male¹ and in a 24-year-old female.² In addition, many cases of duplication-deletion following pericentric inversions of chromosome 3, inv(3)(p25q21) or inv(3)(p25q25) have been reported,² all of whom had monosomy of 3p25→pter and trisomy of segments of 3q. Trisomy 1q32→qter because of a familial rearrangement was observed in three neonates who died in early infancy³⁻⁵ and in two male adults.⁶ Probable de novo direct duplication of a similar segment has also been reported in two newborns.^{7,8} The combination of the two previously mentioned aberrations was assumed from G banded karyotypes of a 1-year-old girl with a de novo rearrangement of chromosome 3.⁹

The table lists major clinical features of the proband compared to the case of Yunis *et al*⁹ and to cases with pure monosomy 3p25→pter^{1,2} and to cases with familial trisomy 1q32→qter.³⁻⁶ As many dysmorphic features are age dependent or even age specific, and as some of the patients were observed in adulthood and others in early infancy, young infants and adults are compared separately. The proband, who is the only patient who was followed clinically from early infancy to adulthood, is included in both age groups.

As seen in the table, it is at present not possible to define a characteristic pattern of abnormalities for any of the three aberrations because of the small numbers of cases with duplications of 1q32→qter, deletion of 3p25→pter, and a combination of the two aberrations. Both the more uncharacteristic findings in the proband (hypertelorism, short mandible, malformed auricles) and the more specific findings (hypertrichosis, ptosis, synophrys) were found in a proportion of cases who had only the 1q32→qter duplication or only the 3p25→pter deletion. We expect that further reports will show which aberrations are particularly characteristic of trisomy 1q32→qter, monosomy 3q25→pter, and of the combination of the two.

The author is grateful to Professor W Schmid for reading the manuscript and to Dr D Vischer for data from an early examination of the patient. He also acknowledges the skilful technical assistance of Ms Regula Zellweger.

A SCHINZEL

Institute of Medical Genetics, University of Zurich, Switzerland

References

- 1 Verjaal M, de Nef J. A patient with a partial deletion of the short arm of chromosome 3. *Am J Dis Child* 1978;132:43-5.
- 2 Fineman RM, Hecht F, Ablow RC, Howard RO, Breg WR. Chromosome 3 duplication q/deletion p syndrome. *Pediatrics* 1978;61:611-8.

- 3 Bonfante A, Stella M, Rossi G. Partial trisomy of the long arm of chromosome 1 due to a familial translocation t(1;10)(q32;q26). *Hum Genet* 1978;45:339-43.
- 4 Bourrouillou G, Colombies P, Blanc P. Trisomie 1q secondaire à une translocation réciproque maternelle. *C R Soc Biol (Paris)* 1978;172:359-62.
- 5 Rehder H, Friedrich U. Partial trisomy 1q syndrome. *Clin Genet* 1979;15:534-40.
- 6 Taysi K, Sekhon GS. Partial trisomy of chromosome No 1 in two adult brothers due to maternal translocation (1q-;6p+). *Hum Genet* 1978;44:277-85.
- 7 Steffensen DM, Chu EHY, Speert DP, Wall PM, Meilinger K, Kelch RP. Partial trisomy of the long arm of human chromosome 1 as demonstrated by in situ hybridization with 5S ribosomal RNA. *Hum Genet* 1977;36:25-33.
- 8 Flatz S, Fonatsch C. Partial trisomy 1q due to tandem translocation. *Clin Genet* 1979;15:541-2.
- 9 Yunis E, Egel H, Zuniga R, Ramirez E, Torres de Caballero OM, Leibovici M. 'De novo' trisomy 1q32→1qter and monosomy 3p25→3pter. *Hum Genet* 1977;36:113-6.

Requests for reprints to Dr A Schinzel, Department of Medical Genetics, University of Zürich, Steinwiesstrasse 75, CH-8032 Zürich, Switzerland.

Trisomy 14 mosaicism in a translocation 14q15q carrier: probable dissociation and isochromosome formation

SUMMARY A case of trisomy 14q mosaicism is described and compared with three other similar reported cases. The clinical picture is characterised by severe developmental retardation, failure to thrive, and somatic abnormalities including skeletal asymmetry, high arched or cleft palate, and low set dysplastic ears. The present chromosome imbalance probably resulted from dissociation of a balanced 14q15q translocation with subsequent formation of a 14q isochromosome.

Chromosome 14 trisomy appears to be exceedingly rare in newborns. Trisomy 14 mosaicism and partial trisomy 14 have also been very infrequently reported; a survey of published reports reveals three cases of trisomy 14 mosaicism.¹⁻³ We report an infant with trisomy 14 mosaicism probably caused by an unstable 14q15q translocation with the resulting formation of an isochromosome 14q.

Case report

The proband was born after a term pregnancy to a gravida 4, para 3, 30-year-old mother. Pregnancy and Received for publication 2 April 1980

Case reports

FIG 1 Proband at age 17 months.

delivery were uneventful and birthweight was 3604 g. Physical examination in the newborn period revealed an unusual facies, a dysplastic left ear, a cleft palate, and dislocation of the hip.

At the age of 17 months the patient weighed 8.7 kg (5th centile) and was 71 cm in length (less than 5th centile). Her occipital-frontal circumference was 46.5 cm (40th centile). The following physical abnormalities were noted (fig 1): left maxillary hypoplasia, low set ears with a dysplastic left ear, stenosis of the left exterior auditory canal, external deviation and depression of the left eye, hypoplasia of the left orbital rim, oval cleft of the soft palate, and short incurved fifth digits. Finger ridge patterns and palmar and digital creases were normal; total ridge count was not performed. There were no focal neurological deficits, no pathological reflexes, and muscle strength and movement appeared normal. Her electroencephalogram showed a normal waking pattern with background activity of 6 to 7 Hz. There was no focal slowing and no epileptiform activity. On audiological examination it was felt that the patient had an approximate 80 dB sensorineural hearing loss in the left ear. Skull and chest x-rays were normal. A CT scan of the head was normal.

Developmental testing was done at the age of 17 months. The Bayley Mental and Motor Skills of Infant Development placed the patient at a 4 to 6 month age level. She had no apparent recognition of verbal language.

Since her initial hospital discharge the proband has been in good health. She has not had seizures or recurrent respiratory infections and has been on no chronic medication.

The patient has three older sibs. There is no history of birth defects in any of her relatives including second degree relatives.

CYTOGENETIC STUDIES

Blood

A total of 287 cultured lymphocytes was analysed from the three blood samples. Of these, 255 cells (89%) had a balanced translocation $t(14q15q)$ (fig 2a). Twenty-eight cells (10%) had an apparent isochromosome of the long arm of the number 14 in place of one number 14 (fig 2b). Three cells had a clear break between centromeres of the 14q15q chromosome (fig 2c), producing chromosomes which appeared to be in satellite association. Three cells had a 46,XX complement with no discernible association between any of the D group chromosomes.

Skin

A total of 164 skin fibroblasts was analysed. Of these, 163 were 45,t(14q15q) and one was 46,-14,+i(14q).

FIG 2 D group chromosomes of proband after Giemsa banding: (a) showing the 14q15q; (b) showing the iso-14q; (c) showing centromere separation of the 14q15q.

FIG 3 D group chromosomes of proband. (a) C banding; (b) NOR staining.

In order to study further the structure of the 14q15q translocation chromosome, C banding and nucleolar organiser (NOR) staining were performed. Fig 3 shows D groups from metaphases analysed with these techniques. Inspection of C banded preparations showed two closely spaced C bands in the 14q15q chromosome (fig 3a). NOR staining in the 14q15q chromosome was not observed (fig 3b). The translocation chromosome, although similar in size to a number 3 chromosome, was easily identified by its unique staining characteristics with both C banding and NOR staining.

Examination of 20 cultured lymphocytes from both parents of the proband indicated no chromosome abnormality in either.

Discussion

The chromosome findings in the present case indicate that the patient has significant trisomy of the entire long arm of chromosome 14 and monosomy for chromosome 14 short arm (deletion of the short arms of human acrocentrics is generally not felt to be deleterious). We found three other cases of trisomy 14 mosaicism in published reports.^{1-3*} Features of these cases are summarised in the table.

Trisomy for various sections of chromosome 14 has been reported by Martin *et al*² and reviewed more recently by Miller *et al*⁴ and Lopez Pajares *et al*.⁵ Most of these cases have been trisomic for the proximal part of 14q, and a rough clinical picture of trisomy for the proximal half to two-thirds of 14q has emerged. This is characterised by mental and motor deficiency, short stature, broad flat nose with bulbous tip, large down-turned mouth, oral clefts or high arched palate, low set malformed ears, and subtle craniofacial dysmorphism manifesting in a variety of ways.

*Murken *et al*⁹ reported a case of non-mosaic trisomy 14 based on autoradiographic studies. However, since autoradiography is not a reliable means of identifying D group chromosomes¹⁰ this patient may not represent trisomy 14.

TABLE Comparison of cases with trisomy 14 mosaicism

Case	% trisomy 14 Blood	cells Skin	Clinical description
Rethoré <i>et al</i> ¹	10	10	Mental retardation, microcephaly, hypertelorism, epicanthal folds, low set dysplastic ears, short neck, malformed extremities, high arched palate, heart defect
Martin <i>et al</i> ²	8	3	Developmental retardation, failure to thrive, wide flat nose, large mouth, high arched palate, asymmetrical palpebral fissures, short neck, fifth finger clinodactyly, hypotonia
Johnson <i>et al</i> ³	41	Not done	Developmental retardation, failure to thrive, microcephaly, dysplastic ears, heart defect, skeletal asymmetry
Present case	10	<1	Developmental retardation, failure to thrive, facial asymmetry, low set dysplastic left ear, cleft soft palate, short fifth finger with clinodactyly

There have been very few descriptions of trisomy for the distal segment of 14q. Fryns *et al*⁶ reported trisomy for the terminal quarter of 14q associated with multiple severe abnormalities suggestive of the Smith-Lemli-Opitz syndrome. The patient died at the age of 2.5 months. This patient, who was also monosomic for a small portion of the terminus of 11q, had severe retardation with relatively minor somatic abnormalities. The only 'pure' trisomy 14q distal was reported by Trunca and Opitz.⁷ This patient was trisomic for 14q21→14qter and was clinically similar to those mentioned above as having proximal 14q trisomy.

To our knowledge there have been no confirmed reports of full, non-mosaic chromosome 14 trisomy in liveborns, although this condition has occasionally been seen in abortuses.⁸ Thus, it appears that trisomy for either a small segment of terminal 14q or a sizeable segment of proximal 14q, as well as low levels of full trisomy 14 mosaicism, are somatically fairly well-tolerated. However, all these conditions are marked by severe mental and motor retardation, and neurological function seems more profoundly affected than physical features.

Although other interpretations are possible, we think the apparent iso-14q in the proband is most likely to have arisen from an unstable sporadic dicentric by dissociation and subsequent misdivision of the centromere. This interpretation is borne out by the presence of a few cells in which the dissociation had occurred (fig 2c). Such dissociation of 'dicentrics'

Case reports

has been observed in humans,¹¹⁻¹³ and this topic has been considered theoretically with particular regard to mouse chromosomes.¹⁴ A similar scheme of dissociation and isochromosome formation was proposed by Vianna-Morgante and Nunesmaia¹⁵ to explain the production of a subject with iso-21q trisomy 21 from a 15q21q balanced translocation, and by Fryns *et al*¹⁶ to explain a case of trisomy 13 mosaicism from a de novo 13q13q translocation. Atkins and Bartsocas¹⁷ also possibly observed such an event, although the trisomic cell line in their case was the major line. It thus seems that dissociation of some centric fusion translocations may be expected to give rise to chromosomally unbalanced subjects in a small number of instances.

The reason for this occasional appearance of an unstable dicentric is of obvious interest. Daniel and Lam-Po-Tang¹⁸ and Hsu *et al*¹⁹ have reviewed Robertsonian translocations in man and concluded that most, if not all, of these are actually dicentric and, as with dicentrics in general, the reason for their stability is the suppression of the activity of one of the two centromeres. It is also possible that this stability is not absolute and that, if carefully searched for, a small percentage of cells in many Robertsonian translocation heterozygotes will show evidence of dissociation. These dissociated chromosomes, which may appear as two acrocentrics in satellite association, may still be connected by interchromosomal strands.²⁰

We thank Ruth Klefsas, Glenna Swanda, and Donalee Casseday for assistance.

MALCOLM B JENKINS*, ROBERT KRIEL†, AND LLOYD BOYD*

*Human Genetics Unit, Minnesota Department of Health, 717 SE Delaware Street, Minneapolis, Minnesota 55440; and

†Department of Pediatrics, St Paul-Ramsey Hospital, 640 Jackson Street, St Paul, Minnesota 55101, USA

References

- Rethoré MO, Couturier J, Carpentier S, Ferrand J, Lejeune J. Trisomie 14 en mosaïque chez une enfant multimalformée. *Ann Hum Genet* 1975;18:71-4.
- Martin AD, Ford M, Khalil N, Turk K, MacIntyre M. 46,XX/47,XX,+14 mosaicism in a liveborn infant. *J Med Genet* 1977;14:214-8.
- Johnson VP, Aceto T, Likness C. Trisomy 14 mosaicism: case report and review. *Am J Med Genet* 1979;3:331-9.
- Miller JQ, Wilson K, Wyandt H, Jaramillo MA, McConnell T. Familial partial 14 trisomy. *J Med Genet* 1979;16:60-5.
- Lopez Pajares I, Delicado A, Cobas PV, Lledo B, Peralta A. Partial trisomy 14q. *Hum Genet* 1979;46:243-6.
- Fryns JP, Van Eygen M, Tanghe W, Van den Berghe A. Partial trisomy 14q due to familial t(14q-,11q+) translocations. *Hum Genet* 1977;37:105-10.
- Trunca C, Opitz JM. Pericentric inversion of chromosome 14 and the risk of partial duplication of 14q(14q21→14qter). *Am J Med Genet* 1977;1:217-28.
- Boué A, Boué J. Chromosome abnormalities and abortion. *Basic Life Sci* 1974;4(A):317-39.
- Murken JD, Bauchinger M, Palitzsch D, Pfeifer H, Suschke J, Haendle H. Trisomy D₂ bei einen 2 1/2 jährigen Mädchen (47,XX,14+). *Humangenetik* 1970;10:254-68.
- Hill FS, Summitt RL. Delineation of Robertsonian translocation in man by means of chromosome banding. *Eur J Pediatr* 1977;126:203-9.
- Angell R, Gianelli R, Polani PE. Three dicentric Y chromosomes. *Ann Hum Genet* 1970;34:39-50.
- Jacobs PA, Melville M, Ratcliffe S, Keay AJ, Syme J. A cytogenetic survey of 11,680 newborn infants. *Ann Hum Genet* 1974;37:359-76.
- Niebuhr E. Dicentric and monocentric Robertsonian translocation in man. *Humangenetik* 1972;16:217-26.
- Lau YF, Hsu TC. Variable modes of Robertsonian fusions. *Cytogenet Cell Genet* 1977;19:231-5.
- Vianna-Morgante A, Nunesmaia H. Dissociation as probable origin of mosaic 45,XY,t(15;21)/46,XY,i(21q). *J Med Genet* 1978;15:305-10.
- Fryns JP, Caesar P, Van den Berghe H. Mosaic 13 trisomy due to de novo 13/13 translocation with subsequent fission. Karyotype: 46,XX,-13,+t(13;13)(p11;q11)/46,XX,del(13)(q11). *Hum Genet* 1979;46:237-41.
- Atkins L, Bartsocas C. Down's syndrome associated with two Robertsonian translocations, 45,XX,-15-21,+t(15q21q) and 46,XX,-21,+t(21q21q). *J Med Genet* 1974;11:306-9.
- Daniel A, Lam-Po-Tang PRLC. Structure and inheritance of some heterozygous Robertsonian translocations in man. *J Med Genet* 1976;13:381-8.
- Hsu TC, Pathak S, Chen T. The possibility of latent centromeres and a proposed nomenclature system for total chromosome and whole arm translocations. *Cytogenet Cell Genet* 1975;15:41-9.
- Bahr GF. Chromosomes and chromatin structure. In: Yunis J, ed. *Molecular structure of human chromosomes*. New York: Academic Press, 1977:143-203.

Requests for reprints to Dr M B Jenkins, Human Genetics Unit, Minnesota Department of Health, 717 SE Delaware Street, Minneapolis, Minnesota 55440, USA.

Monosomy 22 with mosaicism

SUMMARY A 2-year-old male child with mosaicism for monosomy of chromosome 22 is described. He had moderate psychomotor retardation, generalised hypotonia, large ears, epicanthus, synophrys, and cutaneous syndactyly between all the fingers.

Before the availability of chromosome banding techniques, attempts to delineate syndromes resulting from monosomy of G group chromosomes were

Received for publication 25 April 1980