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ORIGINAL INVESTIGATION

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Nondisjunction of human acrocentric chromosomes: studies of 432 trisomic fetuses and liveborns

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Abstract The present report summarizes molecular studies on the parent and meiotic stage of origin of the additional chromosome in 432 fetuses or liveborns with an additional chromosome 13, 14, 15, 21, or 22. Our studies suggest that there is little variation in the origin of nondisjunction among the five acrocentric trisomies and that there is no association between the origin of nondisjunction and the likelihood of survival to term of the trisomic conceptus. The proportion of cases of paternal origin was similar among the five trisomies: 12% for trisomy 13, 17% for trisomy 14, 12% for trisomy 15, 9% for trisomy 21, and 11% for trisomy 22. The stage of nondisjunction was also similar among the five trisomies, with the majority of cases of maternal origin being due to nondisjunction at meiosis I, whereas for paternally derived cases, nondisjuction occurred primarily at meiosis II.

Introduction

Over the past few years, DNA polymorphisms have been used to investigate the parent and meiotic stage of origin of a number of different autosomal and sex chromosome trisomies, including trisomies 18 (e.g., Kupke and Muller 1989; Fisher et al. 1993) and 21 (e.g., Antonarakis 1991; Antonarakis et al. 1992; Sherman et al. 1991) and the 47,XXY (Hassold et al. 1991a) and 47,XXX (May et al. 1990) conditions. The results indicate a surprising level of variation in the genesis of the different abnormalities. For example, the vast majority of cases of trisomy 21 and 47,XXX are attributable to nondisjunction at maternal meiosis I, while trisomy 18 is usually maternal but more likely to involve an error at meiosis II (Fisher et al. 1993; P. A. Jacobs, unpublished observations), and 47,XXYs are equally likely to be paternal as maternal in origin (Hassold et al. 1991a). Thus, the analyses of these conditions suggest the existence of different, chromosome-specific mechanisms of nondisjunction.

However, these studies have been based primarily on analyses of liveborn trisomic individuals. Consequently, there has been little opportunity to compare the origin of the additional chromosome in fetuses and liveborn conceptuses with the same abnormality (e.g., spontaneously aborted versus liveborn trisomy 21 offspring) or to examine nondisjunction for those trisomies that are incompatible with survival to term.

For the past several years, we have been conducting a cytogenetic study of human spontaneous abortions, one purpose of which has been to identify and characterize numerical chromosome abnormalities (e.g., Jacobs et al. 1987). As part of this study, we have reported preliminary observations on the origin of trisomy in fetuses with an additional chromosome 16 (Hassold et al. 1991b). In the present report, we extend these studies to include analyses of nondisjunction in spontaneous abortions trisomic for an acrocentric chromosome (i.e., 13, 14, 15, 21, or 22). Results from studies of 82 such fetuses are compared to those obtained in our large, ongoing study of liveborn individuals with trisomy 21 (Sherman et al. 1991), and to those from a smaller number of therapeutic abortions or liveborns with trisomies 13, 14, or 22. Our results suggest no major differences in the parent or meiotic origin of trisomy among the five acrocentric chromosomes, nor any obvious association between the mechanism of nondisjunction and likelihood of survival to term of a trisomic conception.

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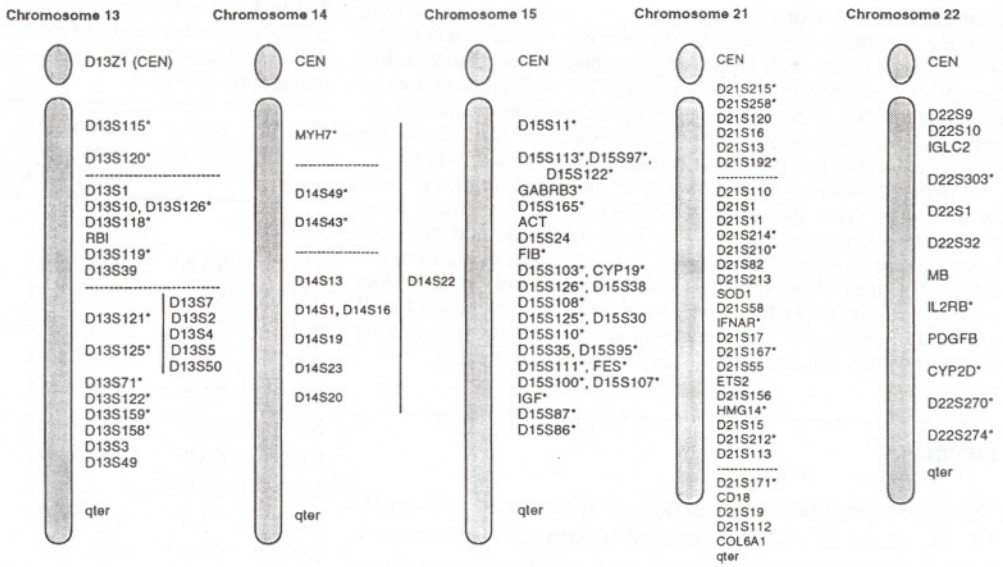

Fig. 1 DNA markers used in the study. The 101 polymorphisms are ordered using available information from published reports and the Genome Data Base. For chromosomes 13, 14, and 21, the *dotted lines* separate loci considered to be proximal, medial, and distal in making determinations of meiotic versus mitotic origin of trisomy. For chromosomes 15 and 22, these regions were not defined since there were no cases of trisomy 15 or 22 in which such determinations were necessary. *Asterisks* indicate PCR-based microsatellite polymorphisms

Materials and methods

Study population

The present study population consists of 432 fetuses or liveborns with an additional acrocentric chromosome, collected from three main sources. First, 82 trisomic fetuses (consisting of 10 cases of trisomy 13, 11 of trisomy 14, 17 of trisomy 15, 22 of trisomy 21, and 22 of trisomy 22) were ascertained as part of ongoing cytogenetic studies of spontaneous abortions. Second, 12 trisomic fetuses (9 cases of trisomy 13, 1 of trisomy 14, and 2 of trisomy 22) were ascertained because of prenatal testing, with the fetal tissue being obtained at the time of termination of the pregnancy. Third, 330 cases of trisomy 21 were ascertained because of clinical features of Down syndrome, as part of an ongoing study of chromosome 21 nondisjunction (Sherman et al. 1991). For these Down syndrome individuals, as well as for the 22 spontaneous abortions with trisomy 21, we included only those cases that were nonmosaic, single trisomies on cytogenetic examination, and for which the parental origin of trisomy was known. A detailed description of this series will be presented separately.

In addition to these cases, we studied 5 liveborns and 1 stillborn infant with trisomy 13 and, in 2 other cases of trisomy 13, the reason for ascertainment was uncertain.

Preliminary results on 104 cases of trisomy 21 (consisting of 79 liveborns, 18 therapeutic abortions, and 7 spontaneous abortions; Sherman et al. 1991) and 7 cases of trisomy 13 (consisting of 1 liveborn and 6 spontaneous abortions; Hassold et al. 1987) have been reported previously.

Cytogenetic studies

Cytogenetic studies of blood and tissue samples were carried out using standard procedures (e.g., Hassold et al. 1987). For trisomy 21 only, we excluded from further analysis all cases identified as being mosaic trisomies; these will be discussed in a separate report.

DNA marker analysis

Southern hybridization or polymerase chain reaction (PCR) amplification methodology was used to analyze DNA polymorphisms of trisomic fetuses/liveborn individuals and their parents, as described previously (Sherman et al. 1991; Petersen et al. 1993). Altogether, a total of 101 polymorphisms were used in the study, consisting of 23 for chromosome 13, 10 for chromosome 14, 26 for chromosome 15, 30 for chromosome 21, and 12 for chromosome 22 (Fig. 1).

For each case, we first determined the parent of origin of trisomy, with most determinations being based on results from three or more markers, and with over 90% being made on the basis of at least two markers. Subsequently, we inferred the stage of origin of trisomy by comparing proximal long arm markers of the parent who contributed the extra chromosome with those of the trisomic offspring. If parental heterozygosity was retained in the trisomic offspring (nonreduction), we concluded an error at meiosis I; if parental heterozygosity was reduced to homozygosity (reduction), we concluded a meiosis II error. We based these meiotic stage determinations on proximal long arm markers, since highly informative, chromosome-specific centromere polymorphisms are not available for any of the acrocentric chromosomes. For chromosome 13 we used D13S115, reported as approximately 20 cM from the alpha satellite marker D13Z1 (Bowcock et al. 1993); in one instance, D13Z1 itself was informative. For chromosome 14, we used MYH7, approximately 20 cM from the proximal 14q marker 140HT (Genome Data Base), but at an unknown distance from the centromere of chromosome 14. For chromosome 15, we used D15S11, reported as approximately 13 cM from the centromere (Mutirangura et al. 1993). For chromosome 21 we used the most proximal informative marker of D21S215, D21S258, D21S120, D21S16, D21S13, and D21S192, all of which are within 5–10 cM of the centromere (Jabs et al. 1991; Genome Data Base). For chromosome 22, we used D22S9, D22S10, and IGLC2, all of which are in proximal 22q (Genome Data Base) but are at an unknown distance from the centromere. These determinations of meiotic stage must be viewed with caution, since they assume tight linkage between the proximal markers being used and the centromeres. In fact, there is relatively little information on centromere-gene distances for any of the acrocentric chromosomes. Thus, for chromosomes 14 and 22 the genetic distances between the centromere and our most proximal markers are unclear; for chromosomes 13 and 15 our proximal markers are over 10 cM away from the centromere; and for chromosome 21 the distance is between 5–10 cM. Thus, it is likely that some of our meiotic stage determinations will be in error.

Trisomies that were reduced at proximal loci could have resulted from either meiosis II or mitotic nondisjunction. To distinguish between these two alternatives, we examined other, nonproximal markers. If the trisomic offspring was nonreduced at one or more of these loci, we concluded a meiosis II origin. However, if the trisomic offspring was reduced for all informative loci, including at

least one each in the proximal, medial and distal regions of the long arm, we concluded a postzygotic, mitotic error (note that this also would be consistent with failure of recombination at meiosis I, followed by nondisjunction at meiosis II). The definition of loci as proximal, medial, or distal was arbitrary and was based on both genetic and physical mapping information (Genome Data Base); the assignment of the loci into these categories is provided in Fig. 1.

Finally, trisomies uninformative at proximal markers could have resulted from meiosis I, meiosis II, or mitotic errors. Most such cases were nonreduced for at least one locus and therefore were meiotic in origin. These cases were scored as being of meiosis I or II origin. However, for a few such cases only reduced loci were identified. These too were scored as being of meiosis I or II origin, despite the fact that they were also consistent with mitotic origin; thus the mitotic category may be underrepresented.

Results

The study population consisted of 80 cases of trisomies 13, 14, 15, or 22 and 352 cases of trisomy 21. Information on ascertainment, parental ages, and results of cytogenetic and DNA studies for the 80 cases of trisomies 13, 14, 15, and 22 are provided in Table 1. Similar data on a subset of the trisomy 21 cases have been presented previously (e.g., Takaesu et al. 1990), and are not provided here. Summaries of the molecular studies on all trisomies are given in Tables 2 and 3.

Cytogenetic analysis

The results of the cytogenetic analysis for the 80 cases of trisomies 13, 14, 15, and 22 are provided in Table 1. In 72 of the cases, the karyotype was consistent with nonmosaic, single trisomy. Four cases were double trisomies (S1445, S96, S636, and S654) and two (K3362 and K3034) were trisomic for an acrocentric chromosome and monosomic for a sex chromosome. One case (S1411) was an unusual mosaic double trisomy, with one cell line having an additional chromosome 12 and a second cell line an additional chromosome 22. The remaining two cases (X16 and B2) were mosaic trisomies.

DNA studies

The results of the DNA marker studies of parental and meiotic stage of origin are summarized in Table 2. For trisomies 13, 14, 15, and 22, we were able to determine the parental origin in 73 of the 80 cases, with 9 (12.3%) being paternal and 64 (87.3%) maternal in origin. This was little different from the comparable values for trisomy 21, with 32 (9.1%) paternal and 320 (90.9%) maternal cases.

There was also little evidence that parental origin of trisomy affected likelihood of survival to term. For trisomy 13, 2 of 11 spontaneous abortions and 1 of 5 liveborns had an additional, paternally derived chromosome. For trisomy 21, none of the 22 spontaneous abortions were paternal in origin, while 32 of the 330 liveborns (9.7%) were; however, this difference was not significant ($P > 0.1$).

Table 1 Ascertainment, parental ages, and results of cytogenetic and DNA marker studies for 80 cases of trisomies 13, 14, 15, and 22. (*LB* livebirth, *SAB* spontaneous abortion, *SB* stillbirth, *TAB* therapeutic abortion)

ID no.	Ascertainment	Chromosome constitution	Maternal age	Paternal age	Origin
Trisomy 13					
S17	SAB	47,XY,+13	37	33	Mat I
S47	SAB	47,XY,+13	39	42	Pat I
S64	SAB	47,XY,+13	35	24	Mat I or II
S101	SAB	47,XX,+13	29	43	Mat I
S110	SAB	47,XY,+13	39	43	Mat I or II
S262	SAB	47,XY,+13	31	26	Mat I or II
S763	SAB	47,XX,+13	36	36	Mat I
S823	SAB	47,XX,+13	30	28	Mat-mitotic
K3392	SAB	47,XY,+13	27	29	Mat I or II
K3362[a]	SAB	46,X,+13	30	36	Pat I or II
W011	TAB	47,XX,+13	27	29	Mat I or II
W012	TAB	47,XY,+13	39	35	Mat I or II
W013	TAB	47,XX,+13	33	41	Mat I
W016	TAB	47,XY,+13	38	?	Mat I or II
W018	TAB	47,XY,+13	37	?	Mat I or II
W020	TAB	47,XY,+13	38	?	Mat I or II
W022	TAB	47,XX,+13	30	?	Mat I or II
W023	TAB	47,XX,+13	42	?	Mat I or II
W024	TAB	47,XY,+13	47	42	?
X16	LB	46,XX/47,XX,+13	?	?	Mat I or II
W009	LB	47,XX,+13	28	37	Pat II
W010	LB	47,XX,+13	33	44	Mat I or II
W014	LB	47,XX,+13	30	30	Mat I or II
W019	LB	47,XY,+13	40	?	Mat I or II
W015	SB	47,XY,+13	26	41	Mat I or II
W017	?	47,XX,+13	36	?	Mat I or II
W021	?	47,XX,+13	?	?	?
Trisomy 14					
S41	SAB	47,XX,+14	30	31	Pat II
S86	SAB	47,XY,+14	40	40	Mat I
S142	SAB	47,XX,+14	25	25	Mat-mitotic
S349	SAB	47,XX,+14	33	36	Mat I
S482	SAB	47,XX,+14	30	33	Mat I or II
S516	SAB	47,XX,+14	36	44	Pat II
S520	SAB	47,XX,+14	24	27	Mat II
S684	SAB	47,XY,+14	29	34	Mat I or II
S722	SAB	47,XX,+14	34	35	Mat II
S818	SAB	47,XX,+14	29	29	Mat II
S1445[b]	SAB	48,XX,+4,+14	37	40	Mat II
Z52	TAB	47,XX,+14	21	26	Mat I

We inferred the stage of origin of trisomy for 31 of the cases of trisomies 13, 14, 15, and 22 and for 265 of the cases of trisomy 21. The most frequent stage of origin of trisomy was maternal meiosis I. Errors at this stage were approximately three times as common as maternal meio-

Table 1 (continued)

ID no.	Ascertainment	Chromosome constitution	Maternal age	Paternal age	Origin
Trisomy 15					
S96[c]	SAB	48,XX,+10,+15	44	43	Mat I or II
S104	SAB	47,XX,+15	34	40	Mat I or II
S112	SAB	47,XY,+15	38	36	Mat I or II
S287	SAB	47,XY,+15	38	42	Mat I
S359	SAB	47,XY,+15	42	43	Mat II
S387	SAB	47,XX,+15	38	44	Mat I
S467	SAB	47,XX,+15	34	30	Pat I or II
S494	SAB	47,XX,+15	33	32	Mat I or II
S550	SAB	47,XY,+15	28	30	Mat I or II
S557	SAB	47,XX,+15	32	34	Pat II
S636[d]	SAB	48,XY,+15,+16	36	34	Mat I or II
S654[e]	SAB	48,XY,+15,+21	42	50	Mat I
S687	SAB	47,XY,+15	37	43	Mat I
S811	SAB	47,XX,+15	31	37	Mat I or II
S814	SAB	47,XX,+15	38	31	Mat I or II
S826	SAB	47,XY,+15	36	36	Mat I
S827	SAB	47,XX,+15	35	37	Mat II
Trisomy 22					
S51	SAB	47,XX,+22	35	35	Mat I
S133	SAB	47,XX,+22	40	42	Mat I or II
S286	SAB	47,XY,+22	40	32	Mat I
S298	SAB	47,XX,+22	40	39	?
S351	SAB	47,XY,+22	40	43	Mat I or II
S419	SAB	47,XY,+22	35	28	Mat I or II
S461	SAB	47,XX,+22	37	39	Mat I or II
S661	SAB	47,XX,+22	28	34	Mat I
S672	SAB	47,XY,+22	32	33	Mat I or II
S686	SAB	47,XX,+22	35	42	Mat I
S764	SAB	47,XX,+22	36	44	Mat I
S820	SAB	47,XY,+22	32	32	Mat I or II
S1411[f]	SAB	47,XY,+12/47,XY,+22	34	27	Pat I or II
K3034[a]	SAB	46,X,+22	36	37	Mat I or II
K3217	SAB	47,XY,+22	35	33	Mat I
K3272	SAB	47,XY,+22	31	35	?
K3296	SAB	47,XY,+22	29	29	?
K3323	SAB	47,XX,+22	32	33	?
K3359	SAB	47,XX,+22	23	28	Mat I or II
K3400	SAB	47,XX,+22	33	28	Mat I or II
K3418	SAB	47,XX,+22	27	31	?
K3450	SAB	47,XX,+22	42	25	Mat I or II
B1	TAB	47,XX,+22	34	36	Pat I or II
B2	TAB	46,XY/47,XY,+22	31	28	Mat I or II

[a] Single X chromosome is maternal in origin
[b] Origin of +4 is unknown
[c] +10 is maternal in origin
[d] +16 is maternal in origin
[e] Origin of +21 is unknown
[f] Origin of +12 is unknown

sis II errors for trisomies 13, 14, 15, and 22, as well as for trisomy 21. In contrast, paternally derived trisomies were more likely to involve nondisjunction at meiosis II than meiosis I, regardless of the chromosome involved. Eleven other cases (1 trisomy 13, 1 trisomy 14, and 9 trisomies 21) were reduced for all informative proximal, medial, and distal loci, and were therefore considered to be of mitotic origin (see Materials and methods). However, as all 11 were maternal in origin, it is likely that at least some were, in fact, the result of maternal meiotic nondisjunction.

Table 3 provides information on parental age, by parent and stage of origin of trisomy. This analysis was restricted to spontaneous abortions and liveborns, since advanced maternal age was the reason for ascertainment for most of the therapeutic abortions. Trisomy 21 was considered separately but, because of the relatively small number of cases of trisomy 13, 14, 15, and 22, data from these trisomies were pooled. Surprisingly, the data provide little evidence for variation in parental age among the different categories of nondisjunction. For example, there was a slight reduction in mean maternal age for cases of paternal versus those of maternal origin, both for trisomies 13, 14, 15, and 22 and for the trisomy 21 liveborns, but these differences were not significant. Additionally, there was no significant difference in maternal age between maternal meiosis I and maternal meiosis II nondisjunction for any of the three categories of trisomy.

Discussion

The purpose of the present study was twofold: first, to determine whether nondisjunctional patterns vary among the five acrocentric chromosomes and, second, to determine whether differences exist between spontaneously aborted and liveborn trisomic offspring. The results of our analysis provide little evidence for such differences. The proportion of cases of paternal origin was remarkably similar among the five trisomies, ranging from a low of 9% for trisomy 21 to a high of 17% for trisomy 14. Overall, the proportion of paternally derived cases among all acrocentric trisomies was approximately 10%. This is only slightly higher than the comparable values for the other two autosomal trisomies that have been studied in any detail, namely, trisomy 18, with a level of paternal nondisjunction of approximately 5% (Kupke and Muller 1989; Fisher et al. 1993) and trisomy 16, for which paternally derived cases have not yet been identified (Hassold et al. 1991b). Thus, it appears that paternal nondisjunction plays a minor role in the genesis of human autosomal trisomies, at least those involving the small chromosomes.

The timing of the nondisjunctional event also appeared similar for the different acrocentric chromosomes. Nondisjunction at maternal meiosis I was the most common cause of trisomies 13, 15, 21, and 22 and, overall, errors at this stage were about three times as common as errors at maternal meiosis II. Trisomy 14 was the only exception, with four cases identified as being of maternal meiosis II origin and three of maternal meiosis I origin. However, this may well be due to misclassification of meiosis I cases as meiosis II, since the proximal chromosome 14 marker we used is an unknown distance from the cen-

Table 2 Parental and meiotic stage of origin according to ascertainment for 432 cases of trisomies 13, 14, 15, 21, and 22

Trisomy	Ascertainment	No. of cases	Paternal			Maternal			Mitotic	Unknown	% Paternal
			I	II	I or II	I	II	I or II			
13	SAB/SB	11	1	0	1	3	0	5	1	0	
	TAB	9	0	0	0	1	0	7	0	1	
	LB	5	0	1	0	0	0	4	0	0	
	Unknown	2	0	0	0	0	0	1	0	1	
	Total	27	1	1	1	4	0	17	1	2	3/25 = 12%
14	SAB	11	0	2	0	2	4	2	1	0	
	TAB	1	0	0	0	1	0	0	0	0	
	Total	12	0	2	0	3	4	2	1	0	2/12 = 17%
15	SAB	17	0	1	1	5	2	8	0	0	
	Total	17	0	1	1	5	2	8	0	0	2/17 = 12%
21	SAB	22	0	0	0	12	4	6	0	0	
	LB	330	9	15	8	162	54	73	9	0	
	Total	352	9	15	8	174	58	79	9	0	32/352 = 9%
22	SAB	22	0	0	1	6	0	10	0	5	
	TAB	2	0	0	1	0	0	1	0	0	
	Total	24	0	0	2	6	0	11	0	5	2/19 = 11%

Table 3 Mean parental ages by parent and stage of origin of trisomy, excluding all known mosaic trisomies and double aneuploids

	Origin of error	No. of cases	Maternal age ± SD	Paternal age ± SD
Trisomies 13, 14, 15, and 22[a]	Paternal	6	33.2 ± 4.0	36.3 ± 5.8
	Meiosis I	1	39.0 ± 0.0	42.0 ± 0.0
	Meiosis II	4	31.5 ± 3.4	36.5 ± 5.6
	Maternal	45	34.1 ± 4.7	35.3 ± 5.9[b]
	Meiosis I	15	35.5 ± 3.4	38.2 ± 4.5
	Meiosis II	5	32.8 ± 6.8	34.2 ± 6.4
	Mitotic	2	27.5 ± 3.5	26.5 ± 2.1
Trisomy 21 spontaneous abortions	Paternal	–	–	–
	Maternal	22	33.1 ± 5.3	34.8 ± 5.1
	Meiosis I	12	33.0 ± 5.3	35.0 ± 5.0
	Meiosis II	4	30.0 ± 5.5	22.5 ± 5.7
Trisomy 21 livebirths	Paternal	32	28.5 ± 6.0	31.1 ± 6.2
	Meiosis I	9	26.4 ± 6.7	29.6 ± 6.2
	Meiosis II	15	28.1 ± 4.7	30.5 ± 5.3
	Maternal	289	30.3 ± 5.9	32.8 ± 6.8
	Meiosis I	162	30.1 ± 5.5	32.4 ± 5.9
	Meiosis II	54	31.2 ± 7.3	33.5 ± 7.8
	Mitotic	9	28.3 ± 7.1	32.8 ± 8.7

[a] Excluding all therapeutic abortions and case W017 with unknown ascertainment
[b] Excluding case W019 with unknown paternal age

tromere. Thus, it seems likely that there are mechanisms of maternal meiosis I nondisjunction that are shared by all the acrocentric chromosomes, and that these are the most common cause of nondisjunction involving the acrocentrics. These results are consistent with a recent study of nondisjunction of chromosome 15 in maternal uniparental disomy, in which the majority of cases were attributed to errors at meiosis I (Robinson et al. 1993).

Unlike the maternally derived cases, trisomies of paternal origin were more likely to involve errors at meiosis II than meiosis I. This was the case both for trisomy 21 and for the limited number of paternal cases of trisomies 13, 14, 15, and 22. Overall, there were 19 cases of meiosis II and 10 cases of meiosis I origin, nearly the reverse of the situation for maternally derived trisomies. Thus, it seems likely that mechanisms of paternal nondisjunction are similar for all acrocentric chromosomes, and that they are dissimilar from those associated with maternal nondisjunction.

There was little evidence that parent or meiotic stage of origin of trisomy affected viability of conceptuses with an additional chromosome 13 or 21, the only acrocentric trisomies compatible with livebirth. Furthermore, among

the spontaneously aborted trisomies, there was no obvious association between gestational age and the parent or stage of nondisjunction (data not shown). Thus, at least for this rather crude measure of phenotype, the consequences of trisomy appear unrelated to the mechanism of nondisjunction, both for chromosomes known to be imprinted, i.e., chromosomes 14 (Antonarakis et al. 1993b) and 15 (Nicholls et al. 1989) and for those for which imprinting effects have not been demonstrated, chromosomes 13 (Stallard et al. 1993), 21 Blouin et al. 1993), and 22 (Schinzel et al. 1994).

Somewhat surprisingly, we observed no significant differences in parental age between any of the categories of nondisjunction. For example, mean maternal ages were not significantly different between paternally and maternally derived cases, between meiotic and mitotic cases, or between maternal meiosis I and maternal meiosis II cases. For the former two comparisons the failure to detect a significant effect may be attributable to small sample size, since previous studies of larger data sets have identified significant differences. For example, in a recent study of paternal trisomy 21, cases from the present study population were combined with those from another group studying chromosome 21 nondisjunction (i.e., Antonarakis and colleagues; for recent reference, see Antonarakis et al. 1993a). The combined data set consisted of 36 paternally derived cases and 429 maternally derived cases, and in that analysis a significant reduction in maternal age was identified in the cases of paternal origin (Petersen et al. 1993).

Similarly, for mitotic trisomy 21 Antonarakis et al. (1993a) recently reported a significant reduction in mean maternal age for 11 cases of mitotic origin, by comparison with 217 cases of maternal meiotic origin. This is consistent with our results on trisomies 13, 14, 15, and 22 and trisomy 21 in livebirths, in which we identified nonsignificant reductions in mean maternal age in cases of mitotic origin.

However, small sample size cannot explain the lack of difference between maternal meiosis I and II nondisjunction since, in total, there were 189 cases of meiosis I and 63 cases of meiosis II origin. This observation is at variance with our earlier studies of trisomy 21, which were based on 104 cases, and in which the effect of maternal age appeared to be restricted to meiosis I cases (Sherman et al. 1991). With the addition of new cases this effect has now disappeared, suggesting that for the acrocentric chromosomes there may be maternal age-dependent mechanisms of nondisjunction that act on meiosis II. If so, the behavior of the acrocentric chromosomes would be similar to that observed for chromosome 18 (Fisher et al. 1993; P. A. Jacobs, unpublished observations), but dissimilar to that observed for the X chromosome (Hassold et al. 1991a; May et al. 1990). Alternatively, it may be that the maternal age-related acrocentric trisomies are restricted to errors at meiosis I, but that our use of nonpericentromeric markers to infer meiotic stage leads to frequent misclassification of meiosis I cases as being of meiosis II origin. This might be the case if increased pericentromeric recombination is important in the genesis of acrocentric trisomies. A resolution of this question, as well as a better understanding of the association between maternal age and human trisomy, awaits the identification of reliable centromeric polymorphisms for the acrocentric chromosomes.

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