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The Parental Origin of the Extra X Chromosome in 47,XXX Females

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Summary

We used X-linked DNA polymorphisms to study the parental origin of X chromosome nondisjunction in 28 47,XXX live-born females. Errors in oogenesis accounted for 26 of the cases, with the majority of these being attributable to an error at meiosis I. We observed an association between advanced parental age and meiosis I nondisjunction—but not meiosis II nondisjunction—in the maternally derived cases. In studies of recombination we found little evidence for an association between pairing failure and X chromosome nondisjunction, but our results suggest that increased recombination near the centromere may play a role in the etiology of the 47,XXX condition.

Introduction

The 47,XXX chromosome constitution is observed in approximately 1 in 1,000 newborn females (Hook and Hamerton 1977). Although it is one of the more common chromosome abnormalities in live-born individuals, virtually nothing is known about the origin of the additional X chromosome in 47,XXX females. Analysis of the inheritance of Xg blood group markers has been used to determine the parental origin of nondisjunction in 45,X and 47,XXY individuals. However, since Xg(a) is a dominant trait, it cannot yield direct evidence for the parental origin of the extra X chromosome in individual cases of 47,XXX. Sanger et al. (1971) provided indirect evidence of parental origin by analyzing the relative proportions of Xg(a+) and Xg(a−) phenotypes in groups of 46,XX and 47,XXX females. They found an "ultrafemale" distribution of Xg(a) alleles in the trisomic group, suggesting that, in most cases, nondisjunction occurred in oogenesis.

The availability of X-linked RFLPs now makes it possible to determine the origin of all types of sex-chromosome aneuploidy. We have applied this technique to study 45,X spontaneous abortions and live births (Hassold et al. 1988; Jacobs et al. 1989) and 47,XXY live-born males (Jacobs et al. 1988). Data from these studies indicate that, in contrast to autosomal aneuploidies which most frequently result from maternal nondisjunction (Buraczynska et al. 1989; Hassold and Takaesu 1989; Kupke and Müller 1989), errors involving the paternal sex chromosomes account for the majority of 45,X conceptuses and for approximately one-half of 47,XXY males (Jacobs et al. 1988, 1989).

We have now extended our DNA studies to include 47,XXX females. In this report we present our observations on an initial series of 28 individuals. Most cases resulted from nondisjunction occurring in oogenesis, and, of these, meiosis I errors were more common than meiosis II errors. An analysis of maternal age in these cases indicates that the effect of increasing age on sex-chromosome nondisjunction may be restricted to errors at the first meiotic division. Preliminary results on the study of recombination suggest that abnormally high levels of crossing-over in the pericentromeric region may be important in X-chromosome nondisjunction.

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Material and Methods

Ascertainment of Cases

Blood or DNA samples from live-born 47,XXX females and their parents were provided by laboratories

in the United States, Scotland, England, and Denmark. Table 1 summarizes available information on the 28 probands, including chromosome constitution, method of ascertainment, and parental ages. In most cases, the 47,XXX individuals were identified through cytogenetic screening programs of newborn or school-age children; in addition, four patients were ascertained through antenatal testing for advanced maternal age, three patients through clinical referrals, and one patient through amniocentesis for an elevated maternal alpha-fetoprotein level.

Cytogenetic Analysis

Chromosome analysis of the proband was performed by the referring laboratory using standard Q-, G-, or R-banding techniques. In 27 of the 28 cases the chromosome analyses were consistent with nonmosaic trisomy. In one instance (Y1) the proband was a 46,XX/47,XXX mosaic with the trisomic cell line being present in 27 of 30 cells.

DNA Analysis

DNA was extracted from peripheral blood either by using modifications of the standard chloroform-phenol extraction technique of Maniatis et al. (1982) or by the salting-out method of Miller et al. (1988). Approximately 5–6 μg of DNA were digested with an excess of restriction endonuclease under conditions specified by the manufacturer, separated electrophoretically on a 0.7%–1% agarose gel, and transferred to Zetabind (AMF, Cuno) nylon membranes by the method of Southern (1975). The DNA was hybridized to X chromo-

Table 1

Chromosome Constitution, Method of Ascertainment, Parental Origin of Trisomy, and Parental Ages for 28 Cases of 47,XXX

Case	Chromosome Constitution	Method of Ascertainment	Parental Age (years)		Parental Origin[b]
			Mother	Father	
Y1	46,XX/47,XXX	Maternal alpha-fetoprotein[a]	31	32	Maternal (4)
Y7[c]	47,XXX	Newborn screen	26	26	Maternal (6)
Y13	47,XXX	Newborn screen	28	31	Maternal (7)
Y14	47,XXX	Newborn screen	23	23	Maternal (7)
Y15	47,XXX	School screen	24	. . .	Maternal (8)
Y16	47,XXX	Newborn screen	31	24	Maternal (4)
Y18	47,XXX	Clinical referral	30	30	Maternal (7)
Y19[c]	47,XXX	Clinical referral	30	36	Paternal (3)
Y20	47,XXX	Clinical referral	24	30	Maternal (7)
Y21	47,XXX	Newborn screen	45	39	Maternal (4)
Y51	47,XXX	Advanced maternal age	37	36	Maternal (3)
Y61	47,XXX	Advanced maternal age	40	41	Maternal (6)
Y65[c]	47,XXX	Newborn screen	17	18	Maternal (5)
Y68	47,XXX	Advanced maternal age	34	. . .	Maternal (8)
Y71	47,XXX	Advanced maternal age	37	40	Maternal (2)
Y78	47,XXX	Newborn screen	23	27	Maternal (4)
Y79	47,XXX	Newborn screen	38	42	Maternal (2)
Y87[c]	47,XXX	Newborn screen	36	40	Maternal (4)
Y88	47,XXX	Newborn screen	30	29	Maternal (5)
Y89	47,XXX	Newborn screen	30	31	Maternal (3)
Y90[c]	47,XXX	Newborn screen	42	38	Paternal (4)
Y92	47,XXX	Newborn screen	44	36	Maternal (2)
Y93	47,XXX	Newborn screen	30	37	Maternal (5)
Y94	47,XXX	Newborn screen	25	32	Maternal (3)
Y95[c]	47,XXX	Newborn screen	21	24	Maternal (4)
Y96	47,XXX	Newborn screen	18	21	Maternal (4)
Y97	47,XXX	Newborn screen	25	27	Maternal (4)
Y98	47,XXX	Newborn screen	43	43	Maternal (4)

[a] Amniocentesis for elevated maternal alpha-fetoprotein level.
[b] Number in parentheses is number of loci informative for parental origin.
[c] Paternal blood was unavailable.

some probes which had been radiolabeled with ^{32}P-dCTP by the method of Rigby et al. (1977) or Feinberg and Vogelstein (1983).

The following X-linked probes were used in the present study: pTAK10A (DXS89), CRI-S232 (DXS278), pXUT23 (DXS16), p99-6 (DXS41), pXG-16 (DXS92), pERT87-1 (DXS164), p754 (DXS84), L1.28 (DXS7), TIMP, M27B (DXS255), p58-1 (DXS14), pBAMX9 (DXZ1), pXG-17 (DXS91), cpX289 (DXS159), pDP34 (DXYS1), p19-2 (DXS3), pXG-12 (DXS94), p43-15 (DXS42), c11 (DXS144), St1 (DXS86), DX13 (DXS15), and St14 (DXS52). Detailed descriptions of the probes and the polymorphisms they recognize have been provided elsewhere (Kidd et al. 1989).

For each family, we first used probes M27B (DXS255), CRI-S232 (DXS278), and St14 (DXS52), all of which detect multiple-allele polymorphisms, to determine the parental origin of the additional X chromosome. Parental origin was confirmed at two or more loci.

Maternally derived cases were then studied with pBAMX9 (DXZ1), which detects a highly polymorphic marker of α satellite DNA at the centromere of the X chromosome (fig. 1). Willard et al. (1986) have determined that virtually all X chromosomes have unique α satellite restriction patterns with *Hin*dIII, *Xba*I, *Eco*RI, *Bgl*II, or *Msp*I; therefore, analysis with pBAMX9 provides a straightforward approach to determination of the meiotic stage of nondisjunction of the X chromosome. For these studies we compared the positions and relative intensities of bands detected by pBAMX9 with each of two restriction enzymes, *Hin*dIII and *Xba*I, in mother/daughter pairs.

Finally, the maternal cases were analyzed with each of the remaining 18 probes to determine whether and where recombination had occurred between the mother's X chromosomes. Examples from two families are shown in figure 2.

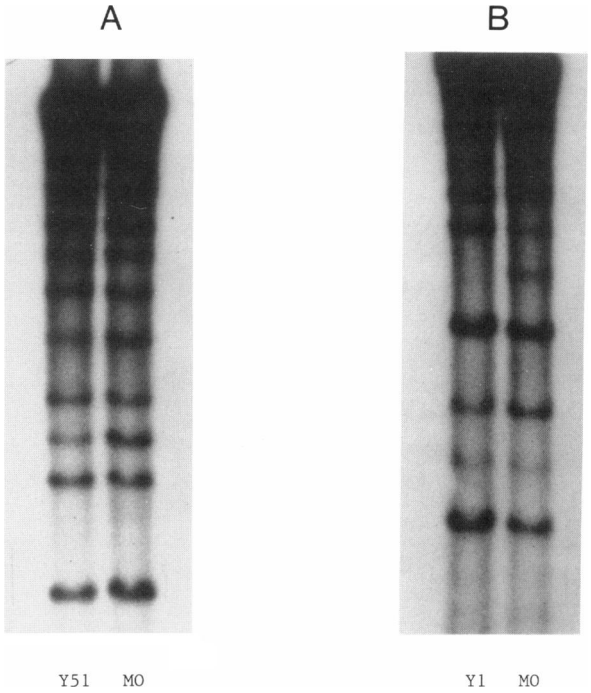

Figure 1 Determination of meiotic stage of X chromosome nondisjunction in two maternally derived cases of 47,XXX. DNA from the proband and DNA from the mother were digested with *Hin*dIII and hybridized to probe pBAMX9. *A*, Meiosis I error, specified when all maternal bands, representing both maternal X chromosomes, were also present in the proband's DNA. *B*, Meiosis II assignment, made when only a subset of the mother's bands were observed in the proband's DNA.

Results

Table 1 provides results of the parental origin studies for each of the 28 cases. We identified the mother as the parent of origin of trisomy in all 22 cases in which DNA was available from both parents. In the six cases in which we did not have DNA from the father, the results were consistent with maternal nondisjunction in four cases and with paternal nondisjunction in two cases. Thus, in all, 26 of the 28 cases (92.8%) were attributable to errors in maternal meiosis. This includes one 46,XX/47,XXX mosaic (Y1) in whom three different parental alleles were identified with probe M27B (DXS255), indicating that the trisomic line must have arisen as a meiotic rather than as a mitotic error.

Table 2 summarizes information on parental origin and age and on the meiotic stage at which nondisjunction occurred. For 26 cases of maternal origin we were able to specify the meiotic stage in 21, with 15 occurring in meiosis I and six occurring in meiosis II. When the four cases ascertained for advanced maternal age are excluded, the mean maternal age of the meiosis I errors is 30.6 ± 8.7 years. This is significantly elevated over the 24.3 ± 5.4 years observed for the meiosis II cases ($t = 1.84$, $P < .05$).

We also analyzed the maternally derived cases for evidence of recombination. Recombination between the two maternal X chromosomes was considered to have occurred if (*a*) one or more loci for which the mother was heterozygous was reduced to homozygosity in a proband of meiosis I origin, (*b*) maternal heterozygosity was maintained—or nonreduced—at one or more

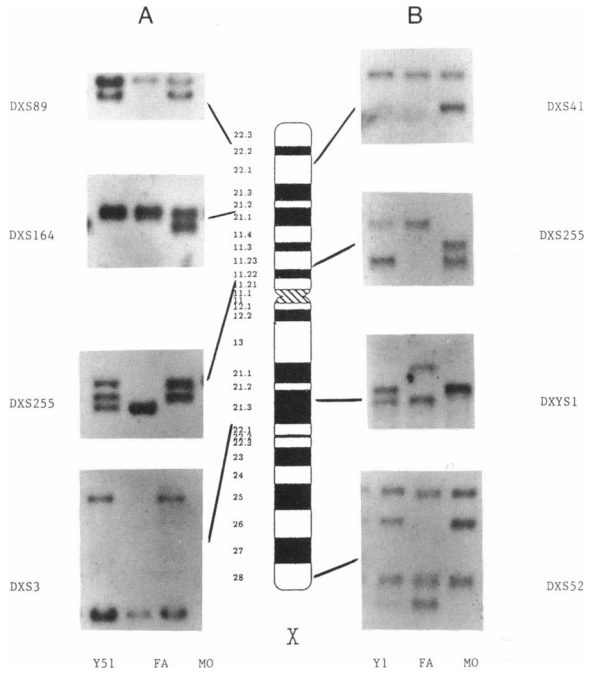

Figure 2 Analysis of parental origin and recombination in one 47,XXX of maternal meiosis I origin (Y51) and in one 47,XXX of maternal meiosis II origin (Y1). *A:* In Y51, maternal origin is based on DXS255, and meiosis I origin is based on DXZ1 (see fig. 1*A*). Y51 has inherited both maternal alleles at DXS89, DXS255, and DXS3 but is homozygous at DXS164. Therefore, a single (or odd number of) crossover(s) must have occurred between DXS89 and DXS164 and between DXS164 and DXS255. *B:* In Y1, maternal origin is based on DXS255, DXYS1, and DXS52 (for this locus, the highest and next-to-lowest molecular-weight fragments are constant bands), and meiosis II origin is based on DXZ1 (see fig. 1*B*). YI has inherited only one of the two maternal alleles at DXS41 and DXS255, the only markers informative for recombination. Since Y1 is reduced to homozygosity at these two markers and at the centromere, there is no evidence for crossing-over between any of the loci illustrated in this panel.

loci in a proband of meiosis II origin, or (*c*) both reduced and nonreduced loci were present in a proband for whom the meiotic stage of origin was unknown.

Tables 3 and 4 summarize the information on recombination for maternally derived cases of meiosis I, meiosis II, and unknown meiotic stage of origin. Nine of the 15 cases of meiosis I origin had at least one crossover, and for most of these the results were compatible with the presence of two or more crossovers. There was no evidence for recombination in the remaining six cases, but, with the exception of Y21 and Y71—for which we have information at 11 and six loci, respectively—relatively little information was available on those cases (i.e., fewer than five informative loci had been analyzed). Three meiosis I cases—Y7, Y68, and Y96—were homozygous at all informative loci on both the short arm and the long arm of the X chromosome (table 3).

All six cases of presumptive meiosis II origin were heterozygous at one or more loci, a result consistent with a meiotic—but not with a mitotic—origin for the additional X chromosome (table 4). Of the four cases of unknown meiotic stage of origin, only Y89 (nonreduced at four loci) provided no evidence for recombination.

Discussion

The purposes of the present study were threefold: (1) to provide information on both the parent of origin and the meiotic stage of nondisjunction of 47,XXX females, (2) to correlate the results of the parental origin studies with parental ages, and (3) to evaluate the possible role of abnormally high or low levels of recombination in the etiology of the 47,XXX chromosome constitution.

Table 2

Summary of Results on Parental Origin, Parental Age, and Meiotic Stage of Nondisjunction for 28 47,XXX Females

Parental Origin	No. of Cases	Mean ± SD Age (N) (years)	
		Mother	Father
Paternal	2	36.0 ± 8.5 (2)	37.0 ± 1.4 (2)
Maternal	26	29.2 ± 7.9 (22[a])	30.6 ± 6.9 (21)
Meiosis I	15	30.6 ± 8.7 (11)	32.2 ± 7.8 (11)
Meiosis II	6	24.3 ± 5.4 (6)	27.6 ± 7.3 (5)
Meiosis I or meiosis II	5	31.8 ± 7.4 (5)	30.2 ± 4.3 (5)

[a] Excludes the four cases ascertained on the basis of advanced maternal age.

Table 3

Summary of Recombination Studies on 15 Maternally Derived Cases of 47,XXX of Meiosis I Origin

Locus	Case Number														
	Y7	Y13	Y14	Y21	Y51	Y61	Y68	Y71	Y79	Y87	Y88	Y94	Y96	Y97	Y98
Xp:															
DXS89	...	...	R	...	N	...	R[a]	N							
DXS278	R[a]	N[a]	R	N[a]	N[a]	N[a]	R[a]		N[a]	N[a]	N[a]		R[a]	N[a]	R[a]
DXS16		...			...	...[a]	R	...	...	...	...	...[a]	R[a]	...	...[a]
DXS41	...[a]	...[a]	R	N											
DXS92		...[a]	...	...	...	...	R	N							
DXS164				N	R	...									
DXS84	...	...[a]	...	N											
DXS7	...[a]	...	...[a]	N	...	R[a]			...	...	...			N	
TIMP	...[a]	...[a]	N	...	N	...	R[a]	...	...	...	...	N	R	R[a]	N
DXS255	R[a]	R[a]	N[a]	N[a]	N[a]	...	R[a]	N[a]	N[a]	N[a]	N[a]	...[a]	R[a]	R[a]	N[a]
DXS14		N	...[a]		...	...[a]	...	...							
Xcen:															
DXZ1	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Xq:															
DXS91			...		N	...	...	N							
DXS159	...	...	N	...											
DXYS1	R	...	...[a]	...	...	N			...	...	...				
DXS3			...	N	N	N	R[a]	N							
DXS94	...[a]		N	N											
DXS42	R	...	N[a]	N	...	...	R[a]	...							
DXS144				N	N	...									
DXS86	R	N		...	...	...	R	...[a]	N	N	...[a]			...[a]	N
DXS15	R	N	...[a]	...[a]	N	...[a]	...[a]	...	N	...[a]	...[a]	...[a]	R	R	N
DXS52		...[a]	R[a]	...[a]	...[a]	...[a]	R[a]		...	N[a]	N[a]		R[a]	...	N[a]

Note.—N = maternal heterozygosity retained in daughter; R = maternal heterozygosity reduced to homozygosity in daughter; ... = analysis performed but locus uninformative for recombination studies (i.e., mother homozygous at locus).

[a] Locus informative for parental origin of trisomy.

1. *Origin of the Additional X Chromosome in 47,XXX Females*

The results of the present study demonstrate that nondisjunction at maternal meiosis I is the most common cause of the 47,XXX condition. All but two of 28 cases studied were maternal in origin, and, in those cases in which we were able to specify the meiotic stage of origin, approximately 70% were consistent with meiosis I errors. Mitotic errors appear to have little, if any, role in the etiology of X chromosome trisomy. That is, all six cases which were scored as meiosis II errors were heterozygous at one or more loci and, therefore, could not have arisen from postzygotic duplication of a single X chromosome.

These results differ markedly from the other sex-chromosome aneuploidies, since errors in division of the paternal sex chromosomes account for 50% of 47,XXY individuals (Jacobs et al. 1988, 1989), for 80% of 45,X cases (Hassold et al. 1988), and for all cases of 47,XYY. Thus the origin of 47,XXX is unlike the other sex-chromosome abnormalities and more closely resembles the autosomal trisomies thus far studied in which maternal meiotic nondisjunction also predominates (Hassold 1986; Buraczynska et al. 1989; Hassold and Takaesu 1989; Kupke and Müller 1989).

2. *Parental Origin and Parental Age*

An effect of increasing maternal age, although much smaller than that observed for trisomy 21, has been reported for both 47,XXY males and 47,XXX females (Carothers et al. 1978). More recently, Jacobs et al. (1988) correlated parental ages with the parental origin of 47,XXY individuals and reported that, for this abnormality, only maternally derived cases were associated with increased maternal age. In the present study, the low level of paternal nondisjunction prevents meaningful comparison of parental ages between 47,XXX's of paternal and maternal origin. However,

Table 4

Summary of Recombination Studies on 11 Maternally Derived Cases of 47,XXX of Meiosis II or Unknown Meiotic Stage of Origin

	Meiosis II Origin						Meiotic Stage Unknown				
Locus	Y1	Y15	Y65	Y78	Y93	Y95	Y16	Y18	Y20	Y89	Y92
Xp:											
DXS89	...	...	R				...	...	...[a]		
DSX278	N[a]	N[a]	R[a]	N[a]	R[a]	R[a]	N[a]	R[a]	R[a]	N[a]	R[a]
DXS16		...	...	...	...[a]	R	N	R		N	...
DXS41	R	R[a]					...	...[a]	N		
DXS92	...	...	...[a]				...[a]	...	...		
DXS164	...		...[a]								
DXS84	...	...[a]					N	...[a]	...[a]		
DXS7	...	...	...	...[a]		...	...[a]	...	N		
TIMP	...	R	N	...	...[a]	...	N	...[a]	N	...	...
DXS255	R[a]	R[a]	N[a]	R[a]	N[a]	R[a]	N	N[a]	N[a]	N[a]	N[a]
DXS14	R[a]	...[a]	...[a]				...	...	N		
Xcen:											
DXZ1	R	R	R	R	R	R	?	?	?	?	?
Xq:											
DXS91	...	...	...				...	...	...		
DXS159	N	...					...	N	N		
DYXS1	...[a]	N[a]	R	R				...	N		
DXS3	...	...[a]	...					N	N		
DXS94	...								N		
DXS42	...	...	...				...	...	...		
DXS144	N		...			...					
DXS86	...	...	...	...	...	...[a]	...	...[a]	...[a]	...	...
DXS15	N	...	...	...		N	...	...	...[a]	N	N
DXS52	N	...[a]	...	...[a]	...[a]	N[a]	R[a]	...[a]	...[a]	...[a]	

Note.—See notes to table 3.

among our maternally derived cases of 47,XXX, we found that meiosis I errors had a significantly elevated mean maternal age by comparison with meiosis II errors. Jacobs et al. (1988) reported a similiar effect for maternally derived cases of 47,XXY. Thus, for both 47,XXX and 47,XXY conditions, advanced maternal age appears to be restricted to maternal meiosis I nondisjunction. This contrasts with the situation in trisomy 21, the only other trisomy studied in any detail, in which there is no obvious difference in mean maternal age between cases of maternal meiosis I origin and cases of maternal meiosis II origin (Juberg and Mowrey 1983). However, the data on trisomy 21 are based on cytogenetic determinations of both the parent and the meiotic stage of origin, and this type of analysis is more subjective in nature and consequently more error prone (Hassold 1985; Carothers 1987). It may be that for all human trisomies the maternal age effect is associated with meiosis I nondisjunction, suggesting that future investigations of the basis of this effect should focus on processes unique to maternal meiosis I.

3. *Recombination and Nondisjunction*

Studies of experimental animals have provided clear evidence for an association between errors of recombination and nondisjunction. For example, in both yeast and *Drosophila,* meiotic mutants have been identified which are known to decrease the level of recombination and to increase the frequency of aneuploidy (e.g., see Sandler 1981; Surosky and Tye 1988). Furthermore, in chromosomally normal *Drosophila* females, Merriam and Frost (1964) observed that X chromosome nondisjunction is more likely to involve bivalents that have undergone zero or two exchanges than to involve those which have undergone one exchange, suggesting that either failure to pair (or exchange) or excess recombination can result in trisomy.

The possible relationship between recombinational errors and human nondisjunction is less clear. Warren et al. (1987) recently provided evidence for a major role of pairing failure in the etiology of trisomy 21, but we have been unable to confirm their observations in pre-

liminary studies of trisomy 13 (Hassold et al. 1987), trisomy 21 (Stewart et al. 1988; Buraczynska et al. 1989), and maternally derived cases of 47,XXY (Jacobs et al. 1988, 1989). Furthermore, in the present study, recombinants were observed in virtually all maternally derived cases of 47,XXX for which sufficient information was available. Thus, it seems likely that absence of recombination is relatively unimportant in the origin of human trisomy, although we cannot rule out an effect in a minority of cases.

A second possible type of recombinational error is that of excess recombination. This could occur either as an increased number of crossovers along the entire bivalent or as a specific area of increased recombination. Either form may result in "chromosome entanglement," as proposed by Bridges (1916). In previous studies of trisomy 13 and trisomy 21 we occasionally observed cases in which crossing-over had occurred between the centromere and the most proximal markers studied (Hassold et al. 1987; Stewart et al. 1988). In the present study we found that five of 13 cases of meiosis I origin had a crossover between the centromere and DXS255, a locus that has been physically mapped to Xp11.21 (Fraser et al. 1989) and is estimated to be only 8 cM from the centromere in conventional linkage analysis (I. Craig, personal communication). These results may reflect the small number of cases studied or may be due to misclassification of the meiotic stage of origin of nondisjunction, e.g., see case Y68 (see table 3). We think it unlikely that this type of error occurred, since Willard et al. (1986) have demonstrated that virtually all X chromosomes have a unique α satellite restriction pattern with various restriction enzymes and since we have analyzed two patterns for each sample. Therefore, we think it more likely that, if this is confirmed on a larger sample set, our data may reflect either (1) an association between pericentromeric recombination and nondisjunction of the X chromosome or (2) an association between nondisjunction and "globally" increased recombination which will become apparent as more cases and loci are examined and compared to conventional linkage data. Regardless of the correctness of these or other interpretations, it is clear that future molecular studies of human trisomy should consider increased, as well as decreased, recombination as a potential contributor to nondisjunction.

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