family.

**References**


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