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Trisomy 18: Studies of the Parent and Cell Division of Origin and the Effect of Aberrant Recombination on Nondisjunction

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Summary

We have studied the mechanism of origin of 63 cases of trisomy 18. In 2 the additional chromosome was paternal in origin, and in the remaining 61 it was maternal in origin. Both paternal cases were attributable to a postzygotic mitotic (PZM) error. Among the 54 maternal cases for which the cell division of error was established, only 16 were attributable to an error at the first meiotic division (mat MI), whereas no fewer than 35 were due to an error at the second meiotic division (mat MII), the remaining 3 being the result of a PZM error involving the maternal chromosome 18. A standard map of chromosome 18 was constructed and compared with the nondisjunctional map. Approximately one-third of the mat MI errors were associated with complete absence of recombination, whereas in the remaining two-thirds and in all the mat MII errors recombination in the nondisjoined chromosomes appeared to be normal. All the maternal errors were associated with an increased maternal age, although this reached significance only for the mat MII category of nondisjunction. Our observations on chromosome 18 are compared with those on other chromosomes for which there are comparable data.

Introduction

Trisomy 18 is one of the more common autosomal trisomies, occurring with a frequency of 0.18% among all pregnancies that survive long enough to be clinically recognized. The great majority of conceptions with an additional chromosome 18 spontaneously abort, only 5% surviving to birth (Hassold and Jacobs 1984). Nevertheless, trisomy 18 is the second most common autosomal trisomy at birth, having a newborn frequency of 1/8,000 (Hook and Hamerton 1977). Trisomy 18, in common with most other autosomal trisomies, demonstrates a strong association with increased maternal age (Hassold and Chiu 1985). Studies of the parental origins of the additional chromosome in trisomies of chromosomes 13, 16, and 21 have shown that the majority arise as the result of errors of maternal meiosis (Hassold and Jacobs 1984; Hassold et al. 1987, 1991*a*; Antonarakis 1991; Sherman et al. 1991). Furthermore, several studies have shown that alterations in the levels of recombination are associated with nondisjunction (e.g., see Warren et al. 1987; Morton et al. 1990; Sherman et al. 1991; MacDonald et al. 1994). Trisomy 21 has been shown to be associated with a significant reduction in recombination in the nondisjoined bivalent (Sherman et al. 1994); and nondisjunction of the XY bivalent, resulting in 47,XXY males, is similarly associated with a marked reduction in recombination (Hassold et al. 1991*b*). It has recently been shown that maternal nondisjunction of the X chromosome can be nullichiasmate, normochiasmate, or associated with an excess of pericentromeric recombination (MacDonald et al. 1994).

The analysis of inherited DNA markers, RFLPs, and, more recently, microsatellite repeat polymorphisms (Weber and May 1989) in the nondisjoined bivalent of trisomic probands provides a method of studying both the parent and cell division of origin and the effects of perturbations of recombination in the genesis of human trisomy. We have previously published data on the parental origin of a series of 50 trisomy 18 individuals including spontaneous and induced abortions, stillbirths, and live births. In common with other reports on trisomy 18 (Kupke and Müller 1989; Nothen et al. 1993; Ya-gang et al. 1993), we found the additional chromosome to be maternal in origin in the great majority of cases (Fisher et al. 1993). However, our previous study and all other published reports on the origin of trisomy 18 were concerned only with the parent of origin of the additional chromosome. In this paper we report our findings on the parent and cell division of origin and on the relationship of increased maternal age and aberrant recombination to the nondisjunctional event in a series of 63 trisomy 18 conceptions that include our original 50 cases.

Subjects, Material, and Methods

Study Population and Probes

The study population consisted of 63 probands with trisomy 18 and their parents (table 1). DNA was available

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Table 1

Study Population

Ascertainment	No. of Cases			Mean Maternal Age ± SE (years)
	Total	Male	Female	
Spontaneous abortion	8	4[a]	4	36.8 ± 3.0
Prenatal diagnosis:				
Increased maternal age	23	9[b]	14	40.1 ± 0.7
Other than maternal age	17[c]	7	8	32.8 ± 1.6
Stillbirth	3	2	1	33.0 ± 5.5
Live birth	12	2	10[b]	29.6 ± 2.0
Total	63	24	37	

[a] Includes one case of 48,XXY,+18.
[b] Includes one mosaic.
[c] Includes two cases of unknown sex.

from all probands and both parents, with the exception of two cases where DNA was available from only one parent. Two patients were mosaics with both a normal and a trisomic cell line, but the remaining 61 appear to be nonmosaic trisomy 18. The methods used for extraction of DNA have already been reported elsewhere (Fisher et al. 1993). In total, 39 DNA polymorphisms spanning the length of chromosome 18 were used: 15 analyzed by Southern blot analysis and hybridized with radioactive probes (see methodology in Fisher et al. 1993) and 24 microsatellite repeats amplified by standard PCR amplification (Saiki et al. 1988; Petersen et al. 1990). Eight of these latter markers were described in our previous report, whereas the 16 additional ones are MIT MS156 (D18S36), MFD153 (D18S38), CU18-001 (D18S40), CU18-002 (D18S41), CU18-006 (D18S45), and CU18-009 (D18S50) (Straub et al. 1993); AFM036ya1 (D18S53), AFM080xd7 (D18S54), AFM178xc3 (D18S59), AFM197xh12 (D18S62), AFM205td6 (D18S63), AFM240vh6 (D18S65), AFM248tel (D18S67), AFM254vd5 (D18S70), and AFM254yd5 (D18S71) (Weissenbach et al. 1992); and CU18-013 (D18S170) (R. E. Straub, personal communication). Complete descriptions of the probes, primers, details of the allele frequencies, and cytogenetic assignments are available from the Genome Data Base and the references cited.

Construction of the Standard Map

A standard chromosome 18 linkage map, incorporating all the markers used in our study and additional markers ordered by linkage, was generated for comparison with the nondisjunctional map, to determine the effects of aberrant recombination in the etiology of trisomy 18. The standard map was constructed in two stages. Sex-specific lod scores were generated from the CEPH version 6 data (Dausset et al. 1990) by the program CRIMAP (Green et al. 1988) and were combined with lod scores from Hughes et al. (1994). The MAP93 program (Morton and Andrews 1989; Morton and Collins 1990) was used to generate sex-specific linkage maps. An initial framework map incorporating 21 of the 51 markers within CEPH, whose approximate order was known from earlier genetic and physical maps (O'Connell et al. 1987; Le Beau et al. 1993; Straub et al. 1993), was constructed, into which 27 additional loci were subsequently added in the best supported order. The final sex-specific maps contained 48 loci. The exact position of the centromere was unknown; therefore it was inserted at the midpoint between two markers known to flank the centromere. The CEPH sex-specific maps were entered into the location database (LDB; Morton 1991), together with additional genetic maps for which the lod scores were unavailable (Straub et al. 1993; Buetow et al. 1994; Gyapay et al. 1994; Matise et al. 1994; van Kessel et al. 1994; Berrettini et al., in press). Sixty-five additional loci were interpolated into the CEPH map by LDB. The final LDB map therefore contained 113 loci.

In our analysis we considered only the 32 loci used in the recombination analysis of the trisomic probands (table 2). We used an earlier version of MAP93 (MAPY) to obtain standard errors of intervals and map lengths, computed as $\sqrt{\Sigma_i \Sigma_j C_{ij}}$, where C_{ij} is the covariance between disjoint intervals i and j. MAPY does not filter errors and makes only partial allowance for interference, and so the map is inflated. The standard and nondisjunctional maps were analyzed in exactly the same way.

Parental Origin, Cell Division of Error, and Effect of Recombination

The parental origin, stage of the nondisjunctional error, and recombination data were obtained by following the segregation of the polymorphic markers from the parents to the trisomic proband. The alleles were scored by visual inspection of the autoradiographs. The presence of three alleles in the trisomic proband unambiguously determined two alleles from one parent and one from the other. When only two alleles were present in the trisomic proband, one allele normally amplified to a greater intensity (PCR mark-

Table 2

Loci in Standard Map (MAPY)

Locus	Cytogenetic Assignment	Genetic-Map Distance (cM)	
		Male	Female
D18S170	pter-p11.21	.0	.0
D18S59	pter-p11.22	.0	.0
D18S63	pter-p11.22	17.0	2.0
D18S54	pter-p11.22	17.0	2.0
D18S62	pter-p11.22	35.6	7.2
D18S53	p11.22-p11.21	55.0	36.9
D18S71	p11.22-p11.21	55.0	44.7
D18S40	p11.13-p11.2	55.3	52.1
D18S32	p11.31-p11.22	55.6	53.5
cen	cen-cen	55.6	54.1
D18S45	q11.1-q11.2	55.9	54.9
D18S44	q11.1-q11.2	55.7	56.2
D18S36	q12.2-q21.1	57.4	67.6
D18S67	q12.2-q12.3	58.7	75.5
D18S6	q12.3-q12.3	58.7	75.5
D18S65	q12.2-q12.3	58.7	81.0
D18S46	q12.2-q21.1	61.9	92.9
DCC	q21.1-q21.1	61.9	101.5
D18S8	q21.3-q21.3	65.3	102.5
D18S35	q21.2-q21.3	67.9	105.5
D18S41	q21.2-q21.3	70.9	107.1
D18S38	q21.31-q21.31	73.6	121.5
D18S51	q21.3-q22.1	75.1	127.7
D18S42	q21.3-q22.1	90.1	129.9
D18S19	q22-q22	76.6	133.7
D18S5	q22-q22	86.7	146.6
D18S43	q22.3-q23	91.4	146.3
MBP	q23-q23	103.7	150.0
D18S50	q23-q23	105.4	154.1
D18S70	q23-q23	113.3	161.1
D18S11	q23-q23	113.3	161.1
D18S17	q23-q23	118.5	163.2
D18S31	q22.3-q23	118.5	163.2

ers) or was clearly of double intensity on autoradiographs of Southern blots representing two copies of that allele. Parental heterozygotes on each autoradiograph acted as controls to ensure that alleles were of a similar intensity. The parental origin of the additional chromosome 18 was determined by either the presence of both of one parent's alleles or the increased dosage of a unique parental allele in the trisomic proband. In all but one case this was achieved with a minimum of two informative markers.

Once parental origin of the additional chromosome is known, the cell division resulting in the nondisjunctional error—whether MI, MII, or a PZM event—can be inferred from the centromeric genotype that is unaffected by recombination. In the event of an MI error the centromere of the nondisjoined bivalent will not be reduced (N), whereas in a MII or PZM error it will be reduced to homozygosity (R). The recombination study allows a distinction to be made between the latter two types of error (see below). In the absence of a highly polymorphic centromere marker for chromosome 18, the cell division of the nondisjunctional error was established by using markers flanking the centromere. With this approach, a small proportion of the cases, depending on the distance (in cM) between the loci, may be wrongly assigned. If both markers flanking the centromere were N, the error occurred during MI. If they were both R, but more distal loci were N, the error occurred at MII. If they were both R and ≥ 10 informative loci along the chromosome were also all R, the error was assumed to be postzygotic.

The recombination analyses depended on identifying heterozygous loci in the parent from which the additional chromosome was derived and determining if these loci remained heterozygous (i.e., were N) or were reduced to homozygosity (i.e., were R) in the trisomic proband. The recombination fractions and lod scores calculated from the numbers of N and R observations at each locus by TETRAD (Shahar and Morton 1986; Morton et al. 1988) were subsequently used in the MAPY program to generate linkage maps for the nondisjoined chromosomes. The role of aberrant recombination in the nondisjunctional event was determined by comparing the nondisjunctional maps with the standard female genetic map of chromosome 18.

Results

Standard Map

The map length is 108.8 cM in males and 151.3 cM in females when interference (measured by a mapping parameter of 0.04) and an error frequency of .011 are estimated simultaneously by the MAP93 program. These lengths were increased to 118.5 and 163.2 cM, respectively, with MAPY (table 2). No recombination was seen between two loci (D18S63 and D18S54) on 18p and two loci (D18S70 and D18S11) on 18q on the standard map. However, if the order of these loci, from pter to qter, is D18S54–D18S63–D18S11–D18S70, double exchanges within a small distance are observed in the recombination study. Therefore, the preferred order of these loci, from pter to qter, is D18S63–D18S54–D18S70–D18S11.

Table 3

Cell Division of Error of 59 Cases of Maternal Origin, and Number of Exchange Events in the Nondisjoined Chromosomes

Cell Division of Error	Total No.	No. of Exchanges					
		0	1	2	3	4	5
MI	16	5	3	4	1	3	0
MII	35	...	3	19	6	5	2
Unknown	5	1	0	0	2	2	0
PZM	3	3	...	...	...	...	...

Table 4

Comparison between Nondisjunctional Map Lengths and Those of the Standard Female Map

Data Set	Mean Map Length D18S59–D18S17 ± SE (cM)	Comparison with Standard Map
Standard female map	163.2 ± 3.6	...
Entire data set	131.0 ± 8.7	$P < .001$
All MI errors	103.6 ± 12.3	$P < .001$
MI errors excluding nullichiasmates	186.8 ± 30.3	$P > .05$
All MII errors	190.9 ± 30.1	$P > .05$
All meiotic errors	166.3 ± 13.9	$P > .05$
Meiotic errors excluding nullichiasmates	180.5 ± 17.4	$P > .05$

Parent and Cell Division of Origin

All 63 cases were informative for parent of origin; 61 (96.8%), including both the mosaics, were found to have an additional maternal chromosome, and 2 (3.2%) were found to have an additional paternal chromosome. The two paternal cases were reported previously, and in both the data were consistent with a PZM error involving the paternal chromosome 18.

Two cases were not investigated for the cell division of error, because there was insufficient DNA. The cell division of the nondisjunctional event in the remaining 59 maternal cases is shown in table 3. The four loci mapping closest to the centromere are D18S71 (18p11.22-p11.21), D18S40 (18p11.3-p11.2), D18S44 (18q11-q11.2), and D18S45 (18q11-q11.2). If there are normal levels of recombination in the nondisjoined chromosomes, the use of these loci to determine the cell division of origin will result in a maximal mistyping frequency of ~1% if both a short- and a long-arm marker are informative. However, if only one locus (excluding D18S71) is informative, the rate of mistyping of the centromere will be ~2%. Only five cases were uninformative, three because both flanking markers were uninformative and two because of recombination between the markers. Sixteen of the remaining 54 were consistent with an MI origin, and 35 were consistent with an MII origin, while 3 cases were shown to be an R, one at 21, one at 22, and one at 25 markers, along the length of the chromosome and therefore were assumed to be the result of a PZM error involving the maternal chromosome 18.

Recombination

The numbers of recombinant events are summarized in table 3. Of the 59 cases with an additional maternally derived chromosome, 50 had informative loci that were both N and R, indicating at least one recombinational event and therefore a meiotic origin. In six cases with ≥10 informative loci, all loci were N. These six cases consisted of five resulting from an MI error and one in which the centromere flanking probes were uninformative. Thus, of the 16 cases that, on the basis of centromere typing, were seen as arising at MI, 5 were nullichiasmate. The number of nullichiasmate MI divisions expected by chance in our data is only 0.4, and therefore maternal nullichiasmate nondisjunction appears to be one cause of trisomy 18. Furthermore, MII errors occurring after a nullichiasmate MI division will appear reduced at all loci and thus indistinguishable from those of PZM origin. The expected number of MII errors occurring after a nullichiasmate MI division in our material is ~1, so it may well be that one of the three maternal PZM errors is in reality an MII nullichiasmate error.

Table 4 shows the lengths of the nondisjunctional maps in comparison with those of the standard map. The lengths derived from the whole data set or from all MI errors are significantly shorter than those of the standard map. However, after removal of the nullichiasmate cases there are no significant differences between the length of the standard map and any of the nondisjunctional maps. Thus, with the exception of the nullichiasmate MI divisions, the number of exchange events in the nondisjoined chromosomes or chromatids, and hence the level of recombination, is not significantly different from that occurring in normal female meiosis.

The normal map was divided into eight sections to determine if the distribution of recombinant events in the nondisjunctional maps was different from that of the normal map. The interlocus distance in the normal map was compared both with that in the MI map excluding the nullichiasmates and with that in the MII map (table 5). With the exception of a single interval proximal to the telomeric section of the q arm, there were no significant differences, in the distribution of recombinant events, between normal meiosis and nondisjunctional meiosis involving either MI or MII. Thus, an aberrant distribution of recombinant events does not appear to play a significant role in the nondisjunction of chromosome 18.

Parental Age

The two cases of paternal origin had a mean maternal age of 22.5 years and a mean paternal age of 26.0 years. The maternal ages of the 61 cases with an additional maternal chromosome are shown in table 6, both for the whole study population and after exclusion of the 22 cases ascer-

tained because of prenatal diagnosis for advanced maternal age. While we have no precisely matched control population, the maternal age of a series of 47,XXY individuals with an additional paternal sex chromosome recently studied in our laboratory was 27.4 ± 0.7 years, and we have used this as our control. After exclusion of those cases ascertained because of advanced maternal age, the maternal age of each group is elevated in comparison with that of the control but only significantly so in two groups, the whole data set and the MII errors. The failure of the increase in the MI class to reach significance is likely to be a result of the small numbers within this group.

Discussion

The parental origin of the additional chromosome in trisomy 18 has been determined and in the majority (96.8%) of cases was maternal in origin. Only two (3.2%) of the cases were of paternal origin, thus demonstrating the rarity of paternally derived trisomy 18. These results are similar to those obtained by Kupke and Müller (1989), Nothen et al. (1993), Ya-gang et al. (1993), and Bugge et al. (1994). The rarity of paternally derived trisomy 18 is comparable with that of trisomies 13, 21, and 47,XXX, which all have a paternal error rate of ~5%. Trisomy 16 is unique in appearing to be exclusively maternally derived. This may reflect either an extremely low frequency of paternal errors, none of which have yet been detected, or that chromosome 16 is imprinted and that two copies of the paternal chromosome results in lethality prior to the clinical recognition of the pregnancy. In contrast, approximately half of 47,XXY individuals have both an X and a Y inherited from the father, suggesting that the XY bivalent is particularly susceptible to nondisjunction (Hassold et al. 1991*b*). Both of our cases of paternally derived trisomy 18 were consistent with a PZM error, and, similarly, initial observations by Ya-gang et al. (1993) indicate that their six paternal cases may also be due to mitotic errors. This suggests that paternal meiotic errors leading to trisomy 18 are extremely rare.

The recombination study showed that meiotic errors accounted for 56 of the 59 maternally derived trisomy 18 cases. Of the 51 informative cases, 16 (31.4%) were consistent with an MI error and 35 (68.6%) were consistent with an MII error. The preponderance of MII errors was unexpected, since all previous autosomal trisomy studies have shown most errors to occur during mat MI. The predominance of MII errors in trisomy 18 could be due to (i) a genuine proclivity of chromosome 18 to not disjoin during MII and/or (ii) a reduced susceptibility of the chromosome to nondisjunction during MI. In an attempt to determine which of these was the case, we calculated both the predicted proportion of disomic oocytes from the known proportions of maternal errors and the frequency of each trisomy among all clinically recognized pregnancies (CRPs) (table 7). These calculations assume that the frequencies of various trisomies among CRPs reflect their actual rate at conception and that there is no gametic selection prior to or at conception. As can be seen, the predicted proportion of disomic oocytes resulting from MII errors is very similar for chromosomes 18 and 21, suggesting similar frequencies of MII nondisjunction for these two chromosomes. In both cases, MII nondisjunction is associated with elevated maternal age, which suggests that the mechanism of mat MII nondisjunction is likely to be the same for these two chromosomes.

The predicted proportion of disomic oocytes resulting from mat MI nondisjunction for chromosome 18 is extremely low in comparison with that for chromosomes 21 and 16, but it is rather similar to that for the X chromo-

Table 5

Sectional Analysis of Female Nondisjunctional Maps, and Comparison with the Standard Map

Region	Standard Female Map (cM)	Mean No. for Nondisjunctional Map ± SE: MI Errors Excluding Nullichiasmates	Mean No. for Nondisjunctional Map ± SE: All MII Errors
D18S59–D18S62	7.2	18.0 ± 13.1	24.1 ± 11.9
D18S62–D18S53	29.7	29.5 ± 16.2	57.6 ± 30.8
D18S53–D18S71	7.8	0	3.8 ± 2.4
D18S71–D18S67	30.8	47.8 ± 19.6	24.5 ± 4.7
D18S67–D18S35	30.0	37.6 ± 12.5	20.1 ± 5.1
D18S35–D18S38	16.0	0	22.1 ± 6.1
D18S38–D18S5	25.1	36.4 ± 11.5	11.4 ± 5.0*
D18S5–D18S17	16.6	17.5 ± 7.8	27.3 ± 6.1

* $P < .05$.

Table 6

Maternal Ages of the Cases with an Additional Maternally Derived Chromosome 18

Cell Division of Error	All Cases: No.	All Cases: Mean Maternal Age ± SE (years)	Excluding Cases Ascertained because of Advanced Age: No.	Excluding Cases Ascertained because of Advanced Age: Mean Maternal Age ± SE (years)
All	61	35.4 ± 0.9**	39	32.8 ± 1.2**
MI	16	36.1 ± 2.2**	8	31.0 ± 3.4
MI nullichiasmate	5	35.6 ± 4.4	3	31.3 ± 6.4
MI chiasmate	11	36.4 ± 2.6**	5	30.8 ± 4.5
MII	35	35.7 ± 1.1**	23	33.6 ± 1.4**
PZM	3	34.0 ± 3.5	3	34.0 ± .5

** $P < .001$.

Table 7

Predicted Frequencies (%) of Disomic Ova

Chromosome Abnormality	Frequency among All CRC	Proportion Due to Error Involving Maternal Chromosome	Proportion of Cases of Maternal Origin Due to Meiotic Errors	Predicted Frequency of Disomic Ova	Proportion Due to Maternal MI and Maternal MII Errors		Predicted Frequency of Disomic Ova	
					Maternal MI	Maternal MII	Maternal MI	Maternal MII
XXY	.08	54	97	.04	74	26	.03	.01
XXX	.05	90	97	.04	78	22	.03	.01
+16	1.13	100	100	1.13	100	0	1.13	0
+18	.18	97	97	.17	31	69	.05	.12
+21	.45	92	97	.40	75	25	.30	.10

some. However, while the frequency of mat MI nondisjunction appears to be similar for chromosomes 18 and X, the mechanisms are somewhat different. In both chromosomes nullichiasmate nondisjunction accounts for ~30% of all mat MI errors, but in chromosome 18 the remaining mat MI errors all appear to be normochiasmate and related to increased maternal age, while in the X chromosome only some 45% are attributable to this mechanism, the remaining 25% being associated with an excess of pericentromeric recombination that is not related to increased maternal age. This latter mechanism does not appear to contribute to nondisjunction of chromosome 18.

Thus chromosome 18 appears to be very similar both to chromosome 21, with respect to the frequency and mechanism of mat MII nondisjunction, and to the X chromosome, with respect to the number of mat MI nondisjunctional events. However, while mat MI nondisjunction of chromosome 18 appears, like that of the X, to be associated with both nullichiasmate and normochiasmate mechanisms, on the basis of the limited data available to date, there is no evidence of an excess of pericentromeric recombination that is associated with MI nondisjunction of the X chromosome.

Our observations on chromosome 18 serve to emphasize the variety of mechanisms associated both with nondisjunction of human chromosomes and with the way in which the relative importance of different mechanisms varies among chromosomes. Chromosome 18 is the first chromosome in which mat MII is a much more frequent source of error than is mat MI. This is all the more surprising given that mat MII errors are unknown for chromosome 16, a chromosome that is rather similar—in size, shape, and female genetic length—to chromosome 18. Clearly, we still have much to learn about human nondisjunction.

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