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ORIGINAL INVESTIGATION

Daniele DeBrasi · Maurizio Genuardi
Antonio D'Agostino · Fabrizio Calvieri · Carla Tozzi
Stelio Varrone · Giovanni Neri

Double autosomal/gonosomal mosaic aneuploidy: study of nondisjunction in two cases with trisomy of chromosome 8

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Abstract We report cytogenetic and molecular investigations performed in two cases of mosaic trisomy 8 combined with mosaic sex chromosome aneuploidy. In a 35-year-old female, presenting with short stature, gonadal dysgenesis, and a multiple congenital anomalies/mental retardation syndrome typical of trisomy 8, chromosome analysis from peripheral lymphocytes showed the presence of three cell lines, whose karyotypes were 45,X (59.2%), 46,X,+8 (1.2%), and 47,XX,+8 (39.6%), respectively. The same cell lines were found in a skin fibroblast culture, though in different proportions. The second patient, a 9-month-old male with multiple skeletal abnormalities, showed a 47,XY,+8 and a 47,XXY cell line in both peripheral lymphocytes (61.7% and 38.3%, respectively) and skin fibroblasts (92.8% and 7.2%, respectively). To determine the events underlying the origin of these complex karyotypes we performed Southern blot and polymerase chain reaction (PCR) analysis using polymorphic DNA markers from the X chromosome and from chromosome 8. Both supernumerary chromosomes 8, and, in case 2, the two X chromosomes, appeared to be identical, lacking detectable recombination events. We conclude that, in both cases, the most likely mechanism underlying the origin of the mosaic cell lines was formation of a normal zygote, followed by mitotic errors during early divisions.

D. DeBrasi · A. D'Agostino · S. Varrone
Servizio Speciale di Citogenetica,
Facolta' di Medicina e Chirurgia, Universita' Federico II,
Napoli, Italy

D. DeBrasi
CEINGE, Facolta' di Medicina e Chirurgia,
Universita' Federico II, Napoli, Italy

M. Genuardi · G. Neri (✉)
Istituto di Genetica Medica,
Facolta' di Medicina e Chirurgia "A. Gemelli",
Universita' Cattolica del Sacro Cuore, Largo Francesco Vito, 1,
I-00168 Rome, Italy

F. Calvieri · C. Tozzi
Laboratorio di Citogenetica, Ospedale S. Giovanni, Rome, Italy

Introduction

The mechanisms underlying the origin of numerical chromosome abnormalities in man vary according to the type of aberration. Nondisjunction leading to autosomal and gonosomal trisomies usually occurs during meiosis, more frequently at the first meiotic division in the maternal germline (Hassold 1986; Antonarakis et al. 1991; Jacobs et al. 1988; Antonarakis et al. 1992). On the other hand, gonosomal monosomy frequently involves loss of the paternal sex chromosome (Zinn et al. 1993).

The simultaneous presence of two different numerical abnormalities in the same individual is a rare event. The supernumerary chromosomes may be present in the same cell line, consequent upon a double nondisjunction event in a single parent or fertilization of an aneuploid oocyte by an aneuploid sperm. In other cases, two abnormal cell lines, one of which is directly derived from the other by a postzygotic event, may be present in the same individual (e.g., one line with trisomy 21 and another line with 48,XXY,+21 karyotype). Finally, and even more rarely, two apparently unrelated aneuploid cell lines may coexist. In such cases it is very hard to trace the sequence of causative events by pure speculation, since several alternative mechanisms can be proposed.

Ascertainment of two exceptional cases of double mosaic aneuploidy with trisomy 8 and gonosomal imbalance allowed us to study the stages of nondisjunction and/or anaphase lag by Southern blotting and the polymerase chain reaction (PCR). We were able to reconstruct a hypothetical sequence of events, finding that in both cases the most likely explanation was a series of post-zygotic errors.

Subjects, materials and methods

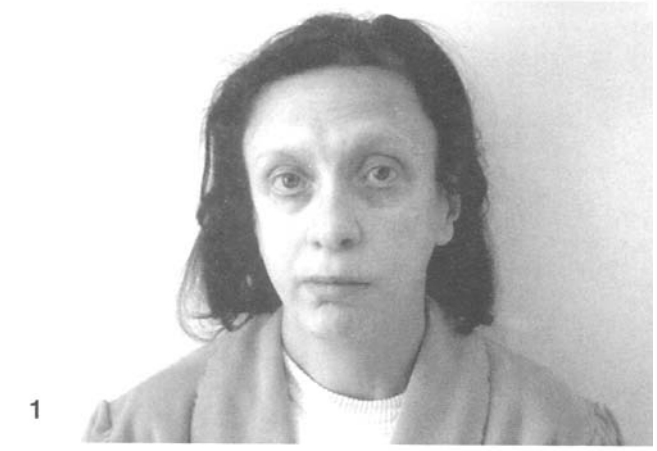
Case reports

Case 1

The patient (Fig. 1) came to our observation at the age of 35 years owing to mental retardation and multiple congenital anomalies. She was the third daughter of healthy, unrelated parents (father 39, mother 35 years of age at the time of her birth). Birthweight was 3750 g. She had menarche at 13 years of age, but menses stopped 1 year later. At the time of examination, head circumference (OFC) was 53 cm (3rd-50th centile), height 143 cm (< 3rd centile), and weight 31.5 kg (< 3rd centile). Physical examination showed an elongated face and cranio-facial asymmetry with high forehead, exophthalmos, bulbous nose, everted lower lip, micrognathia, abnormal ears, high-arched palate, a corneal opacity in the upper portion of the left eye, multiple nevi, and kyphoscoliosis. Her fingers were long and knotty and showed camptodactyly of digits 4–5 and clinodactyly of digit 3 on right, and camptodactyly of digit 2 on left. Dermatoglyphics were: t, ab, L^u A L^u L^u L^u (right); t, abcd, A A A L^u W (left). The nails and the skin of the toes were dystrophic owing to diabetic neuropathy. The distal phalanges of toes 3–5 were medially deviated bilaterally, and there was camptodactyly of the 2nd toe bilaterally. External genitalia and breasts were hypoplastic. Skeletal roentgenograms showed kyphoscoliosis, generalized osteoporosis and osteomalacia. Pelvic ultrasonography demonstrated hypoplastic uterus, streak gonads, bilateral kidney malrotation, and duplication of the renal pelvis on the left. Type I diabetes was present.

Case 2

The patient (Fig. 2) is a 9-month-old male, third child of unrelated parents. Birthweight was 3730 g. Bottle-feeding was necessary because of poor sucking. At the time of our examination, his weight was 6.6 kg (< 3rd centile), length 68 cm (3rd centile), OFC 44.4 cm (25th centile). He had brachycephaly, sparse hair with abnormal hairline, prominent and hairy forehead, hypertelorism with broad and flat nasal bridge, antimongoloid eye slant with bilateral inverse epicanthal folds, low-set, abnormally shaped ears with a preauricular fistula between tragus and antitragus on the left, high-arched palate, short upper lip and lingual frenula, hypoplastic philtrum, micrognathia, two paramedian parallel furrows on the upper lip and one in the middle of the lower lip, skin redundancy on the neck and back, chest asymmetry, pectus excavatum, small umbilical hernia, presacral dimple, and anteriorly displaced anus. The right testis was not palpable. Hands showed proximally set thumbs, ulnar deviation of the 2nd and 3rd rays with camptodactyly of the 4th ray on right, and ulnar deviation with apparent brachydactyly of the 3rd ray and clinodactyly of the 5th ray on left. Palmar creases were deep and abnormal bilaterally; the 3rd interphalangeal flexion creases on left and the 5th on right were absent. Dermatoglyphics were: t', L^u L^u pL^r pL^u L^u (right); t', L^u L^r W W W (left). Cutaneous syndactyly of the 2nd and 3rd toe with hypoplasia of the 2nd metatarsus was present bilaterally. Clinocamptodactyly of the 5th toe was present on left.



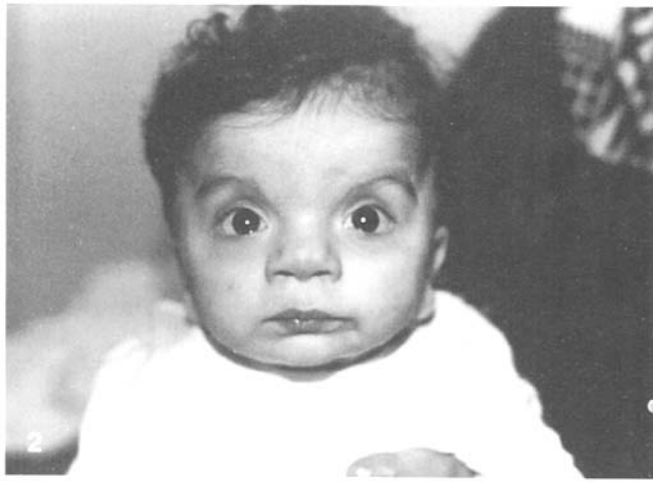


Fig. 1 Patient 1 at age 35 years

Fig. 2 Patient 2 at age 9 months

Cytogenetic and molecular methods

Trypsin-Giemsa and 5-bromodeoxyuridine reverse banding were performed on stimulated peripheral blood lymphocytes and skin fibroblasts following conventional techniques. Chromosome 8 and X-chromosome polymorphisms were investigated by Southern blotting or by PCR. Loci DXS1, DXS3, DXS11, DXS15, DXS52, DXS159, DXS278, PGK1, D8S3, D8S7, and TG were analyzed by Southern blotting followed by hybridization to ^{32}P-labeled probes (Feinberg and Vogelstein 1983). All other loci were investigated by PCR, using genomic DNA (50–100 ng) extracted from total peripheral leukocytes for amplification. For short tandem repeat polymorphisms, a ^{35}S end-labeled primer was added to the PCR mixture, and amplified fragments were separated by denaturing polyacrylamide gel electrophoresis and visualized by autoradiography. A *Hind*III restriction fragment length polymorphism (RFLP) at the F8C locus and a *Bgl*I RFLP at the TIMP locus were detected by ethidium bromide staining of the agarose gel after enzymatic digestion of the PCR products. The cytogenetic map location of probes and primers used in this study is shown in Table 1. Detailed information regarding these DNA markers can be found in the Genome DataBase and in previous publications (Feener et al. 1991; Williamson et al. 1991; Kumar et al. 1992; Rogaev et al. 1992; Gu et al. 1993; Sleddens et al. 1993; Thomas and Drayna 1993; Ward et al. 1993). Additional hypervariable loci mapping to chromosomes 2, 6 and 12 were tested by PCR in case 2 and his parents to determine whether the mosaicism could be consequent upon the formation of a chimeric embryo.

Results

In case 1, chromosome analysis, performed on 250 metaphases from peripheral lymphocytes, showed the presence of three different cell lines, whose karyotypes were 45,X (148 cells; 59.2%); 46,X,+8 (3 cells; 1.2%); and 47,XX,+8 (99 cells; 39.6%), respectively. The same cell lines were found in a skin fibroblast culture (108 cells analyzed),

Table 1 List and location of X-chromosome (a) and chromosome 8 (b) polymorphic loci tested

a			b		
Cytogenetic location	Locus symbol	Probe[a]	Cytogenetic location	Locus symbol	Probe[a]
Xp22.3	DXS278	CRI-S232	8p23–pter	D8S201	
Xp21.2	DMD		8p23	D8S7	pSW50
Xp11.23–p11.3	TIMP		8p22–cen	D8S339	
Xp11.21	DXS14	p58-1	8p21	NEFL	
Xq11.2–q12	DXS1	p8	8p12	D8S87	
Xq11–q12	AR		8p	D8S307	
Xq13	DXS159	cpX289	8cen–q13	PENK	
Xq13.3	PGK1	pXPGK-R10.9	8q11–q22	D8S88	
Xq21–q22	DXS456		8q13	CRH	
Xq22	DXS3	19-2	8q21–q22	D8S85	
Xq24–q25	DXS11	p22-33	8q23–qter	D8S199	
Xq24–q26	DXS424		8q23–qter	D8S198	
Xq26.1	HPRT		8q24	TG	pCHT16/8.0
Xq27.3	DXS548		8q24	MYC	
Xq27.3–q28	DXS1113		8	D8S3	86B
Xq28	F8C				
Xq28	DXS52	St14			
Xq28	DXS15	DX13			

[a] Only probes used for Southern blotting are listed

Table 2 Results of molecular analysis in family 1. Loci are listed according to their relative chromosomal order from pter to qter. Genotype numbers represent the different alleles at a specific locus. a chromosome X, b chromosome 8

a

Locus on X chromosome	Genotypes		
	Proband	Father	Mother
DMD	1/2	1	2/2
AR	1/3	3	1/2
DXS424	1/2	1	2/2
F8C	1/2	1	1/2
DXS52	1/2	2	1/2

b

Locus on chromosome 8	Genotypes		
	Proband	Mother	Father
D8S201	1/1/1	1/1	1/1
D8S339	1/1/1	1/1	1/1
NEFL	1/1/2 or 1/2/2	2/2	1/2
D8S87	2/2/4 or 2/4/4	3/4	1/2
D8S307	2/2/2	2/2	1/2
PENK	1/1/2 or 1/2/2	1/1	1/2
D8S88	1/1/1	1/2	1/1
CRH	1/1/4 or 1/4/4	1/2	3/4
D8S85	2/2/2	2/2	1/2
D8S199	1/1/3 or 1/3/3	2/3	1/2
D8S198	3/3/3	2/3	1/3
TG	1/1/1	1/1	1/1
MYC	2/2/3 or 2/3/3	1/3	2/4

where the proportions of cells with 45, 46, and 47 chromosomes were 34.2% (n = 37), 14.8% (n = 16), and 50.9% (n = 55), respectively.

As expected, analysis of X-chromosome polymorphisms tested in case 1 and her parents demonstrated the presence of both a paternal and a maternal allele at all loci tested (Table 2a). In the proband, the intensity of the paternal allele was consistently lower than the maternal one (Fig. 3), paternal band intensity being approximately 30%–40% of the maternally derived one. However, given the caveats inherent in dosage estimation of PCR products in mosaic tissues, and also considering that the relative proportions of the different cell lines in dividing lymphocytes, used for cytogenetic analysis, might not be the same in whole white blood cells, used for molecular analysis, this information was disregarded for the purpose of determining the parental original of the aneuploidies in this study.

Case 1 was homozygous at three and heterozygous at ten chromosome 8 loci tested (Table 2b). Representative autoradiograms of PCR products are shown in Fig. 4. At five of these loci (D8S87, CRH, D8S199, D8S198 and MYC) four or three different alleles were recognized in the parents, but only two or one in the proband. Genotyping results at loci D8S307 and D8S85 could be considered informative only if two maternal chromosomes 8 were present in the 47,XX,+8 cell line, in which case the proband should have inherited two copies of the same maternal allele. Likewise, homozygosity at locus D8S88 in the proband indicates that, if the extra chromosome were paternal, she would possess two identical copies of paternal allele 1. Thus, the combined data from all chromosome 8 loci, which demonstrated reduction to homozygosity in the 47,XX,+8 cell line, indicate that the error had occurred either at meiosis II or postzygotically.

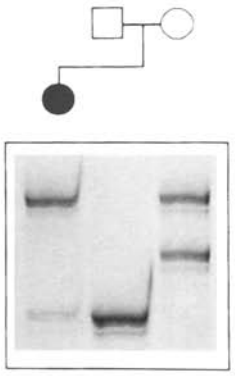


Fig. 3 Case 1. Autoradiogram showing genotypes at the X-linked AR locus

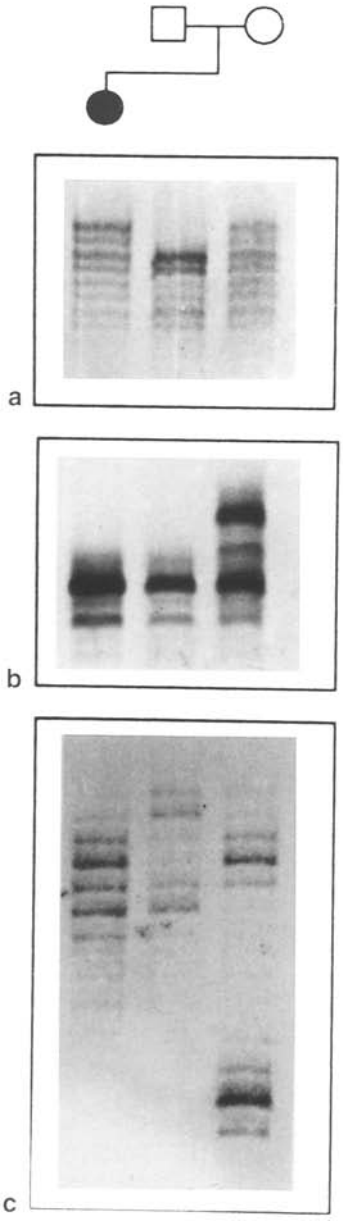


Fig. 4 a–c Case 1. Chromosome 8 polymorphisms: **a** NEFL, **b** D8S85 and **c** MYC loci

Cytogenetic analysis in case 2 showed a 47,XY,+8 and a 47,XXY cell line in both peripheral lymphocytes (61.7% and 38.3%, respectively; 140 cells examined) and fibroblasts (47,XY,+8, 92.8%; 47,XXY, 7.2%; 70 cells examined).

Table 3 Results of molecular analysis in family 2. Loci are listed according to their relative chromosomal order. Genotype letters and numbers indicate the different alleles at a single locus. a Chromosome X, b chromosome 8

a

Locus on X chromosome	Genotypes		
	Proband	Father	Mother
DXS278	B/B	C	A/B
DMD	2/2	3	1/2
TIMP	1/1	1	1/2
DXS14	2/2	1	1/2
DXS1	1/1	1	1/1
AR	1/1	1	1/2
DXS159	1/1	2	1/1
PGK1	1/1	1	1/1
DXS456	1/1	1	1/2
DXS3	1/1	2	1/2
DXS11	1/1	1	1/2
DXS424	1/1	1	1/1
HPRT	1/1	2	1/3
DXS584	1/1	2	1/3
DXS1113	1/1	1	1/2
F8C	1/1	1	1/1
DXS52	2/2	2	1/2
DXS15	1/1	2	1/1

b

Locus on chromosome 8	Genotypes		
	Proband	Father	Mother
D8S7	1/1/1	1/2	1/1
D8S339	1/1/1	1/2	1/2
NEFL	1/1/2 or 1/2/2	1/2	1/1
D8S87	2/2/2	1/2	1/2
D8S307	3/3/4 or 3/4/4	2/4	1/3
PENK	1/1/1	1/1	1/2
D8S88	2/2/3 or 2/3/3	3/4	1/2
CRH	1/1/3 or 1/3/3	1/2	2/3
D8S85	1/1/2 or 1/2/2	2/2	1/2
D8S199	1/1/2 or 1/2/2	2/3	1/3
D8S198	2/2/3 or 2/3/3	1/2	3/4
TG	1/1/2 or 1/2/2	2/2	1/2
MYC	2/2/3 or 2/3/3	2/4	1/3
D8S3	1/1/1	1/1	1/1

All X-chromosome informative loci tested showed the presence of a single maternally derived allele (Table 3 a, Fig. 5). Of the ten informative chromosome 8 markers (Table 3, Fig. 6), eight (D8S339, D8S87, D8S307, D8S88, CRH, D8S199, D8S198, MYC) demonstrated the presence of two identical copies of the same allele (reduction to homozygosity) in the 47,XY,+8 cell line, independently of the parental origin of the supernumerary chromosome 8. Identical conclusions could be drawn for loci D8S7 and PENK, but only in the case of paternal or maternal derivation of the additional chromosome 8, respectively.

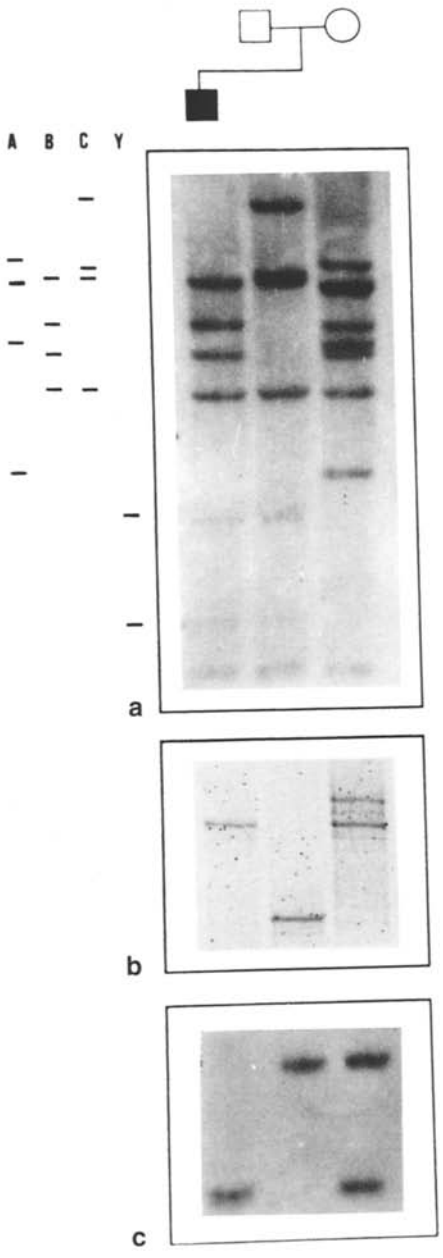


Fig. 5 a–c Case 2. X-chromosome polymorphisms: **a** DXS278, **b** DMD and **c** DXS14 loci. *A*, *B*, *C*, and *Y* in **a** indicate the two maternal haplotypes (*A*, *B*), the paternal X-chromosome haplotype (*C*), and invariant fragments mapped to the Y chromosome (*Y*), respectively

PCR analysis of additional autosomal polymorphisms demonstrated the presence of a single paternal and a single maternal allele at each tested locus (Table 4).

Discussion

Constitutional mosaicism resulting from sex chromosome aneuploidy and autosomal trisomy, specifically trisomy 8, is an extremely rare event. The first case, a female with 45,X/46,XX/47,XXX/47,XX,+8 mosaicism, was described by Gafter et al. (1976), who interpreted the cytogenetic results as evidence of post-zygotic mitotic nondisjunction. Tegenkamp et al. (1980) reported on a 45,X/48,XXY,+8 post-term infant with a streak gonad on the right and testicular tissue on the left, as well as other anomalies. Hoovers et al. (1989) described a 47,XY,+8/48,XXYY karyotype in a man of normal intelligence with neurological abnormalities. Finally, Schofield et al. (1992) reported on a double mosaic aneuploidy 45,X/47,XY,+8 in a male infant with abnormal genitalia. Both previous and present cases showed phenotypic manifestations characteristic of both trisomy 8 and of gonosomal imbalance.

Trisomy 8 mosaicism is a relatively common chromosome abnormality with a well-defined phenotype (Riccardi

Fig. 6 a–c Case 2. Chromosome 8 polymorphisms: **a** NEFL, **b** D8S85 and **c** D8S88 loci

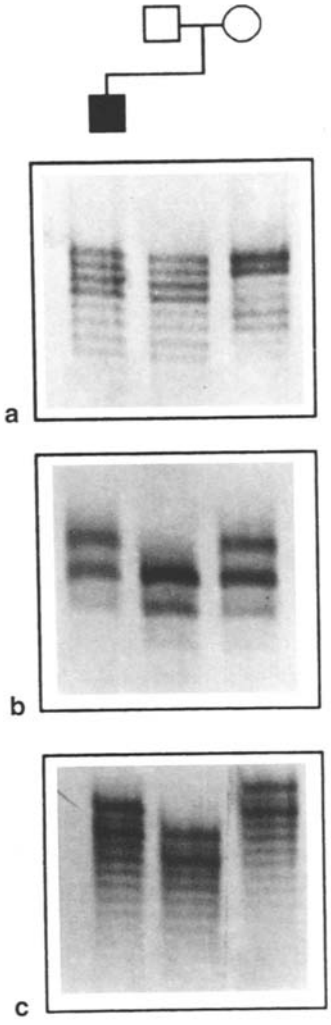


Table 4 Genotypes of family 2 at hypervariable autosomal loci

Locus	Map location	Genotypes		
		Proband	Father	Mother
D2S44	2p	2–3	1–2	3–4
F13A1	6p24–p25	1–3	3–4	1–2
F8VWF	12p12–pter	2–3	1–2	1–3

1977), ranging from minimal effects to severe malformations (Chandley et al. 1980; Schinzel 1984). This variability probably depends on the distribution of the aneuploid cell line in the different tissues (Kurtyka et al. 1988). The accompanying cell line usually has a normal chromosome complement, which is compatible with the occurrence of a meiotic error leading to an aneuploid zygote, followed by appearance of a normal cell line due to mitotic nondisjunction or anaphase lag during the first post-zygotic divisions. Two lines of evidence support this hypothesis. First, parental age was slightly increased among couples who had children with mosaic trisomy 8 (Schinzel 1984). Second, nondisjunction of chromosome 8 is a more common event than it appears from cytogenetic surveys of liveborn individuals, since non-mosaic trisomy 8 is a frequent abnormality in spontaneous abortions (Boué and Boué 1978).

The relatively high prevalence of Klinefelter syndrome has allowed it to be established with a high level of confidence that the causative error can occur equally during paternal or maternal meiosis (Jacobs et al. 1988; Lorda-Sanchez et al. 1992).

The origin of X monosomy in Turner syndrome is more difficult to ascertain. Meiotic errors could be involved in the majority of cases, but it has also been proposed, in consideration of the high prenatal lethality of 45,X fetuses, that there is no 45,X liveborn without mosaicism for a normal cell line (Zinn et al. 1993). In such cases the zygote would probably start with a normal karyotype, followed by early somatic loss of one X chromosome.

On the other hand, mosaicism for two abnormal, apparently unrelated, cell lines, as observed in the two individuals reported in the present study, requires at least two independent errors. Though unlikely, both of these could occur in two different germ cells during meiosis, and in such a case the resulting offspring would be a chimera. Other possibilities include a combination of meiotic and mitotic errors or, alternatively, a series of somatic events (with loss of karyotypically normal lines).

In case 1, molecular analysis was indicative of a mitotic error in 47,XX,+8 cells, since in no instance was retention of heterozygosity for polymorphic markers spanning chromosome 8 observed. Although we did not examine polymorphic alpha-satellite markers to investigate the origin of chromosome 8 centromeres, it has been shown that such analysis can be omitted with little consequence on the significance of the results, provided that markers sufficiently close to the centromere are investigated (Robinson et al. 1993). Case 1 also had a low proportion of cells with a 46,X,+8 karyotype, intermediate between the two major lines. While loss of an X chromosome in 1.2% peripheral lymphocytes is not an unusual finding among adult females, the proportion of pseudodiploid cells in skin fibroblasts was considerably above normal levels relative to the age of the patient. In view of the presence of this cell line, a plausible sequence of events, implicating the occurrence of two asynchronous somatic errors, is the following: (1) normal 46,XX zygote; (2) early somatic nondisjunction of chromosome 8 (possibly at zygote division), with loss of the non-viable monosomic cell line, and persistence of a single 47,XX,+8 line; (3) loss of an X chromosome by anaphase lag or nondisjunction (in the latter case a 48,XXX,+8 product should have been formed, and subsequently eliminated) with formation of a 46,X,+8 line; (4) further anaphase lag or nondisjunction, this time involving chromosome 8, and appearance of 45,X cells. Again, nondisjunction would require the presence of the reciprocal product, which should be simultaneously tetrasomic for chromosome 8 and monosomic for chromosome X, presumably a non-viable combination. Similarly, the low proportion of 46,X,+8 cells, which are aneuploid for two different chromosomes, may be explained by their relatively low viability compared with the other two lines. A higher proportion of 46,X,+8 cells was found in skin fibroblasts. This finding is in accordance with previous observations indicating that the trisomic line is overrepresented in fibroblasts relative to lymphocytes in subjects that are mosaic for trisomy 8 (Schinzel 1984). We also found a higher proportion of 47,XX,+8 and 47,XY,+8 cells in skin fibroblasts of patients 1 and 2, respectively.

On the other hand, the results obtained in case 1 are also compatible with a meiosis II nondisjunction of chromosome 8 following achiasmatic meiosis I, but this is a much less likely event, given the genetic length of chromosome 8.

In case 2, the presence of not more than two alleles at all chromosome 8 loci and of a single allele at all X-chromosome informative loci investigated indicates that the errors must have occurred at meiosis II or at mitosis in the embryo itself, unless two (or multiples thereof) pericentromeric recombinations took place for each chromosome. If both errors had occurred during meiosis, one possibility would be that the individual arose from the fertilization of two oocytes, one resulting from a meiosis II error leading to gonosomal imbalance, followed by fusion of the two zygotes or very early embryos. Such a chimeric individual should contain chromosome complements derived from two different spermatozoa and two different eggs. This could be unraveled by investigation of highly polymorphic loci, for which both parents were heterozygous for different alleles. The probability of finding more than two alleles at a single autosomal locus, for which at least three different alleles are observed in the parents, in the mosaic offspring would be equal to 0.75, and the combined probability of not detecting chimerism by analysis of four loci placed on different chromosomes – that is, chromosomes 2, 6, 8, and 12 – would be $(0.25)^4$, or 6.25×10^{-4}. In addition, a chimera would receive from a heterozygous mother two different alleles at X-chromosome loci with a probability of 0.5. Since only two alleles at fully informative hypervariable sequences located on chromosomes 2, 6, 8, and 12, and a single allele at X-chromosome loci were found in patient 2, the hypothesis of chimerism could be rejected. The complete lack of detectable recombination events suggests that both aneuploid cell lines arose during early embryonic development. Both errors could have occurred at second cleavage division, leading to the formation of four aneuploid cells, with 47,XXY, 45,Y, 47,XY,+8,

and 45,XY,–8 karyotypes, respectively, and subsequent loss of the monosomic lines. The possibility that one or both nondisjunctions took place during later divisions cannot be discarded, since it has been demonstrated that chromosomally normal lines may be lost or may persist at low levels after the occurrence of mitotic errors (Robinson et al. 1994).

Recently, a somatic origin of chromosome aneuploidies has been demonstrated in a higher proportion of cases than previously thought on the basis of cytogenetic heteromorphism analysis (Antonarakis et al. 1993; Robinson et al. 1993, 1994). The present double mosaic aneuploids make a new addition to this expanding category of mitotically derived genome mutations.

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