References

- ¹ Bergsma D, ed. *Birth defects atlas and compendium*. 2nd ed. The National Foundation-March of Dimes. Baltimore: Williams and Wilkins, 1979.
- ² Beighton P, Price A, Lord J, Dickson E. Variants of the Ehlers-Danlos syndrome: clinical, biochemical, haematological and chromosomal features of 100 patients. *Ann Rheum Dis* 1969;**28**:228-42.
- ³ Dockery HE, Neale HC, Fitzgerald PH. Gross congenital abnormality associated with an apparently balanced chromosomal translocation t(9;17)(q34;q11). *J Med Genet* 1982;**19**:380-3.
- ⁴ McKusick VA. *Human genetics*. New Jersey: Prentice Hall, 1964.
- ⁵ Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS, eds. *The metabolic basis of inherited disease*. 5th ed, chap 63. New York: McGraw-Hill, 1983:1434-7.

Correspondence and requests for reprints to Dr P R Scarbrough, Laboratory of Medical Genetics, University of Alabama in Birmingham, University Station, Birmingham, Alabama 35294, USA.

Mosaic hexasomy 21 *

A KETUPANYA†, B F CRANDALL‡, K BLANCHARD†, AND D W ROGERS§

Departments of Obstetrics and Gynecology† and Pediatrics and Psychiatry‡, UCLA; and §Pathology Department, Santa Monica Hospital, Los Angeles, California, USA.

SUMMARY Cases in which there are more than three copies of a sex chromosome, and rarely of an autosome, have been reported, but to our knowledge hexasomy has never been described except in tissue undergoing neoplastic change. This report describes a female infant with multiple malformations in whom we found a mosaic hexasomy 21. This was first detected in amniotic fluid cells and subsequently in skin fibroblasts.

Case report

Spontaneous delivery of this female infant occurred at about 36 weeks' gestation. Birth weight was about 4000 g and the head circumference was 34 cm. Respirations were gasping and irregular and there was acrocyanosis with dusky discolouration of the lips. The anterior fontanelle was large and cranial sutures, including the metopic, were widely open. Despite its circumference, the head appeared small in comparison to the body. There was marked hypertelorism with short upward slanting palpebral fissures. The globes were small and the corneae cloudy. There was a right sided cleft of the lip, complete cleft of the palate, and marked nasal hypoplasia. The ears were low set and rotated, and the lobes were fleshy. The neck was short with redundant soft tissue folds posteriorly.

*This research was supported in part by HD 5615, Developmental Biology in Mental Retardation, and HD 04612, Mental Retardation Research Center grant.

Received for publication 15 September 1983.

Accepted for publication 3 October 1983.

The chest was narrow with hypoplastic nipples. The heart was normal on auscultation. The sternum was of normal length. External genitalia were normal female and the anus was anteriorly placed. The spine appeared normal.

The upper limbs were hypotonic and abnormalities were confined to the hands. Both thumbs were triphalangeal and the fingers were tapered with hypoplastic nails. There was camptodactyly of fingers 4 and 5 on the right and clinodactyly of the right second and left fourth fingers. There were simian lines bilaterally. Dermatoglyphs were unremarkable.

The lower limbs were hypotonic with prominent heels and a midplantar vertical crease bilaterally.

The baby died shortly after birth. Necropsy confirmed the physical observations. The heart was normal on gross examination and the brain on gross and microscopical study. X-ray examination failed to reveal any skeletal abnormalities and confirmed the clinical impression of borderline microcephaly.

The mother and father were both aged 36 and in good health. There had been two previous pregnancies, one ending in an early spontaneous abortion and the second with a normal female whose development has been entirely normal. There was no other relevant family history.

The pregnancy had been unremarkable except for an influenza-like illness early in gestation which lasted about one week. An amniocentesis was requested because of maternal age and was performed at about 16 weeks' gestation.

Case reports

FIGURE Partial karyotypes of (a) chromosomes 21, (b) two marker chromosomes, and (c) chromosomes 22 using G banding. The two marker chromosomes appear to be identical and most likely to be a 21;21 translocation.

CYTOGENETIC STUDIES

Cultures were established in three flasks and four of 48 cells in culture A showed a 48,XX,+mar,+mar pattern (figure). Cells from two additional culture dishes were examined and each one contained a single cell with the same two additional marker chromosomes. Thus, of 150 cells examined, six were hyperdiploid. G, R, and C banding was attempted and the two marker chromosomes appeared to be identical and each probably a 21;21 translocation. It was the mother's decision to continue the pregnancy.

Venous blood and a skin biopsy were taken shortly after birth for chromosome studies and the results of these studies, as well as ones of both parents, are shown in the table. Fewer than 10 mitotic spreads were found in preparations from peripheral blood. In skin fibroblast cells, eight of 86 cells showed the same two marker chromosomes. Only one centromere could be identified. Because of the small number of cells with these two markers,

no attempt was made to measure superoxide dismutase-1 (SOD-1).

Parental chromosomes from both peripheral blood lymphocytes and skin fibroblasts were entirely normal.

Discussion

We have described a severely malformed infant whose phenotype did not resemble Down's syndrome and who appeared to have a mosaic hexasomy 21. This change was found in about 4% of cells examined at amniocentesis and nearly 10% of skin fibroblasts. While some cases have occasionally been reported with multiple X and Y chromosomes, six copies of an autosome have never been described to our knowledge, except in leukaemia or tumour tissue.

There are three published reports of tetrasomy 21.¹⁻³ In one case there were two extra chromosome 21s present in all the peripheral blood lymphocytes counted. Fibroblasts were not studied. The phenotype was typical of Down's syndrome. The infant died at 4 days of respiratory problems complicated by congenital monocytic leukaemia.¹ Another report describes a mosaic 21;21 translocation or isochromosome 21 with severe mental retardation and dysmorphic changes not particularly suggestive of Down's syndrome. The chromosome abnormality was only present in skin fibroblasts where all cells carried the marker chromosome.² SOD-1 levels were reported to be normal. The third case also had a 47,XY,t(21;21) karyotype identified in all skin

TABLE Results of chromosome studies.

Subject	Tissue	No of chromosomes	
		46	48 (%)
Fetus	Amniotic fluid	144*	6 (4)
Neonate	Blood	10	0
	Skin	78	8 (10)
Mother	Blood	50	0
	Skin	60	0
Father	Blood	50	0
	Skin	10	0

*From three separate culture dishes.

fibroblasts examined and in 3% of blood lymphocytes. Facial features were very suggestive of Down's syndrome.³

Tetrasomy of chromosomes 9, 18p, and 22 have also been described.⁴⁻⁶ The apparent rarity of these cases may be because of their loss early in pregnancy, or because of mosaicism with very few aberrant cells, or because the aberration occurred in fibroblasts rather than lymphocytes. It is of interest that autosomal tetrasomy was not detected in one study of spontaneous abortions.⁷

This chromosome change may result from a Robertsonian translocation or an isochromosome. It could have occurred in either parent at meiosis followed by mitotic non-disjunction affecting both the marker and the No 21 chromosome, or the change could have been initiated at an early mitosis followed by a further non-disjunction. Selection against the hyperdiploid cells may account for the infrequency of this cell line. Hyperdiploid cells are known to have a longer cell cycle.

Both the relative infrequency of the hexasomic cell line as well as its distribution suggests the importance of fibroblast studies and the need to count sufficient cells when there is a strong suspicion of a chromosome abnormality.

The authors thank Ms Connie Hsi for excellent

technical support and Ms Sasha Biletsky for clerical assistance.

References

- ¹ Jabs EW, Stamberg J, Leonard CO. Tetrasomy 21 in an infant with Down syndrome and congenital leukemia. *Am J Med Genet* 1982;12:91-5.
- ² Fryns JP, Petit P, Vinken L, Geutjens J, Marien J, Van den Berghe H. Mosaic tetrasomy 21 in severe mental handicap. *Eur J Pediatr* 1982;139:87-9.
- ³ Hunter AGW, Clifford B, Speevak M, Brock MacMurray S. Mosaic tetrasomy 21 in a live born male infant. *Clin Genet* 1982;21:228-32.
- ⁴ Moedjono SJ, Crandall BF, Sparkes RS. Tetrasomy 9p: confirmation by enzyme analysis. *J Med Genet* 1980;17:227-9.
- ⁵ Côté GB, Petmezaki S, Bastakis W. A gene for hypospadias in a child with presumed tetrasomy 18p. *Am J Med Genet* 1979;4:141-6.
- ⁶ Schinzel A, Schmid W, Fraccaro M, *et al.* The 'cat eye' syndrome: dicentric small marker chromosome probably derived from a No 22 (tetrasomy 20 pter to q11) associated with a characteristic phenotype. *Hum Genet* 1981;57:148-58.
- ⁷ Hassold T, Chen N, Funkhouser J, *et al.* A cytogenetic study of 1000 spontaneous abortions. *Ann Hum Genet* 1981;44:151-78.

Correspondence and requests for reprints to Dr B F Crandall, Division of Medical Genetics, Departments of Pediatrics and Psychiatry, University of California, Los Angeles, California 90024, USA.