Hum Genet (1982) 62:167–174

Human Genetics

Paternal Age and Down's Syndrome Genotypes Diagnosed Prenatally: No Association in New York State Data

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Summary. An investigation of a paternal age effect independent of maternal age was undertaken for 98 cases of Down's syndrome genotypes diagnosed prenatally compared to 10,329 fetuses with normal genotype diagnosed prenatally in data reported to the New York State Chromosome Registry. The mean of the difference (delta) in paternal age of cases compared to those with normal genotypes after controlling for maternal age, was slightly negative, −0.27 with a 95% confidence interval of −1.59 to +1.06. A regression analysis was also done in which the data were first fit to an equation of the type $\ln y = (bx + c)$ and then to the equation $\ln y = (bx + dz + c)$ where y = rate of Down's syndrome, x = maternal age, z = paternal age, and b, d, and c are parameters. This also revealed no evidence for a paternal age effect. The value of d (the paternal age coefficient) was in fact slightly negative, −0.0058, with an asymptotic 95% confidence interval of −0.0379 to +0.0263. Lastly, multiple applications of the Mantel-Haenszel test considering various boundaries in paternal age also revealed no statistically significant evidence for a paternal age effect independent of maternal age. These results are at variance with claims of others elsewhere of a very strong paternal age effect detected in studies at prenatal diagnoses. Five different hypotheses are suggested which may account for discrepancies among studies to date in findings on paternal age effects for Down's syndrome: (i) there are temporal, geographic, or ethnic variations in paternal age effects, (ii) there is no paternal age effect and statistical fluctuation accounts for all trends to date; (iii) methologic artifacts have obscured a paternal age effect in some studies which did not find a positive outcome; (iv) methodologic artifacts are responsible for the positive results in some studies to date; (v) there is a rather weak paternal age effect independent of maternal age in most if not all populations, but because of statistical fluctuation the results are significant only in some data sets. The results of all data sets to date which we have been able to analyze by one year intervals are consistent with a mean delta of +0.04 to +0.48 and in the value of d (the paternal age coefficient) of +0.006 to +0.017, and it appears the fifth hypothesis cannot be excluded. Projections based on this assumption are presented.

Introduction

There is still no agreement on whether or not there is a paternal age effect for Down's syndrome that is of significance for genetic counseling. Earlier investigations of the association of parental age with Down's syndrome (Jenkins 1933; Penrose 1933) concluded that maternal age was much stronger than any putative paternal age effect. Subsequently in many of his writings Penrose, as well as others, appeared to assume that paternal age was not of significance (see, e.g., Penrose and Smith 1966) although at least some observers pointed out that a modest paternal age effect could not be excluded with the available data (Mantel and Stark 1966). The issue was reopened recently with the discovery that in about 20% of Down's syndrome cases the extra chromosome can be shown to be of paternal origin (see, e.g., Hansson and Mikkelsen 1978). Despite the fact that there is no positive parental age effect for the XYY genotype (see, e.g., Carothers et al. 1978) in which the extra chromosome is known to be of paternal origin, this discovery led some to the apparent inference that paternal age independent of maternal age must be a significant risk factor for Down's syndrome (Holmes 1978). Several further investigations of a possible age effect have been done recently without any apparent consensus being reached.

One of the limitations of such investigations is that maternal age and paternal age are so highly correlated that it is very difficult to demonstrate a modest effect of one variable in the face of a strong effect of the other. In addition, maternal age specific rates of Down's syndrome rise rapidly with maternal age while fertility plunges even more quickly, (see, e.g., Hook 1981) leading to possible statistical artifacts. As an example, one of the first recent studies of paternal age since the discovery of patroclinous extra 21st chromosomes was that of Stene et al. (1977) who found "statistically significant" evidence for a two-fold paternal age effect for cases born to men 55 years and over. While no evidence was reported for an effect in men younger than this age, they also inferred a strong paternal age effect at ages below 55 years. Their analysis, however, was by < 35, 35–39, and ≥ 40 maternal age intervals. Erickson (1978) showed that he could construct an artifactual paternal age effect using the methodology of Stene et al. (1977) applied to another data set. This disappeared when he used a more appropriate method carrying out an analysis by one year maternal age intervals. Similarly Matsunaga et al. (1978) reported statistically significant evidence for a paternal age effect for men 55 years and over in data analyzed by five year intervals, but Lamson et al. (1980) showed that the methodology used here could produce artifacts which disappeared when analysis was by one year intervals. Subsequent reanalysis of some of these data by Cross and Hook (unpublished work) by one year intervals revealed that a trend originally reported to an increase in men 55 years and over could still be found in the data of Matsunaga et al., but was weaker and no longer significant at the 0.05 level.

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0340-6717/82/0062/0167/$01.60

Investigations in livebirths by other investigators which have been controlled by one year maternal age intervals have yielded differing trends, some showing no evidence for a paternal age effect (Erickson 1978; Regal et al. 1980; Hook et al. 1981), others finding a suggestive but not significant effect (Erickson 1979), and others finding significant effects, albeit not of strong magnitude (Hook et al. 1981; Erickson and Bjerkedal 1981). One study has suggested that a weak effect of the order of about 1% increase in risk with each year of paternal age was consistent with all the observations to date (Hook et al. 1981), and tables have been constructed projecting what these expected rates should be at various combinations of maternal and paternal ages (Hook and Cross, to be published). No studies in *livebirths* to date done by one year intervals have revealed effects as large as those claimed by Stene et al. (1977).

Stene et al. (1981) have recently published data on 60 cases of Down's syndrome diagnosed prenatally at amniocentesis and claim a very strong paternal age effect similar in magnitude to that claimed by Stene et al. (1977) which analyzed livebirth data by five year intervals. They have projected from these observations putative risks for women of *any* age married to men of 41 years or older sufficient to justify amniocentesis (Stene et al. 1981). We present here data on prenatal cytogenetic diagnoses derived from the New York State Chromosome Registry (Hook et al. 1981) on about 100 Down's syndrome cases, over 1.5 fold greater than the number investigated by Stene et al.

Materials and Methods

Data reported to the New York State Chromosome Registry from January 1, 1977 to September 15, 1981 inclusive were used. Fetuses were only included if their mother had been studied because of a reason unrelated to a putative risk factor for chromosome analysis except advanced parental age. Data were only included from the 10 centers that reported data on both maternal ages and paternal ages on at least 90% of the cases studied (see Acknowledgements). From these 10 centers there were data on 10,919 fetuses with normal genotypes, and 101 with genotypes associated with Down's syndrome. Data were unavailable on paternal and/or maternal age for 590 fetuses with normal genotype (5.4%) and three with 47,+21 (3.0%).

With regard to the women undergoing amniocentesis included in this study, they are not of course a random sample of all pregnant women of comparable age. Those 35 years and over (with no other known cytogenetic risk factor) are likely to differ in social and economic status from other pregnant women of the same age. Many of those under 35 years in this study also differ from younger pregnant women of the same age because of the factors that led to amniocentesis. The reasons for study in most younger women (excluding those who were anxious because, despite being under 35 years, they still perceived their maternal-age-specific risk as being high) were usually investigation of amniotic fluid alpha-fetoprotein levels or diagnosis of inborn errors of metabolism in amniotic fluid cells. Chromosome analysis was done incidentally upon such specimens.

In the search for paternal age effects, three different methods were used. One, the "delta" method, is analogous to a case-control comparison (Hook et al. 1981). For each maternal age at which a Down's syndrome fetus was observed, the mean paternal age of all those with normal genotypes was determined—this provided the "control" value for that maternal age. For each Down's syndrome fetus, a value "delta" (Δ) was calculated equal to the paternal age of the case minus the control value, i.e., minus the mean paternal age of all individuals of normal genotype born to mothers of the same maternal age as the case. (These calculations were only done on cases at those maternal ages for which there were at least 10 normals at the maternal age). The values of Δ were then summed and analyzed as a continuous variable. Examination of the distribution of the values for Δ for all cases revealed no grounds to reject the normal distribution theory. Therefore if the mean value of $\Delta \pm 1.96$ its standard error excludes zero, an effect of paternal age may be inferred at the 0.05 level by a 2-tailed test. In addition to searching for effects in pooled data from the 10 centers, we used the method to search for effects in the experience of individual centers. This was done in two different ways. In one the mean value of delta for any center was calculated using control values derived from the experience of that center only. Because of the smaller numbers the control values at individual centers were much less stable than those derived from the pooled data. Therefore a mean delta for each center was also calculated using control values derived from the pooled experience of all 10 centers. For each center there were only trivial differences in the mean values of delta calculated in these two different ways.

While the delta method is a powerful parametric method for determining if there is a paternal age effect and its magnitude, it provides no information on how such an effect may be adjusted for in genetic counseling. Therefore a second approach was taken, using regression methods similar to those used earlier (Hook et al. 1981). A regression equation was fit to the equation $\ln(y-a) = bx+c$) where y is the rate of Down's syndrome, x is the maternal age in years, and a, b, c parameters to be derived (Lamson and Hook 1981). Because of the age distributions of the (relatively) small number of affected fetuses, the iterative analysis did not converge, either for the model chosen or for the "DS" model used by Hook et al. (1981). If however, the parameter a was set equal to zero, a convergent solution was obtained readily. Setting $a=0$ is equivalent to using an equation appropriate only for older mothers, e.g., over 30 years (Hook and Lindsjo 1978). Therefore two regression analyses were done, one restricting analyses for fetuses whose associated maternal age was 31 years or over, the other 32 years or over. These boundaries were chosen because the youngest observed maternal age for a case of Down's syndrome in this series was at age 32 years. The value of the likelihood ratio statistic G^2 was calculated for the agreement of the equation with the observed data. We then calculated a second equation $\ln(y-a)=(bx+dz+c)$ where z is paternal age, b, c, d parameters to be calculated, and $a=0$ as before. G^2 was also calculated for the second equation. A difference between the values of G^2 for the two equations may be compared with a χ^2 distribution with 1 df. A difference of 3.84 indicates an improvement in fit associated with the introduction of a paternal age term significant at 0.05 level. More importantly, the value of d, the coefficient of paternal age, indicates the magnitude of the increase of rate with paternal age. Even if only a nonsignificant effect is found, the value of $d \pm 1.96$ its standard error enables construction of a rough 95% confidence interval upon the range in the possible contribution of paternal age to the rate. In all of the data sets we have examined to date, whenever the delta approach has indicated a result significant at the 0.05 level, we have found a significant result with the regression analysis, and conversely.

Lastly, we also used multiple applications of the Mantel-Haenszel extension of the Cochran test (see, e.g., Fleiss 1981). (This method allows calculation of the observed and expected

Table 1. Distribution of parental ages of fetuses with normal genotypes (continued on following page)

Maternal age (years)	Paternal age (years)																								
	<19[a]	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
<18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	2	2	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	0	2	1	3	2	0	3	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
20	0	1	1	0	1	1	1	0	2	1	0	1	1	0	0	0	0	0	0	0	0	1	0	0	0
21	0	0	0	1	3	4	2	0	0	0	2	0	0	0	0	0	1	0	1	0	0	0	0	0	0
22	0	0	0	1	1	3	2	1	5	1	1	1	2	0	0	0	2	1	0	1	0	0	0	0	0
23	0	0	0	1	1	6	3	1	1	5	5	1	1	1	0	1	0	0	0	0	2	0	0	1	0
24	0	0	0	1	1	2	7	4	3	4	7	6	0	5	1	2	0	1	0	0	0	1	0	0	0
25	0	0	0	1	1	0	1	9	6	3	4	2	0	2	2	0	2	3	0	0	1	1	0	0	1
26	0	0	0	0	0	1	2	2	7	7	7	2	2	6	1	1	1	3	2	1	0	2	0	0	0
27	0	0	0	0	1	0	1	0	4	6	5	8	2	2	1	1	3	1	1	0	1	1	0	0	0
28	0	0	0	0	0	3	2	1	4	6	4	6	11	9	7	4	3	3	2	1	1	0	0	0	1
29	0	0	0	0	0	0	0	0	2	1	3	14	13	15	9	8	4	3	0	0	0	0	1	0	0
30	0	0	0	0	0	0	0	1	1	2	3	9	8	16	8	9	11	1	3	2	1	1	1	2	0
31	0	0	0	0	0	0	0	1	0	1	0	2	11	12	16	15	5	4	5	5	2	3	0	0	0
32	0	0	0	0	0	0	0	0	0	1	2	2	1	10	19	25	15	9	10	5	8	1	5	4	3
33	0	0	0	0	0	2	0	0	1	2	5	5	10	12	14	31	32	32	17	16	15	12	9	2	3
34	0	0	0	1	2	1	4	4	7	9	18	11	23	23	36	59	101	109	97	57	65	37	36	31	20
35	0	0	3	4	0	2	4	9	7	22	29	31	41	53	90	102	165	236	210	203	165	96	102	74	54
36	0	1	1	0	3	2	6	10	15	17	16	36	40	49	46	72	87	119	203	189	153	141	112	83	62
37	0	0	0	1	2	3	3	6	6	12	11	23	36	50	42	56	91	80	128	183	144	103	102	99	71
38	0	0	0	0	1	1	5	5	4	11	18	15	15	20	21	53	44	56	72	73	115	111	85	86	68
39	0	1	0	0	0	5	2	1	2	3	8	6	10	18	25	29	36	32	39	43	62	64	66	58	51
40	0	0	0	2	0	3	1	1	0	1	2	5	11	9	14	12	17	15	29	17	32	35	44	39	47
41	0	0	0	0	0	0	0	2	2	2	3	4	2	4	6	12	6	9	17	16	16	12	17	33	31
42	0	0	0	0	1	0	0	0	0	1	2	1	2	0	4	4	5	8	8	7	12	7	6	10	25
43	0	0	0	0	0	1	0	1	0	0	1	0	2	3	1	1	1	2	3	6	4	5	5	6	5
44	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	3	3	5	2	3	2	1	1
45	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	3	0	1
46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0
>47[c]	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not stated	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	2	7	7	16	21	41	49	59	79	118	157	191	245	320	363	498	634	731	850	831	801	637	597	529	444

[a] For paternal age ≤19, there were two cases at: paternal age (PA) = 18 years, maternal age (MA) = 18 years

[b] For paternal age above 65 years, there were cases at: PA = 66, MA = 37; PA = 67, MA = 35; PA = 68, MA = 43; PA = 69, MA = 33; PA = 71, MA = 36; PA = 72, MA = 37; PA = 76, MA = 37; PA = 79, MA = 37

[c] For maternal age >47 years, there was one case at: MA = 49, PA = 28

number of cases occurring at or over each possible paternal age boundary, as Stene et al. (1981) did.) In this approach, for any particular paternal age, e.g., age 35 years, the population was divided into those at or greater than this boundary and those below. A 2×2 table was then constructed for *each* one year *maternal* age interval as to the occurrence of Down's syndrome at or over the paternal age boundary, in this case 35 years. The weighted trends in all of the tables at varying maternal ages was determined by application of the Mantel-Haenszel test. Thus controlling for maternal age, about 79 cases would be expected to men 35 years or over on the assumption of *no* paternal age effect whereas 73 were observed. The approach was then repeated for all other paternal ages from 36 to 49 years. (One problem in interpretation of such tests arises if different trends are observed at different paternal age boundaries. One may expect if the putative effect is linear over paternal age that results which are least sensitive to statistical fluctuation would occur when the division is made at or close to the median paternal age for the Down's syndrome cases. For our data set this is between 40 and 41 years). The Mantel-Haenszel analysis also provides a summary relative risk of a Down's syndrome birth to fathers at or greater than the boundary paternal age compared to those below it.

Because of the possibility that paternal age is associated with chromosome disorders other than 47,+21, we used only those with normal genotypes for comparison (considering polymorphisms and heteromorphisms as normal variants). If anything, this will tend to enhance detection of Down's syndrome associations with paternal age, as the putative associations of other chromosome abnormalities with paternal age will not contribute to the data on the normal comparison group.

Results

In Table 1 we present data on the parental ages of the cases with normal genotype and in Table 2 data on the parental ages of those with 47,+21 (see also footnotes to these tables on data not presented in the cells). There were a total of 101 cases of Down's syndrome diagnosed. All but four had 47,+21. There were two

(continued)

Paternal age (years)																								Not stated	Total
43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	>65[b]		
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	13
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	24
0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	32
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	46
0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	8	49
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	51
0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	43
1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	73
1	0	0	1	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	85
0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	84
0	0	0	1	0	2	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	6	93
4	1	0	2	0	2	0	1	0	0	0	2	0	0	0	0	1	0	0	0	0	0	0	0	4	137
2	3	2	2	2	0	1	0	0	1	0	1	0	1	0	0	0	1	0	0	0	0	0	1	7	244
15	16	9	9	3	8	6	7	3	3	2	2	3	2	1	0	1	0	0	0	0	0	0	0	29	870
46	36	32	21	23	11	10	10	6	6	5	6	5	1	4	2	2	1	0	1	1	1	0	1	90	2023
49	32	40	32	19	20	19	15	10	5	8	4	8	2	1	0	2	2	0	0	1	0	0	1	95	1828
55	44	38	26	25	18	18	16	10	8	8	8	3	4	5	2	2	3	2	2	0	0	0	4	94	1647
58	47	29	32	22	19	12	13	15	8	5	4	4	4	3	3	2	1	1	0	0	0	0	0	81	1242
49	33	32	23	23	21	21	11	10	6	4	10	5	3	5	0	1	0	0	2	0	0	3	0	46	869
40	44	24	31	15	17	11	13	7	8	2	8	4	3	4	1	0	1	1	1	0	0	1	0	30	602
26	11	14	16	15	17	4	5	6	11	5	5	2	4	3	0	0	1	1	0	0	0	0	0	17	357
20	17	14	12	12	4	7	11	1	2	4	3	1	2	0	2	3	0	0	0	1	0	0	0	13	232
6	6	5	7	4	1	1	4	1	2	2	4	2	2	1	0	0	0	0	1	0	0	0	1	9	106
2	4	3	6	3	6	2	3	2	2	1	6	2	2	0	0	2	0	0	0	1	0	0	0	4	74
0	3	3	1	1	1	2	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	20
1	1	0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6
0	0	0	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	5
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	30	30
375	300	246	223	167	148	116	111	73	65	48	64	41	31	27	10	16	10	6	8	4	1	4	8	590	10919

Table 2. Distribution of parental ages of fetuses with Down's syndrome

Maternal age (years)	Paternal age (years)																							Not stated	Total
	≤29[a]	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	≥51[c]		
≤33[b]	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
34	0	0	0	0	1	1	1	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	1	6
35	1	0	1	0	1	1	0	0	0	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	7
36	1	2	0	1	0	1	1	1	1	0	0	1	0	0	1	0	0	0	0	0	0	1	1	1	13
37	1	1	0	0	1	0	0	0	3	1	1	0	1	2	0	0	0	0	0	0	0	0	0	0	11
38	2	0	0	0	1	0	0	0	2	2	0	1	0	1	0	0	1	0	0	0	0	0	1	1	12
39	1	2	0	0	1	0	0	0	0	1	0	1	0	1	1	1	0	0	0	0	0	0	2	0	11
40	0	1	0	0	0	0	0	0	0	0	0	5	2	1	1	2	2	0	0	1	0	1	2	0	18
41	0	0	1	1	0	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0	6
42	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	1	0	0	0	0	0	0	0	3
43	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	0	1	0	0	8
44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	0	0	1	0	0	4
≥45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not stated	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	7	6	2	2	5	3	3	3	6	5	2	14	3	6	4	5	7	0	2	2	0	4	7	3	101

[a] For paternal age ≤29, there were cases at: paternal age (PA) = 25, maternal age (MA) = 38; PA = 26, MA = 37; PA = 26, MA = 38; PA = 28, MA = 32; PA = 28, MA = 35; PA = 29, MA = 36; PA = 29, MA = 39

[b] For maternal age ≤33, there were cases at: MA = 32, PA = 28; MA = 33, PA = 35

[c] For paternal age ≥51, there were cases at: PA = 52, MA = 39; PA = 52, MA = 41; PA = 53, MA = 39; PA = 53, MA = 40, PA = 54, MA = 38; PA = 57, MA = 36; PA = 64, MA = 40

Table 3. Comparisons of mean paternal age at each maternal age of those with Down's syndrome genotype diagnosed prenatally and those with normal genotypes

Maternal age (years)	Normal genotype			Down's syndrome genotype		
	Number	Mean paternal age (years)	S.D.	Number	Mean paternal age (years)	S.D.
18	6	19.83	2.14	0	0.00	0.00
19	12	22.25	3.02	0	0.00	0.00
20	12	28.83	11.43	0	0.00	0.00
21	14	25.21	4.64	0	0.00	0.00
22	22	27.23	4.47	0	0.00	0.00
23	31	28.03	6.31	0	0.00	0.00
24	45	27.56	3.62	0	0.00	0.00
25	41	29.80	7.05	0	0.00	0.00
26	47	29.43	4.05	0	0.00	0.00
27	39	29.87	4.32	0	0.00	0.00
28	71	30.89	4.85	0	0.00	0.00
29	78	32.03	4.86	0	0.00	0.00
30	80	32.16	3.42	0	0.00	0.00
31	87	33.84	5.28	0	0.00	0.00
32	133	35.62	5.24	1	28.00	0.00
33	237	35.47	5.29	1	35.00	0.00
34	841	36.39	5.28	5	37.20	4.92
35	1933	36.91	5.31	7	34.86	4.63
36	1732	37.71	5.55	12	37.75	8.57
37	1550	38.47	5.85	11	36.55	5.05
38	1161	39.25	5.86	11	37.73	8.15
39	823	40.23	6.40	11	39.45	8.44
40	572	41.32	6.38	18	43.89	7.00
41	340	41.87	6.61	6	39.00	7.85
42	219	42.79	6.43	3	41.67	2.89
43	97	43.00	7.84	8	44.00	4.57
44	70	45.39	7.70	4	46.50	2.65
45	20	44.75	5.88	0	0.00	0.00
46	6	46.33	4.76	0	0.00	0.00
47	5	45.00	9.35	0	0.00	0.00
48	0	0.00	0.00	0	0.00	0.00
49	1	28.00	0.00	0	0.00	0.00

47,+21 mosaics and two with 47,+21 and another abnormal genotype. The maternal and paternal age of each mosaic case were, respectively: case 1: 37, 38; case 2: 39, 38. For those with 47,+21 and another abnormality, these were case 3: 39, 29; case 4: 35, 40. No translocations were observed.

In Table 3, we present the results of the delta analysis by maternal ages. The mean Δ for the entire group was −0.27 with a standard error of 0.68. Thus the 95% confidence interval for delta is about −1.59 to +1.06, overlapping zero. At the 13 maternal ages at which cases of 47,+21 were observed, for eight the mean paternal age was lower than the mean for the normals, for five higher. This analysis does not provide evidence for a significant positive paternal age effect.

In analysis of the experience of separate centers, there were four for which mean delta was positive, two for which delta was zero, and four for which mean delta was negative. For all but one center the values of the mean of delta ranged from +2.1 to −2.4. At one center at which only two cases of Down's syndrome were observed, mean delta was +8.9. This large value was entirely attributable to a single case with a 57-year-old father (who was about 19.5 years older than the control paternal age for his 36-year-old wife). For neither this center nor any of the others was

Table 4. Results of regression analysis for maternal ages 31–49 (years), paternal ages 20–69 (years)

Equation*	Parameters (and asymptotic standard deviations)****				
$\ln y =$	b	c	d	G^2**	ΔG^2***
$bx+c$	0.2451 (0.0346)	−13.9550 (1.354)	—	278.529	
$bx+dz+c$	0.2498 (0.0371)	−13.9046 (1.362)	−0.0058 (0.0164)	278.358	0.171

* y = Rate of Down's syndrome, x is maternal age and z is paternal age. Parental ages are at the time of expected live-birth, that is 0.4 years is added to reported truncated parental ages in the regression analysis. This makes no difference in the parameters b and d but changes the value of x, the intercept, slightly

** G^2 = Likelihood ratio statistic

*** ΔG^2 = Difference in G^2 between equations associated with introducing paternal age term

**** If regression analysis is done for maternal ages 32 to 49 years (paternal ages 20 to 69 years as before) there is only a trivial difference in the parameters. For the 1st equation $b=0.2436$, $c=-13.8926$. For the 2nd equation, $b=0.2482$, $c=-13.8423$, $d=-0.0058$

Table 5. Results of Mantel-Haenszel tests for association of Down's syndrome genotype with paternal age at or greater than boundary values from 35 to 49 years

Boundary (paternal age division) [years]	Number observed at or over the age boundary		Number of expected Down's syndrome[a]	Summary relative odds ratio[b]	P value
	Normal genotype	Down's syndrome			
≥35	7401	73	79.44	0.66	0.08
≥36	6691	70	74.36	0.77	0.27
≥37	5855	67	67.62	0.97	0.88
≥38	5035	61	60.93	1.00	>0.97
≥39	4242	56	54.00	1.11	0.65
≥40	3615	54	47.86	1.37	0.18
≥41	3024	40	41.53	0.93	0.73
≥42	2498	37	35.73	1.07	0.77
≥43	2057	31	30.25	1.04	0.86
≥44	1685	27	25.47	1.10	~0.70
≥45	1391	22	21.18	1.06	0.82
≥46	1149	15	17.84	0.79	0.43
≥47	930	15	14.44	1.05	0.58
≥48	764	13	12.03	1.10	~0.75
≥49	620	11	9.84	1.14	~0.70

[a] The number expected at or over the paternal age boundary on the assumption of no paternal age effect. (These are summed over all maternal ages for each paternal age boundary)

[b] A value greater than one is consistent with a positive paternal age effect if division is made at the boundary indicated. A value less than one is consistent with an negative paternal age effect at the boundary indicated

Table 6. Regression derived rates of Down's syndrome per 1000 live births at selected values of maternal and paternal age assuming a 1% increase per year with paternal age[a]

Maternal age (years)	Paternal age (years)									All paternal ages[a]
	21	27	31	35	39	43	47	51	55	
21	0.6	0.7	0.7	0.7	0.8	0.8	0.8	0.8	0.9	0.7
23	0.7	0.7	0.8	0.8	0.8	0.9	0.9	0.9	1.0	0.8
25	0.8	0.8	0.9	0.9	0.9	1.0	1.0	1.1	1.1	0.8
27	0.9	0.9	1.0	1.0	1.0	1.1	1.1	1.2	1.2	1.0
29	1.0	1.0	1.1	1.1	1.2	1.2	1.2	1.3	1.4	1.1
31	1.1	1.1	1.2	1.2	1.3	1.3	1.4	1.4	1.5	1.2
33	1.5	1.5	1.6	1.7	1.7	1.8	1.9	2.0	2.0	1.7
35	2.4	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.4	2.8
37	4.0	4.2	4.4	4.6	4.8	5.0	5.2	5.4	5.6	4.8
39	6.6	7.0	7.3	7.6	7.9	8.2	8.5	8.9	9.3	8.1
41	10.9	11.6	12.0	12.5	13.0	13.6	14.1	14.7	15.3	13.5
43	18.0	19.1	19.8	20.6	21.4	22.3	23.2	24.1	25.1	22.7
45	29.5	31.3	32.5	33.8	35.1	36.5	38.0	39.5	41.0	37.8
47	48.1	51.0	53.0	55.0	57.2	59.4	61.7	64.1	66.5	62.4
49	77.7	82.2	85.3	88.6	91.9	95.4	98.9	102.6	106.4	101.6

[a] Rates calculated from regression equations derived from data discussed in Hook et al. (1981) for British Columbia 1964 to 1976, assuming 20% underascertainment of rates at all ages. For further discussion see Hook and Cross (to be published)

the value of the mean delta significantly different from zero at $P < 0.05$.

The results of the regression analysis appear in Table 4. The change in the likelihood statistic with the introduction of paternal age is only 0.171, (df 1, $P \cong 0.70$). Moreover, not only does this indicate no significant paternal age effect, but the paternal age coefficient is negative, albeit of small magnitude (−0.0058). The (asymptotic) 95% confidence interval for the coefficient is −0.0379 to +0.0263, consistent with either a positive or a negative paternal age effect.

In Table 5 we summarize the results of 15 separate Mantel-Haenszel tests. The median paternal age is between 40 and 41 years. If division is at age 40 years, the summary relative odds for association of Down's syndrome with paternal age ≥ 40 is 1.37, (χ^2 of association = 1.79 df = 1, $P = 0.18$). If, however, the division is made at age 41 years, the summary relative odds ratio of Down's syndrome for paternal age is 0.93 in the opposite direction ($df = 1$, $\chi^2 = 0.12$, $P \cong 0.73$). These differences illustrate how statistical fluctuation can result in differences in estimation of effects depending on which paternal age boundary is used and some of the difficulties in interpretations of the results of this type of analysis. However, at least all paternal age divisions analyzed revealed no evidence for a statistically significant effect, consistent with the results of the two other types of analyses.

Discussion

The results of these analyses do not prove that there is no paternal age effect for 47,+21 but suggest that if there is such an effect and it is *ubiquitous*, it is not likely to be as large as Stene et al. (1977, 1981) have claimed. There are at least five different hypotheses that may explain discrepancies among studies reported to date: (1) There are temporal, geographic, or ethnic variations in paternal age effects; (2) There is no paternal age effect and statistical fluctuation accounts for all trends to date; (3) Methodologic artifacts have obscured a paternal age effect in some studies which did not find a positive outcome; (4) Methodologic artifacts are responsible for the positive results in some studies to date; (5) There is a weak paternal age effect independent of maternal age in most if not all populations, but because of statistical fluctuation the results are significant only in some data sets.

At the present time it is difficult to conclude arbitrarily that one or another of these hypotheses account for all of the observed variation. Certainly some methodologic artifacts have contributed to the alleged trends in those studies which analyzed data by 5-year intervals, so the fourth hypothesis accounts for at least some of the positive claims.

With regard to the third hypothesis, Stene et al. (1981) have stated that those negative studies which used vital record reports were biased to missing an effect because physicians are biased to report selectively upon birth certificates cases born to older mothers. Our own experience in New York State (see, e.g., Hook and Chambers 1977; Hook and Cross 1981) suggests this is not the case in our jurisdiction at least. The experiences of others elsewhere (Huether, personal communication) suggest our experience is not unique. Even if the alleged type of selective reporting did occur, it is not clear how this would obscure a positive result, unless there was some peculiar paternal age-maternal age interaction (see Hook 1981 for further discussion on this point). Moreover such an alleged artifact is only pertinent to results in the vital record data. This would not acount for those negative studies which used data from chromosome registries, case-control studies, and other sources such as those in Hook et al. (1981), nor for the studies reported here.

It is certainly possible that temporal or geographic factors acount for the differences in studies. However if this is the case then the advice derived from the data by Stene et al. (1981) for genetic counseling may be applicable only to the specific region and time period they studied, and uncritical extrapolation to other time periods or populations cannot be done.

There is, however, no reason of which we are aware at present to reject the ecumenical hypothesis of a slight positive effect,

consistent with all studies. The results of all data sources we have been able to analyze to date using the delta method and regression method are consistent with a mean delta of between +0.04 to +0.48, and in the value of the paternal age coefficient of +0.006 to +0.017. The data from our study reported in this paper certainly do not exclude any values in these ranges. We have not been able to do a similar analysis for the data of Stene et al. (1981) because they are not presented in sufficient detail for this type of evaluation, and the raw data from their study are not available to us for analysis. While further analysis of their data might narrow this range, we doubt that they would exclude it entirely. Note that our study included more than 50% more cases than Stene et al. so that the confidence intervals of parameters derived from their data should be even wider than the confidence intervals of this study.

Stene et al. (1981) have presented values of alleged "risks" for 47,+21 that project very high increases of rates with paternal age. For example for a mother age 40 years married to a father age 40 years they indicate a risk of six per 1000, but for a mother of the same age married to a father age 47 years they indicate a risk of 20 per 1000, a three-fold increase in seven years, or an average increase in this interval of 43% per year (Stene et al. 1981). This is tantamount to an assumption by Stene et al. (1981) that all other analyses of data on this point have reached incorrect conclusions, but that their results can be extrapolated readily to other time periods and regions. For the reasons cited above we do not believe such derived rates can be assumed as applicaple to any population with the possible exception of women studied by Stene et al. in their laboratory in the years in question. Of course if one assumes that significant variation between populations is likely then no observed rates should be cited as risks in *any* group until it is studied in detail (see discussion in Hook and Cross (to be published) on the distinction between "risks" and "rates").

On the ecumenical assumption that there is relatively little underlying difference between populations sampled to date and that statistical fluctuation accounts for the observed differences, it is possible to make alternative estimates of the rates of Down's syndrome with maternal age and paternal age. In Table 6 we present such estimates for livebirths for several ages, assuming a paternal age coefficient of 0.01, i.e., an increase in rate of about 1% per year with each year of paternal age. As these rates are on livebirths, they are of course not directly comparable with rates observed in prenatal diagnoses (because of spontaneous fetal death after amniocentesis, the rates at the time of amniocentesis may be expected to be about (1/0.7) = 1.43 fold higher than the rates in livebirths). It may be noted that there are few if any maternal age–paternal age combinations at which consideration of paternal age would appear likely to change a decision to do amniocentesis based solely on maternal age. *We emphasize such rates are applicable only if the model is correct.* While the model appears to be *consistent* with all data sets which we have been able to analyze, it does not necessarily hold for all populations and time periods.

Acknowledgements. We thank Robert Dorn, Lora Gersch, and Linda Gulotty for assistance with various phases of the analysis. Laboratories (and their Director) from which data were available on both maternal and paternal age from over 90% of cases were: Lawrence R. Shapiro, M.D., NYS Department of Mental Hygiene, Letchworth Village; Robert J. Desnick, M.D., Sara Kaffe, M.D., Mt. Sinai School of Medicine; Richard Doherty, M.D., Lawrence Wisniewski, Ph.D., University of Rochester School of Medicine; Harold M. Nitowsky, M.D., Albert Einstein School of Medicine; Hyon Ju Kim, M.D., Beth Israel Medical Center; Qutub H. Qazi, Ph.D., William Crombleholme, M.D., SUNY Downstate Medical Center; Lillian Y. F. Hsu, M.D., Peter H. Benn, Ph.D., Prenatal Diagnosis Laboratory of New York City; M. Lita Alonso, M.D., New York Hospital; George I. Solish, M.D., Ph.D., Long Island College Hospital; Doris H. Wurster-Hill, Ph.D., Dartmouth Medical School. We thank them for their cooperation. Other laboratories affiliated with the New York State Chromosome Registry were: Ann M. Willey, Ph.D., Birth Defects Institute; Dorothy Warburton, Ph.D., Columbia University College of Physicians and Surgeons; Ram Verma, Ph.D., The Jewish Hospital and Medical Center of Brooklyn; Robin M. Bannerman, M.D., SUNY at Buffalo, Children's Hospital; Lytt Gardner, M.D., James Winkelman, M.D., SUNY at Syracuse Upstate Medical Center; Sandra R. Wolman, M.D., New York University Medical Center; Edward Gendel, M.D., Metropolitan Hospital Center; Ernest Lieber, M.D., Long Island Jewish-Hillside Medical Center; Jessica Davis, M.D., Nataline B. Kardon, M.D., North Shore Hospital; Edward Schutta, M.D., Brookdale Hospital Medical Center; Carolyn Trunca, Ph.D., SUNY at Stony Brook Health Sciences Center; R. S. K. Chaganti, Ph.D., Memorial Sloan Kettering Cancer Center; W. Roy Breg, M.D., Yale University School of Medicine; Leonard Atkins, M.D., Massachusetts General Hospital; Teresita Mendoza, M.D., Rhode Island Hospital; Robert M. Greenstein, M.D., University of Connecticut Health Center; Laurent J. Beauregard, Ph.D., Eastern Maine Medical Center; Elizabeth Allen, Ph.D., Medical Center Hospital of Vermont; Rina Schmidt, M.D., Metpath, Incorporated.

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Received May 3 / Revised July 12, 1982