FIG 3 Partial karyotypes of the proband showing centric fission of chromosome 4 (GTG banding).

Discussion

This appears to be the first published case report of transmitted centric fission of chromosome 4 so far. It is interesting to observe the particular stability of human telocentric chromosomes, which involve a high risk of transmission of non-balanced gametes.

In sibships A and B there are early spontaneous abortions which could be attributed to the unbalanced form of the aberration. Another point worthy of attention is the possible clinical interpretation of the two children of sibship B, who died at 6 months and 12 years, respectively. Their phenotype was deduced from the clinical history and the photographs.

Table 2 lists the symptoms described in cases of partial aberrations of chromosome 4 and allows a comparison with those present in the two dead children as a possible aid to a specific diagnosis.

Of the various clinical manifestations described in table 1, subject IV.11 presented with a normal birth weight, flat and wide nasal bridge, mongoloid slant, absence of strabismus, and died at 6 months. These symptoms are also found in cases

of partial 4q— suggesting that partial monosomy of the long arm of chromosome 4 was present in this child.

Subject IV.15 presented with a beaked nose, pronounced micrognathia, strabismus, and marked hypoplasia of the mandible. Death occurred at 12 years. This appears to be consistent with malformations found in partial monosomy of the short arm of chromosome 4. In particular, the age of death is similar to the only case reported⁶ of survival through the first year of life in a subject with partial 4p monosomy.

We would like to thank Mr Mario Sanchioni for his help with the photographs.

References

- 1 Sinha AK, Pathak S, Nora JJ. A human family suggesting evidence for centric fission and stability of a telocentric chromosome. *Hum Hered* 1972;**22**:423-9.
- 2 Hansen S. A case of centric fission in man. *Hum Genet* 1975;**26**:257-9.
- 3 Fryns JP, Bulcke I, Hens L, Van den Berghe H. Balanced transmission of centromeric fission product in man. *Hum Genet* 1980;**54**:127-8.
- 4 Janke D. Centric fission of chromosome 7 in three generations. *Hum Genet* 1982;**60**:200-1.
- 5 Dallapiccola B, Mastroiacovo P, Gandini E. Centric fission of chromosome 4 in the mother of two patients with trisomy 4p. *Hum Genet* 1976;**31**:121-5.
- 6 Miller OJ, Breg WR, Warburton D, *et al*. Partial deletion of the short arm of chromosome 4 (4p-): clinical studies in five unrelated patients. *J Pediatr* 1970;**77**:792-9.

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Mosaic Down's syndrome with de novo 45,XX,-21,-22,+t(21q;22q)/46,XX,-21,+t(21q;21q) rearrangement

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SUMMARY The occurrence of mosaic Down's syndrome with two independent Robertsonian translocation cell lines is very rare. Such a patient is reported here, in whom an unbalanced Robertsonian translocation between two chromo-

somes 21 was detected in the majority of cells. The patient also revealed a minor cell line with a second Robertsonian translocation involving a chromosome 21 and a 22. The chromosome translocations detected in this patient were de novo in origin.

Received for publication 28 November 1983.
Accepted for publication 20 December 1983.

Down's syndrome is associated with a remarkable degree of karyotypic variation. Approximately 92.5% of all patients with this condition have an additional chromosome 21 resulting in a karyotype with 47 chromosomes. In about 4.8%, the extra chromosome 21 material is present either in the form of an unbalanced Robertsonian translocation (Dq;21q or Gq;21q) or as an isochromosome for the long arm of chromosome 21. Patients with any of the above chromosome complements present the characteristic phenotype of Down's syndrome. The remaining 2.7% have heterogeneous karyotypes such as mosaicisms and double trisomies and often exhibit variability in the expression of the phenotype.¹

A milder Down's syndrome phenotype has been reported in some patients with tandem duplication of the distal long arm of chromosome 21.^{2,3} From the hypotheses of Niebuhr² and Aula *et al*⁴ and from the information available from the family reported by Williams *et al*,⁵ it is evident that the major features of Down's syndrome phenotype are associated with the trisomic state for the 21q22→qter region. By contrast, trisomy for the short arm and the proximal long arm of chromosome 21 (21pter→q21) is associated with minor anomalies and mental retardation without the entire clinical spectrum of Down's syndrome.⁵

Complex balanced translocations involving more than a single event and more than two chromosomes, though very rare, have been recorded in man. The reports of Creasy *et al*,⁶ Bell and Warburton,⁷ Seabright *et al*,⁸ Stoll *et al*,⁹ Simoni *et al*,¹⁰ Tabor *et al*,¹¹ and Chewings *et al*¹² provide examples of translocations involving more than two autosomes in the same cell. Similarly, different Robertsonian translocations leading to at least two cell types in the same person are also known.¹³⁻¹⁶ To our knowledge there are reports of at least four patients with mosaicism for two different Robertsonian translocations, three resulting in mosaic Down's syndrome¹³⁻¹⁵ and the fourth resulting in mosaic trisomy 13.¹⁶ An additional patient with mosaicism for two cell lines, each with a different Robertsonian translocation, 45,XX,-21,-22,+t(21q;22q)/46,XX,-21,+t(21q;21q), is the subject of this report.

Case report

The proband, a black female, was born to a gravida 2, para 1, 34 year old mother and a 35 year old father. The pregnancy and delivery were reported to be normal. At birth the infant weighed 3116 g (between the 25th and 50th centile) and had a length of 45 cm (below the 10th centile). She was referred for genetic evaluation after the age of 6 because of

the clinical diagnosis of Down's syndrome by a public school system soon after enrolment, and because she was found to have a scattered IQ between 25 and 50 on a subsequent test.

On physical examination at the age of 6 years, 11 months the child had a normally shaped head, except that the occiput was flat, and the head circumference was 49 cm (between the 5th and 10th centile). The eyes were prominent with bilateral epicanthic folds and upward slanting palpebral fissures. The ears were small and simple with the helices folded over. The nose was short with a flat nasal bridge and upturned nostrils. The tongue was normal and did not protrude from the mouth. The heart was normal. The nipples were widely spaced. Organomegaly was not present. There was a tiny umbilical hernia. The external genitalia were normal. Arms and legs were symmetrical and proportionate. The hands were broad and short, with short fifth fingers. The palmar creases were normal. Ulnar loops were present on all fingers except the second finger of the left hand. The axial triradii were distally placed. All joints were hyperextensible. Neurologically, no gross defects were seen.

The proband was able to dress and undress, to put on and tie shoes with a neat double knot, button and unbutton, zip jeans, and thread and buckle her belt. Fine motor skills appeared to be well developed. She wrote her name in neat printing using both capital and small letters correctly, held a pencil with no difficulty, and drew animals (cat and dog) with all parts appropriately placed. She was able to distinguish her first and last names, state her age, and indicate the same by holding up the appropriate number of fingers. In general, she demonstrated good vocabulary for her age and appeared to have normal balance and adequate gait.

CYTOGENETIC STUDIES

Karyotype analysis was performed on cultured blood lymphocytes using GTG, QFQ, and RBA banding techniques. Of the 304 metaphase spreads analysed from two independent blood samples obtained on separate occasions, 199 cells contained an unbalanced Robertsonian translocation between the long arms of two chromosomes 21 (or isochromosome for 21q) resulting in trisomy 21 with a karyotype 46,XX-21,+t(21q;21q). The remaining 105 cells had a different Robertsonian translocation involving the long arms of a chromosome 21 and a 22 with a karyotype 45,XX,-21,-22,+t(21q;22q). Chromosome analysis from cultured blood lymphocytes of both parents revealed normal karyotypes. The family refused further investigations including chromosome analysis from the skin of the patient.

Discussion

From a cytogenetic standpoint, our patient and those reported by Atkins and Bartsocas,¹³ Lieber and Shah,¹⁴ and Zellweger and Abbo¹⁵ contained at least two different Robertsonian translocation cell lines that appeared to have originated independently. Zellweger and Abbo¹⁵ described mosaicism for four cell types in their patient. The majority (59.5%) were 45,X,-D,+t(Dq;Gq), 18.5% cells were normal 46,XX, 12.5% were 45,XX,-D,-D,+t(Dq;Dq), and the remaining were 44,X,-D,-D,-G,+t(Dq;Dq) karyotypes. A D;D translocation was also detected in a mosaic state in their patient's father and paternal grandmother. The specific origin of the four cell types in the patient remains to be explained.

The two mosaic cell lines noted in our patient were an unbalanced Robertsonian translocation between chromosomes 21 with a karyotype 46,XX,-21,+t(21q;21q) in 66% of the cells and a Robertsonian translocation between a 21 and a 22 with karyotype 45,XX,-21,-22,+t(21q;21q) in the remaining 34%. No other cell types were noted in the lymphocyte population. Complex chromosome mosaicism with rearrangements of the above type requires more than a single cytogenetic event. The origin of two independent de novo translocations, involving two different chromosome pairs, is difficult to determine with certainty. However, the following hypotheses are advanced to explain the origin of the chromosome abnormalities in our patient.

In the first hypothesis it is assumed that the zygote had a normal 46,XX karyotype. The first

division of this zygote resulted in two cells, one with a normal 46,XX karyotype and the other with a Robertsonian translocation, karyotype 45,XX,-21,-22,+t(21q;22q). The next division of the normal cell resulted in two cells with a 46,XX,-21,+t(21q;21q) or 46,XX,-21,+i(21q) and with a 45,XX,-21 karyotype, respectively. The 45,XX,-21 cell line was subsequently selected against (fig 1). This hypothesis has some deficiencies because it has to be postulated that the two translocation events occurred sequentially at the first and second zygote divisions. Otherwise, one would expect a normal 46,XX cell line at least in small numbers. Although such a normal cell line was not observed in our patient, its existence cannot be ruled out because chromosome studies from other tissues were not performed. It is also presumed that the 45,XX,-21 cell line was either eliminated totally by selection or outgrown by the other cell types.

A second possibility is chimaerism, where two ova or one ovum and a polar body were fertilised by sperms carrying t(21q;22q) and t(21q;21q), respectively. The two zygotes later developed into a single embryo. Heteromorphism studies using QFQ banding did not reveal conclusive differences between the two cell types. Genotype studies to determine chimaerism were not possible because of the lack of cooperation from the parents.

A third explanation is that the zygote had a 47,XX,+21 karyotype. The mother was 34 years old at the time of the proband's conception and, therefore, maternal age can be considered as a likely predisposing factor for non-disjunction. It is further assumed that Robertsonian translocations

FIG 1 Schematic representation of hypothesis 1.

FIG 2 Schematic representation of hypothesis 3.

may occur between single chromatids. Soon after the formation of the 47,XX,+21 zygote two chromosomes 21 and one 22 were very intimately associated in the formation of the nucleolus when an apparent 'insult' occurred to that particular region of the cell. Replication was initiated and proceeded from one 21q continuously into one 22q on one chromatid and from one 21q to another 21q on the other chromatid. The unaffected chromatids were separated at the centromere and segregated as independent chromosomes while the affected ones segregated as t(21q;22q) and t(21q;21q). During the same cell division the extra 21 was eliminated through anaphase lag (fig 2), resulting in two cells with 45,XX,-21,-22,+t(21q;22q) and 46,XX,-21,+t(21q;21q), respectively (U Franke, 1981, personal communication).

While all three explanations put forth are possible, we are inclined to favour the last one because it allows us to postulate that a single 'insult' occurred within a single cell leading to two Robertsonian translocation cell lines. These hypotheses may also explain the origin of similar chromosome abnormalities in the patients reported previously.^{13 14}

The authors acknowledge the review of this manuscript by Dr Robin M Bannerman of the Division of Human Genetics, Department of Pediatrics, SUNY at Buffalo. Preparation of the manuscript for publication was supported by the Department of Health and Human Services, Bureau of Maternal and Child Health, Human Genetics Program,

Project 417. The authors acknowledge the secretarial assistance of Barbara Moore.

References

- de Grouchy J, Turleau C. *Clinical atlas of human chromosomes*. New York, Brisbane, Toronto: Wiley, 1977.
- Niebuhr E. Down's syndrome: the possibility of a pathogenetic segment on chromosome no 21. *Hum Genet* 1974;**21**:99-101.
- Schuh BE, Korf BR, Salwen MJ. A 21/21 tandem translocation with satellites on both long and short arms. *J Med Genet* 1974;**11**:297-9.
- Aula P, Leisti J, van Koskull H. Partial trisomy 21. *Clin Genet* 1973;**4**:241-51.
- Williams JD, Summitt RL, Martens PR, Kimbrell RA. Familial Down syndrome due to t(10;21) translocation: evidence that the Down phenotype is related to trisomy of a specific segment of chromosome 21. *Am J Hum Genet* 1975;**27**:478-85.
- Creasy MR, Crolla JA, Polani PE, Elliott MH. A three chromosome translocation involving two homologous chromosomes in a trisomic abortus. *Clin Genet* 1976;**9**:15-9.
- Bell EF, Warburton D. Two reciprocal translocations associated with microcephaly and retardation. *J Med Genet* 1977;**14**:141-2.
- Seabright M, Gregson N, Pacifico E, et al. Rearrangements involving four chromosomes in a child with congenital abnormalities. *Cytogenet Cell Genet* 1978;**20**:150-4.
- Stoll C, Flori E, Macler J, Renaud R. Prenatal diagnosis and postnatal follow-up of an abnormal child with two *de novo* apparently balanced translocations. *Hum Genet* 1979;**47**:221-4.
- Simoni G, Montali E, Rossella F, Dalpra L, Lo Curto F. A woman carrier of two apparently unrelated reciprocal translocations. *Hum Genet* 1979;**46**:159-62.

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- ¹¹ Tabor A, Jensen LK, Lundsteen C, Niebuhr E. A 5;7, 5;12 double reciprocal translocation in a normal mother and a 5;7 translocation with a recombinant chromosome 5 in her normal child. *J Med Genet* 1981;**18**: 307-9.
- ¹² Chewings WE, Cocks TP, Gardner RJM, Clarkson JE. A malformed baby with two separate de novo translocations. *J Med Genet* 1982;**19**:70-1.
- ¹³ Atkins L, Bartsocas CS. Down's syndrome associated with two Robertsonian translocations, 45,XX,-15,-21,+t(15q;21q) and 46,XX,-21,+t(21q;21q). *J Med Genet* 1974;**11**:306-9.
- ¹⁴ Lieber E, Shah P. Two Robertsonian translocations in a boy with mental retardation. *J Med Genet* 1982;**19**: 229-32.
- ¹⁵ Zellweger H, Abbo G. Familial mosaicism attributable to a new gene. *Lancet* 1965;i:455-7.
- ¹⁶ Anderson CE, Shulkin JD, Mohandas T. Mosaicism for trisomy 13 with 13/13 translocation and a balanced 13/21 translocation in a patient with 13p-. *Am J Hum Genet* 1979;**31**:87A.

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