An unusual case of mosaic Down's syndrome involving two different Robertsonian translocations

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SUMMARY A baby girl with some of the stigmata of Down's syndrome was found to be a mosaic with three different cell lines: 45,XX,−13,−21,+t(13q21q)/(46,XX/46,XX, −21,+t(21q21q). The chromosome rearrangements detected in this patient appear to have arisen de novo. In the normal cell line the terminal end of the p arm of one chromosome 21 is thought to have been damaged. It seems probable that this is related to the other chromosomal anomalies found.

Down's syndrome affects about one in 750 liveborn children[1] and it is associated with a variety of karyotypes. Approximately 92·5% of all cases have primary trisomy 21, while about 4·8% have the extra chromosome 21 material present in the form of either an unbalanced Robertsonian translocation or as an isochromosome for the long arm of chromosome 21. The remaining 2·7% have heterogeneous karyotypes including mosaicism, double trisomies, and reciprocal translocations.[2]

Chromosomal mosaics usually have two karyotypically distinct cell lines and usually whole chromosomes are involved. Sex chromosome mosaicism sometimes involves more than two cell lines and autosomal mosaics with more than two cell lines have been reported occasionally.

However, mosaicism involving an autosomal structural rearrangement is uncommon. True mosaics involving more than one structural rearrangement are extremely rare, with only a few documented cases having two different Robertsonian cell lines.[2–6]

This report describes a girl with three different cell lines, involving two separate Robertsonian translocations. The possible developmental and mechanistic origins of the three cell types are discussed. The most likely clinical prognosis for the proband is suggested, taking relevant published reports on similar cases into consideration.

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Case report

The patient was born at term in February 1987 weighing 2800 g after a normal pregnancy and delivery. The mother was 27 years old and the father 29. This was their first child and neither parent has any family history of Down's syndrome.

Some features of Down's syndrome were noted in the infant soon after birth and she was referred for cytogenetic analysis. Physical examination showed a typical mongoloid slant to the eyes, low set ears, a single palmar crease, broad hands with stubby fingers, a large space between her big toe and the rest of her toes, and a slightly protuberant tongue.

In the abdomen, a few minor abnormalities were noted including diverticulated recti and a small umbilical hernia. The heart and respiratory system appeared normal.

On assessment at the age of nine months her development was found to be well within the normal range.

Materials and methods

Peripheral blood lymphocytes were cultured and harvested by standard methods. G banding,[7] C banding,[8] and nucleolar organiser region silver staining[9] techniques were used to analyse the patients' chromosomes. A total of 1000 cells of the child and each parent was analysed.

Results

The child was found to have three cell lines, a normal line and two containing chromosomal rearrangements. Thus, 62·9% were 45,XX,−13, −21,+t(13q21q), 21·1% were 46,XX, and 16% were 46,XX,−21,+t(21q21q) (fig 1). No other abnormal cell lines were found in the 1000 cells examined.

Close scrutiny of the chromosomes suggested that the normal cell line of the child contained a chromosome 21 that did not resemble those present in the cells of either parent (fig 1). The chromosomes

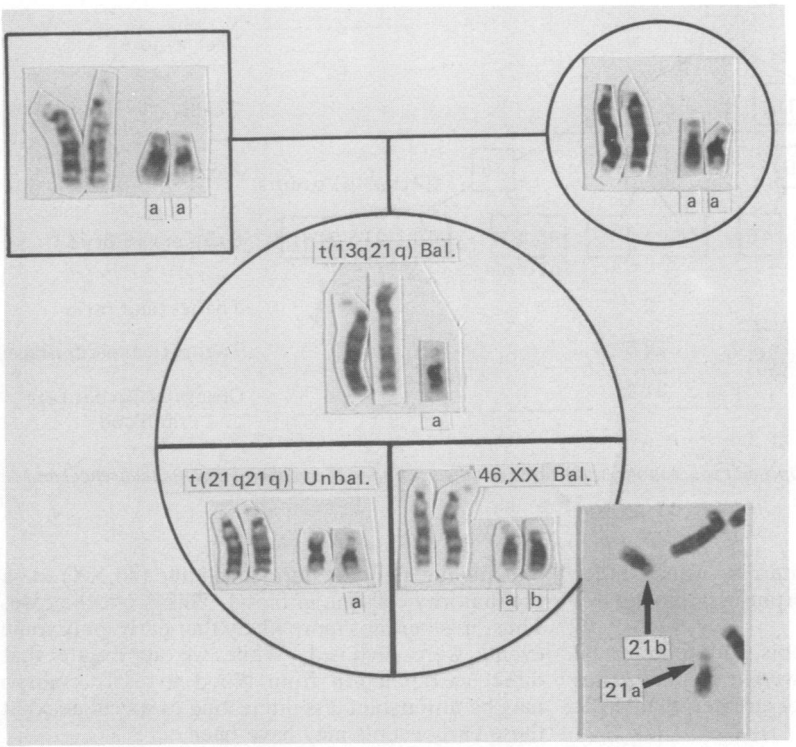

FIG 1 *G banded partial karyotypes from father and mother and all three cell lines from the proband. The polymorphically distinct 21b is illustrated in two partial cells to show the consistency of this observation.*

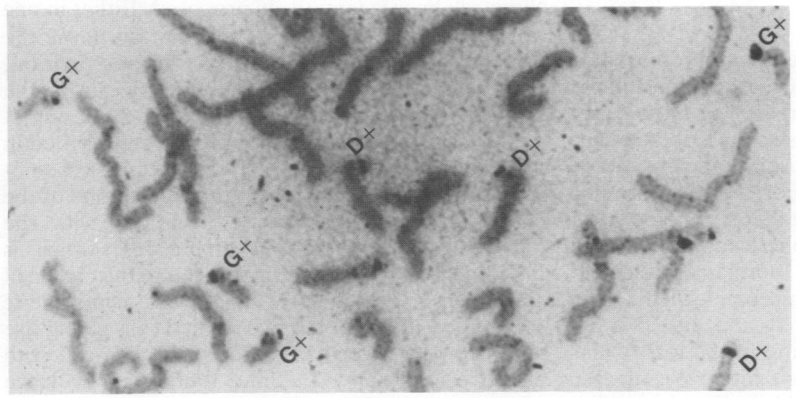

FIG 2 *Partial metaphase (Ag-NOR staining) from the 46,XX cell line in the proband, showing that the stalk regions of all four G group chromosomes stain positively.*

21 from the parents all had long p arms with stalks and satellites (type a) while the polymorphically distinct 21 in the child appeared to have a shorter p arm (type b). Solid staining and various banding methods showed no evidence of satellites being present, but stalk regions were present and stained positively with the Ag-NOR method (fig 2). This altered chromosome 21 (21b) could not be seen as a free chromosome in either of the cell lines of the child that contained a rearrangement, implying that this chromosome was the one involved in both the rearrangements.

Ag-NOR staining showed no active nucleolar organiser regions in either the t(13q21q) or the t(21q21q) and C banding suggested that both translocations were monocentric. Thus, the t(21q21q) may be an isochromosome.

The C banding polymorphisms are the same in all three cell lines of the child, supporting the suggestion that she is not a chimera but a true mosaic. There

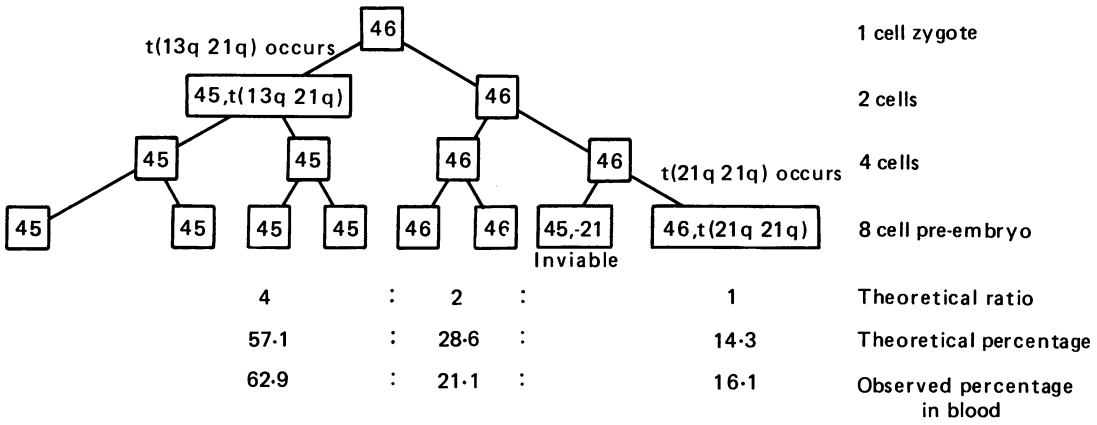

FIG 3 *Diagram to illustrate the proposed explanation for the three cell lines found in the proband and the theoretical and observed relative proportions.*

was no evidence of non-paternity from either C banding or Ag-NOR polymorphism, although this cannot be excluded.

The karyotypes of both parents were found to be normal. One thousand cells were examined, thus ruling out 1% mosaicism with greater than 99% confidence in blood.

Discussion

It has been shown[10] that telocentric chromosomes are unstable and readily give rise to isochromosomes. There have been several reports[11 12] of mosaicisms in which one cell line contains a Robertsonian translocation or an isochromosome and the other cell line carries a telocentric D or G group chromosome. It therefore seems likely that such telocentric chromosomes may undergo Robertsonian translocations more frequently than normal acrocentric chromosomes. While the chromosome called 21b in this report is not telocentric it appears to have sustained some damage resulting in the loss of the terminal end of the p arm or satellites. We suggest that this could have had a similar effect in predisposing chromosome 21b to undergo rearrangements, until a stabilisation event resulted in its present stable form.

The presence of three cell lines, including a normal cell line, suggests postzygotic origin. Unfortunately, it has not been possible to obtain other tissues to verify the mosaicism seen in blood. However, the clinical features suggest that the 46,XX,−21,+t(21q21q) cell line is likely to be present in other tissues. Furthermore, if the abnormalities had occurred late in the developing embryo, one might expect the normal cell line (46,XX) to be the majority cell line in blood. This is not the case. Thus, it is perhaps more likely that early embryonic events were involved. While we appreciate that direct extrapolation from blood to early embryo may be unreliable, it is interesting to speculate what these early events may have been.

The following explanation of the origin of the three cell lines is tentatively proposed. Either in one of the gametes that came together to form the 46,XX zygote, or before the first zygotic division, one chromosome 21 sustained an injury causing the end of the p arm to be lost, thus rendering it unstable. The first division of this zygote resulted in two cells. In one of these cells the unstable chromosome, 21b, underwent translocation with one of the chromosomes 13 giving rise to a cell with the karyotype 45,XX,−13,−21,+t(13q21q), which is functionally normal. During division to the eight cell stage, chromosome 21b underwent centromeric misdivision in one of the two normal cells giving rise to a cell with effective trisomy 21 and a cell with effective monosomy 21. Since there is no evidence of a monosomy 21 cell line, an assumption is made that it may have been inviable. In the other normal cell (at the four cell stage) chromosome 21b is assumed to have become stable, thus limiting the number of abnormal cell lines.

The viable cell lines in the eight cell pre-embryo would then be in the theoretical proportions 4:2:1. It may be purely coincidental that this is a fairly close match to the proportions observed in blood.

Lieber and Shah[6] reported a very similar case of a boy with the same karyotype but in whom the trisomic cell line made up almost 50% of the cells.

Their patient had no clinical features of Down's syndrome but was moderately mentally handicapped. This provides an interesting contrast with the present case in which only 16% of the cells were found to be trisomic together with mild physical Down's stigmata, but apparently normal development to date. While it cannot be said with certainty that the number of trisomic cells will be proportional to the degree of mental handicap, this has been suggested by some authors. We are hopeful that the prognosis for the present case will be as good as, if not better than, the similar case reported by Lieber and Shah,[6] who had a much higher proportion of effectively trisomic cells. The fact that the majority of cells in our patient are balanced or normal (>80%) leads to the tentative suggestion that she will not be greatly handicapped. This is supported by her normal developmental progress at nine months, when she was considered to be a happy, responsive baby, rated as above average by her guardian. It would have been interesting to look at the relevant proportions of the three cell types in other tissues (for example, skin), but it has not proved practical to obtain a skin biopsy. Should the child progress normally, as we predict, this poses a future genetic counselling problem, since preconceptional counselling may be required based on theoretically complicated meiotic possibilities, although prenatal diagnosis may prove to be quite straightforward. We would like to hear from other cytogenetic centres with experience of similar cases.

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