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The Relationship between Maternal Age and Chromosome Size in Autosomal Trisomy

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SUMMARY

The pattern of maternal age-specific incidence of autosomal trisomy in spontaneous abortions was examined for each chromosome for which a sufficient number of trisomies was observed. This included chromosomes 2, 4, 7–10, 13–16, 18, and 20–22. The rate of increase after age 30 for each of the small chromosomes (groups D–G) was similar, with the exception of chromosome 16, which showed a significantly shallower rate. The C group chromosomes tended to have an intermediate rate of increase after age 30, with the exception of chromosome 7, which had a pattern similar to the smaller chromosomes. The larger chromosomes (2 and 4) had the smallest rate of increase. There was a significant relationship between chromosome size and rate of increase after age 30 (after excluding chromosome 16), but not with rate of increase before age 30. The results suggest that autosomal trisomies may be of heterogeneous origin, with a maternal age-related factor associated with chromosome size and other sources unrelated to chromosome size. Additional evidence for and against this hypothesis is discussed.

INTRODUCTION

Previous reports have established a relationship between increased maternal age and autosomal trisomy for chromosomes 21, 18, and 13 in live births and amniocenteses [1, 2] and for all the smaller chromosomes 13–22 as well as some

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larger ones in spontaneous abortions [3, 4]. The previous report of Hassold et al. [4], based on data from New York City and Hawaiian samples of spontaneous abortions, also suggested an inverse relationship between mean maternal age and chromosome size for each trisomy. In previous reports, we [5], using data from New York, and Hassold and Chiu [6], using data from Hawaii, examined age-specific incidence curves by chromosome group. In both studies, there was a suggestion that the large chromosomes, the small chromosomes, and chromosome 16 showed distinct patterns. Here, we more specifically examine the relationship between maternal age and trisomy as a function of chromosome size by looking at the maternal age-specific incidence curves for each chromosome. In addition, we allow for trisomies to be of heterogeneous origin, and therefore use an admixture model, with both a maternal age-dependent and age-independent component, as suggested by Penrose and Smith [7]. Based on live-birth data from trisomy 21, we assume in our modeling an exponential age effect. This type of analysis is similar to that performed by Lamson and Hook on live-birth data for chromosome 21 [8].

MATERIALS AND METHODS

Materials

The data consist of all observed autosomal trisomies from the ongoing study of spontaneous abortion in New York City [9]. Methods for ascertainment, cell culturing, and karyotyping have been described [9]. The total number of observed trisomies for this analysis is 529. This includes both mosaic trisomies (no. = 50) and double trisomies (no. = 14), which were included twice, once for each of the two chromosomes involved. As a baseline, we determined for each maternal age between 15 and 47 the total number of live births and spontaneous abortions occurring in the same hospitals from which the karyotyped abortions were drawn. In total, 6,842 spontaneous abortions (of which 2,517 were karyotyped) and 55,135 live births occurred over the period of study. Here, we are not examining the absolute frequencies of the various trisomies, but rather the relative frequencies and relation with maternal age. Insofar as the baseline frequencies deviate from the true values, our results will be unbiased to the extent that such deviation is constant with respect to maternal age.

Methods

Included in this analysis are those chromosomes for which at least 10 trisomies occurred. The included chromosomes and the total number of trisomies for each are: chromosome 2 (33), 4 (13), 7 (26), 8 (23), 9 (15), 10 (10), 13 (38), 14 (26), 15 (40), 16 (160), 18 (24), 20 (18), 21 (49), and 22 (40). We first examine the relationship between maternal age and trisomy for each chromosome by plotting the log frequency of trisomy as a function of maternal age. Because of the sparseness of the data, we have smoothed these curves as follows. For each 9-year maternal-age interval, starting at age 15, we fit an exponential curve ($y = e^{bx+c}$, where y = frequency and x = maternal age). We then determine the fitted y value for the midpoint of the 9-year interval. Exponential smoothing is employed due to the exponential relationship between maternal age and trisomy frequency. In addition, we calculate the rate of exponential increase for the age intervals 15–30 (referred to as before 30) and 30–47 (referred to as after 30) by fitting an exponential curve to these intervals separately for each chromosome.

Heterogeneity among the slopes (b values) for the various chromosomes is assessed by likelihood ratio tests as described below. The relationship between slope and chromosome size is evaluated by weighted least squares regression (weighted by the

inverse of the estimated variance of the slope), with significance determined by t-tests [10]. Analysis is performed both with and without chromosome 16, which accounts for nearly one-third of all trisomies.

We then perform an admixture analysis, as follows. We assume two components to autosomal trisomy: a maternal age-dependent component that has an exponential relationship with maternal age and a maternal age-independent component. Hence, for a given maternal age x, the probability of occurrence of trisomy for the ith chromosome is given by

$$P_i(x) = a_i + e^{b_i x + c_i}, \tag{1}$$

where the first term, a_i, is the constant frequency of trisomies of chromosome i that are age-independent, and the second term is the frequency of age-dependent trisomies, where b_i is the exponential rate of increase and c_i is a constant factor pertaining to the overall frequency of exponential cases. This formula is the same as that used by Lamson and Hook [8]. There are a total of 42 parameters, three for each chromosome. Parameter estimation and hypothesis testing are by maximum likelihood and likelihood ratio tests. The log likelihood is given by

$$\ln L = \sum_{j=15}^{47} r_{ij} \ln p_i(j) + (n_j - r_{ij}) \ln[1 - p_i(j)], \tag{2}$$

where r_{ij} is the number of trisomies of chromosome i at maternal age j, and n_j is the total number of observed pregnancies (live births plus spontaneous abortions) at age j. In formula (2), we assume that trisomies of the various chromosomes occur independently of each other. For double trisomies, this assumption may be incorrect; however, we felt it was preferable to include the doubles than to omit them from analysis. Tests of hypotheses are obtained by the likelihood ratio criterion: $-2(\ln L_r - \ln L_u)$, where L_u is the unrestricted likelihood, L_r is the restricted (by an hypothesis) likelihood, and the criterion is assumed to have an asymptotic chi-square distribution, with degrees of freedom given by the number of constraints imposed. We use the likelihood ratio criterion to test for heterogeneity among slopes for the various chromosomes, as well as for the significance of admixture for each chromosome. In testing heterogeneity of slopes (b values), there are $k - 1$ d.f. when k chromosomes are being compared. The admixture test has 1 d.f. for each chromosome evaluated individually. All likelihood maximizations are obtained with the computer program MAXLIK [11].

We also test the goodness of fit of the admixture (or exponential) model for each chromosome, classifying observations into 5-year age intervals. Because of small expected numbers of trisomies after age 40, we make a single age category for 40 and older, giving a total of six cells. For an admixture model, there are three parameters estimated (a, b, and c), giving 3 d.f. for the chi-square goodness-of-fit criterion. For the exponential model, two parameters are estimated (b and c), leaving 4 d.f.

RESULTS

Figure 1*A–N* show the smoothed curves of log frequency of trisomy by maternal age for each chromosome. All chromosomes in groups *D*, *E*, *F*, and *G* (13–22) show a linear increase with maternal age on the log scale after age 30. The slopes after age 30 for all these chromosomes appear similar, with the exception of 16. Chromosome 16 shows a shallower slope after age 30, with no difference in slope before vs. after age 30. Chromosome 13 may also have a slightly shallower slope than the other small chromosomes and appears to have

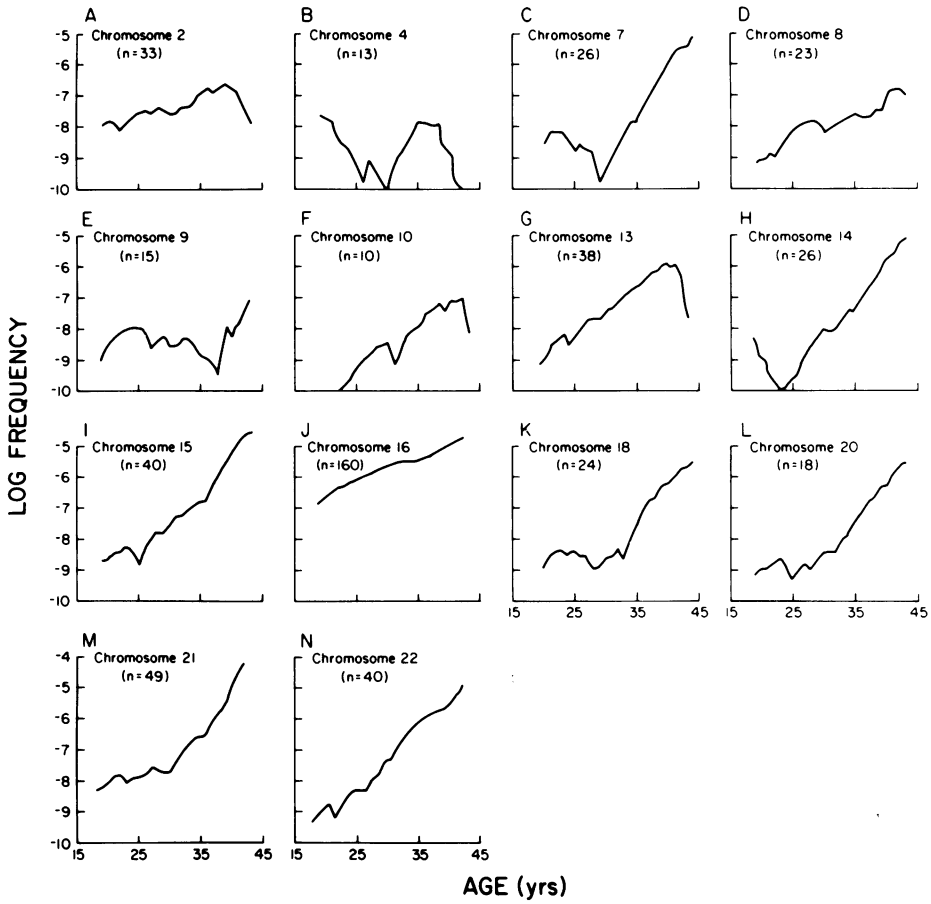

FIG. 1.—Relationship between $\log_e$ (incidence) of trisomy and maternal age for each chromosome after 9-year exponential smoothing.

a drop-off after age 40. The various small chromosomes differ with regard to change in slope before age 30 vs. after age 30: chromosome 13 shows no increase in slope after age 30, chromosomes 15 and 22 show some increase in slope after age 30, while chromosomes 14, 18, 20, and 21 show a dramatic change in slope after age 30. These differences among the smaller chromosomes may be due to small numbers of trisomies before age 30 or may reflect a real difference, with the latter group having a greater admixture of cases not related to increased maternal age. The patterns for chromosomes 13, 18, and 21 replicate those seen in live births and amniocenteses [2, 12]. The shallower rate of increase for chromosome 13 and the drop-off after age 40 have also been observed [2, 12].

The A, B, and C group chromosomes show a somewhat different pattern. Among these, only chromosome 7 appears similar to the small chromosomes. Chromosomes 8, 9, and 10 show a positive slope that does not change after age 30 and is shallower than that of the small chromosomes. Chromosome 4 shows

no increase in frequency with maternal age, while chromosome 2 shows a slightly positive slope with a small increase after age 30.

These impressions are confirmed in table 1 and figures 2 and 3, which show the relationship between chromosome length and slope in log frequency before and after age 30. The meiotic length (percent of total autosomal genome) of each chromosome has been taken from Hultén [13]. For slope after age 30 (fig. 2), the regression of slope on chromosome size is -0.012 with 95% confidence interval (-0.025, 0.001). If we exclude chromosome 16 from this analysis (an a priori exclusion based on its unusually high frequency), the regression coefficient becomes -0.016 with 95% confidence interval (-0.029, -0.002). Examination of figure 2 suggests that chromosome 7 may also be an outlier. If we eliminate chromosome 7 (an a posteriori exclusion) from the analysis as well as chromosome 16, we obtain a regression coefficient of -0.30 with 95% confidence interval (-0.048, -0.012).

The results of likelihood ratio heterogeneity tests among chromosomes for slope after age 30 are as follows. For the small chromosomes of groups D–G, there is evidence for heterogeneity ($\chi^2_7 = 21.0$, $P < .005$), primarily due to chromosome 16, which is significantly different from the other small chromosomes ($\chi^2_1 = 14.8$, $P < .001$). Heterogeneity among the remaining small chromosomes is not significant ($\chi^2_6 = 6.2$, $P > .30$), although examination of each of the single remaining chromosomes with the others suggests that chromosome 13 may also be different from the remaining small chromosomes ($\chi^2_1 = 4.7$), with little heterogeneity among the remaining small chromosomes ($\chi^2_5 = 1.5$). Heterogeneity among the C group chromosomes is not significant ($\chi^2_3 = 5.27$, $P = .10$). However, because of the similarity between chromosomes 8, 9, and 10, the above χ^2 value is entirely attributable to the difference between 7 and the remainder (8, 9, and 10).

TABLE 1

RELATIONSHIP BETWEEN CHROMOSOME LENGTH AND SLOPE BEFORE AND AFTER AGE 30 (ON LOG SCALE)

Chromosome	Length (% of genome)	Slope before age 30	Slope after age 30
2	8.60	.023 (.056)	.089 (.077)
4	5.98	−.258 (.101)	.044 (.131)
7	5.64	−.064 (.081)	.309 (.058)
8	4.73	.076 (.076)	.115 (.090)
9	4.57	.038 (.073)	.123 (.133)
10	4.79	.203 (.163)	.123 (.101)
13	3.83	.153 (.072)	.120 (.054)
14	3.73	.004 (.078)	.229 (.056)
15	3.83	.133 (.078)	.255 (.045)
16	3.10	.111 (.078)	.084 (.032)
18	2.72	−.044 (.086)	.247 (.061)
20	2.45	.016 (.102)	.260 (.067)
21	1.63	.028 (.063)	.263 (.041)
22	1.82	.142 (.090)	.197 (.044)

NOTE: Standard errors in parentheses.

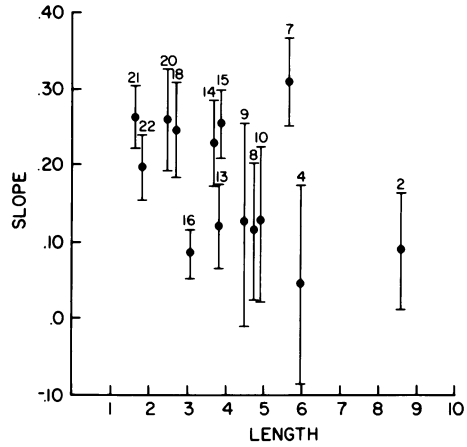

FIG. 2.—Relationship between slope after age 30 (on log scale) of maternal age-specific trisomy incidence and chromosome length. *Bars* represent a single standard error interval. *Nos. above bars* are chromosome nos. Length in percent of genome (taken from Hultén [13]).

In considering slopes before age 30 (fig. 3), we have eliminated chromosome 16 as before (a priori exclusion) due to its unusually high frequency. The regression of chromosome size on slope gives a regression coefficient of -0.010 with 95% confidence interval $(-0.024, 0.004)$. However, the large negative slope of chromosome 4 contributes in a major way to the regression. For example, eliminating chromosome 4 from the analysis reduces the regression coefficient to -0.006.

Table 2 gives the results of the admixture analysis. The test of admixture is obtained as a likelihood ratio test comparing the admixture model (three parameters) with the exponential model (two parameters). Hence, twice the difference of the log likelihoods has a χ^2 distribution with 1 d.f. As suggested by

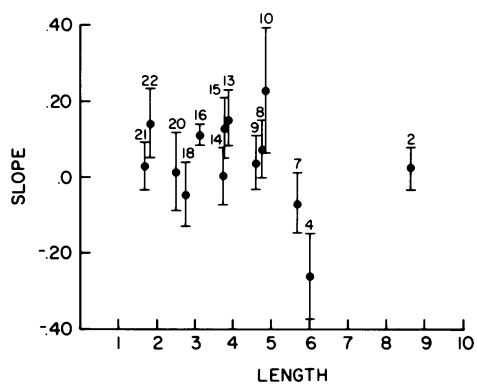

FIG. 3.—Relationship between slope before age 30 (on log scale) of maternal age-specific trisomy incidence and chromosome length. *Bars* represent a single standard error interval. *Nos. above bars* are chromosome nos. Length in percent of genome (taken from Hultén [13]).

TABLE 2

RESULTS OF ADMIXTURE ANALYSIS

CHROMOSOME	Admixture model			Exponential model		ADMIXTURE χ^2_1	GOODNESS-OF-FIT $\chi^{2\dagger}$
	$\hat{a}(\times 10^{-4})$	$\hat{b}$	$\hat{c}$	$\hat{b}$	$\hat{c}$		
2	...	...	...	.052 (.029)	−8.97 (0.83)	0	0.39
4	...	...	...	−.031 (.048)	−7.66 (1.25)	0	12.03*
7	1.72 (0.65)	.343 (.064)	−19.41 (2.52)	.173 (.033)	−12.87 (1.09)	9.60**	3.57
8	...	...	...	.078 (.036)	−10.20 (1.08)	0	0.50
9	...	...	...	.015 (.043)	−8.71 (1.19)	0	5.17
10	...	...	...	.159 (.052)	−13.38 (1.72)	0	1.98
13	...	...	...	.142 (.027)	−11.49 (0.86)	0	3.88
14	1.57 (.069)	.304 (.066)	−17.91 (2.59)	.167 (.033)	−12.66 (1.08)	7.82**	9.87*
15	1.45 (0.83)	.267 (.056)	−15.93 (2.20)	.203 (.027)	−13.42 (0.92)	2.50	1.59
16	...	...	...	.083 (.013)	−8.24 (0.38)	0	3.12
18	1.45 (0.71)	.280 (.069)	−17.11 (2.64)	.162 (.034)	−12.59 (1.11)	3.63	0.95
20	0.96 (0.67)	.279 (.077)	−17.20 (2.88)	.182 (.039)	−13.47 (1.29)	2.34	1.38
21	3.07 (1.04)	.328 (.054)	−18.18 (2.11)	.189 (.024)	−12.76 (0.82)	9.56**	3.74
22	0.41 (0.67)	.220 (.040)	−14.07 (1.54)	.206 (.027)	−13.52 (0.93)	0.22	1.62

NOTE: Values in parentheses are standard errors. * $P < .05$; ** $P < .01$.

† For chromosomes 2, 4, 8, 9, 10, 13, and 16, the goodness-of-fit test has 4 d.f.; for other chromosomes, there are 3 d.f. (see text).

figure 1*A–N*, chromosomes 7, 14, 18, and 21 show significant evidence for admixture; for chromosomes 15 and 20, the evidence is suggestive, but not significant, while for the other chromosomes, there is little or no evidence. The admixture model (for chromosomes 7, 14, 15, 18, 20, 21, 22) and exponential model (for chromosomes 2, 4, 8, 9, 10, 13) provide an acceptable fit to the data, except for chromosomes 4 and 14. Examining figure 1*B* for chromosome 4 indicates that the poor fit is due to a deficit of observed trisomies between ages 25 and 29 and an excess of trisomies between 30 and 34. For chromosome 14, figure 1*H* indicates that the poor fit is due to an excess of trisomies between 15 and 19 and a deficit between 20 and 24.

Based on the results in table 2 for the admixture model for chromosomes 7, 14, 15, 18, 20, 21, and 22, we have calculated, using the age distribution of all pregnant women presenting at the hospitals in our study, the expected proportion of trisomies due to the maternal-age mechanism. The results are given in table 3. We note that these values are dependent on the maternal-age demographics in our studied population and are not directly applicable to other populations. However, we believe that the demographics across populations are similar enough to allow, at least, rough comparison.

DISCUSSION

Figure 1*A–N* and figure 2 suggest a relationship between chromosome size and rate of exponential increase in trisomy frequency after age 30. This relationship appears not to be a function of centromeric index (or acrocentricity) as the metacentric chromosome 20 and submetacentric chromosome 18 show the same pattern as the acrocentrics 13–15 and 21–22. Chromosome 16 is a clear outlier in this relationship as its slope after age 30 is significantly below that of the other small chromosomes (13–22). Chromosome 13 also has a characteristic drop-off after age 40 (replicating the live-birth data), which distinguishes it from the other small chromosomes.

The C group chromosomes 8, 9, and 10 appear to have a shallower slope than the smaller chromosomes. Chromosome 7, another C chromosome, however,

TABLE 3

PREDICTED PROPORTION OF MATERNAL AGE-DEPENDENT (EXPONENTIAL) TRISOMIES FOR CHROMOSOMES WITH ADMIXTURE FOR THE NEW YORK SAMPLE

Chromosome	Proportion age-dependent
7	.595 (.168)
14	.630 (.131)
15	.777 (.143)
18	.628 (.162)
20	.689 (.190)
21	.614 (.114)
22	.941 (.137)

NOTE: Values in parentheses are standard errors.

shows a pattern similar to the smaller chromosomes. We note that this anomalous pattern for chromosome 7 seems not to be present in the Hawaii data [4], as the mean maternal age for chromosome 7 in Hawaii was 28.2 vs. 32.4 in New York. Perhaps with larger numbers of trisomies, the pattern for the C group chromosomes will become clearer. Finally, the large chromosomes 2 and 4 show the shallowest rate of increase after age 30. Slope before age 30 appears to have little relationship with chromosome size.

Based on these findings, we can postulate the following type of model. Autosomal trisomy has multiple causes, one of which is associated with increased maternal age. The relationship with maternal age (i.e., the exponential rate of increase) for each chromosome is related to its size. There is a threshold effect, however, in that all the chromosomes in the D–G groups (except 16) have similar patterns after age 30; that is, small size beyond the size of the D group chromosomes appears to have no additional effect. The other causes of autosomal trisomy are unrelated to maternal age and also unrelated to chromosome size. For example, although all the small chromosomes show similar exponential rates of increase after age 30 (except for 16), the slope before age 30 is quite variable. Hence, for chromosomes 14 and 21, maternal age-independent sources may contribute significantly to the total number of trisomies, while for chromosomes 15, 18, and 20, they contribute more modestly, and for chromosomes 13 and 22, they are relatively less important.

The significant correlation between exponential rate of increase after age 30 and chromosome size is suggestive that the maternal-age effect is related to trisomy formation, rather than to reduced selection with increasing maternal age. If the latter were true, this reduced selection mechanism would have to be able to differentiate between chromosomes based on size, which to us seems relatively less likely.

If the maternal-age effect is related to formation, then certainly it must be associated with events at maternal meiosis I (MM1), as this is the site of origin of the majority of autosomal trisomies [14]. If MM1 trisomies are due to a mechanism associated with maternal age while others are not, then we should see a correspondence between the proportion of trisomies with an identifiable origin that occur at MM1 and the level of admixture determined from the analysis presented here. For chromosome 21, the estimated proportion that are maternal age-dependent (61.4%) is comparable to the estimates of Lamson and Hook [8]. This value is also close to the 68% estimate of MM1 origin for this chromosome from Hassold et al.[14], who used cytological markers.

Similarly, for chromosome 22, our estimate of 94.1% for maternal age-related cases is close to their value of 92% [14]. For chromosomes 14 and 15, the estimate of 93% from Hassold et al. [14] is somewhat higher than our values of 63% and 78%. For chromosomes 13 and 16, for which we found no evidence for admixture, they estimate the proportion of MM1 origin as 77% and 84%, respectively [14]. Hence, there is not total consistency between our estimate of the proportion of maternal age-related trisomies and those of MM1 origin. However, standard errors are large, and differences may ultimately be reconciled.

The fact that trisomy 16 shows a distinct pattern from the other small chromosomes appears not to be due to the operation of maternal age-unrelated factors. This chromosome shows a completely linear increase in frequency (on the log scale) with maternal age, with absolutely no evidence for admixture. For some reason, it shows a slope more typical of the large chromosomes (e.g., chromosome 2). Also, the fact that this particular trisomy is so frequent is suggestive of homogeneity of mechanism (e.g., MM1). If an MM1 origin underlies the maternal-age effect for the other small chromosomes, the mechanism underlying chromosome 16 would have to operate at the same stage (MM1) or earlier; for otherwise, we would expect to see, at least to some extent, the dramatic increase at late ages characteristic of the other small chromosomes. Its absence for chromosome 16 suggests that the mechanism underlying its formation precludes the operation of the mechanism underlying the other small chromosomes. These comments may also apply to chromosome 2, which shows a higher overall frequency than any of the other A, B, or C chromosomes.

The pattern for chromosome 13 is the same as that seen in live births and amniocenteses [2] and appears to be distinct from chromosomes 14 and 15 in its slightly shallower rate of increase after age 30 and the drop-off after age 40. This drop is not characteristic of any of the other small chromosomes. As yet, we have no explanation for this difference in pattern.

Additional evidence in favor of the origin hypothesis is that mean maternal age for double trisomies is significantly elevated over that for single trisomies, both in the Hawaii series (34.6 years [14]) and the New York series (37.9 years), which is suggestive of a "double hit" hypothesis; that is, if double trisomies represent the chance co-occurrence of two independent single trisomies, then the relationship of frequency of double trisomy with maternal age should be the product of two exponentials, which is merely an exponential with rate of increase equal to the sum of the individual rates of increase for the two single trisomies.

Evidence against MM1 being the origin of the maternal-age effect is the lack of difference in maternal-age distribution for trisomies of MM1 origin vs. all others. For example, from the results of our model in table 2, we can predict the proportion of trisomies that are age-related as a function of maternal age. For trisomy 21, these predicted values and their corresponding age intervals are 12% (20–24), 36% (25–29), 64% (30–34), 90% (35–39), and 98% (40–44). Using maternal ages of live-birth trisomies 21 of defined MM1 and non-MM1 origin summarized in the literature review of Stein et al. [15], for the same maternal-age intervals, we obtain the corresponding values of 61%, 61%, 62%, 76%, and 62%. Hence, while the observed proportion of MM1 origin is similar to the proportion predicted to be age-dependent (61%), the even distribution of these proportions across maternal-age groups is not consistent with expectation if MM1 nondisjunction is the source of the maternal-age effect.

At this stage, it is difficult to reconcile the conflicting evidence on the source of the maternal-age effect in autosomal trisomy. With the advent of centromeric restriction fragment length polymorphisms to identify parental origin for

all the autosomal trisomies, we hope that a resolution will be forthcoming in the near future.

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