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Paternal Age and Down Syndrome in British Columbia

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SUMMARY

Among Down syndrome cases born in 1964–1976 reported to the British Columbia Registry for Handicapped Children, the mean paternal age was about half a year greater than in the entire population of live births after controlling for maternal age, a difference significant at the .05 level. After adjustment for maternal age, a regression analysis was consistent with an increase of 1.024-fold for each year of paternal age. Among Down syndrome cases in 1952–1963, however, for which ascertainment appears likely to be less complete, there was no evidence for a significant paternal age effect. The reasons for the variation between the two groups investigated here and the heterogeneity in results among studies of other populations are discussed.

INTRODUCTION

The recent discovery that the extra chromosome in about 30% of cases of 47,trisomy 21 is of paternal origin [1] has revived interest in the possibility of paternal age as a risk factor for a Down syndrome birth, independent of maternal age. Previous analyses have shown that a paternal age effect, if it exists, is much weaker than a maternal age effect [2, 3], but could not exclude the existence of a modest association [4, 5]. Two reports have noted a twofold increase in maternal age specific rates in couples in which the father is 55 and over [6, 7], but this has not been reported in

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other studies [8–10]. We report here the results of analyses that indicate a significant association of elevated paternal age with Down syndrome of live births in 1964–1976 in British Columbia.

MATERIALS AND METHODS

The data are on all live births in the province of British Columbia registered with the Department of Vital Statistics for the years 1952–1976. Cases of Down syndrome were those reported to the British Columbia Health Surveillance Registry [11]. In 1964, sources of ascertainment were expanded to include hospital discharge records, and this was associated with an increase in the observed maternal age-specific rates in 1964 and in later years [12, 13]. Because of this, we subdivided the data into cases born in 1952–1963 and those born in 1964–1976 and analyzed these separately. We include data on mothers aged 14–49 and fathers aged 14–70.

There were 551 affected cases reported in 418,017 live births for the years 1952–1963 (1.3 per 1,000) and 492 in 418,848 live births in 1964–1976 (1.2 per 1,000). The lower rate in the later years, despite the better ascertainment of cases, is attributable to the diminished proportion of older mothers among those having live births [12, 13].

We searched for paternal age effect independent of maternal age using two different statistical methods. (1) Case-control comparisons: For the live-birth populations in each of the two temporal intervals, and for each *1-year* maternal age interval, we determined the mean paternal age of all individuals without Down syndrome. For each case, the difference *delta* between the observed paternal age and the appropriate mean paternal age for unaffected individuals was calculated. Examination of the distribution of the values of delta in both intervals indicated that statistical analysis based on normal distribution theory was appropriate. The 95% confidence limits about the mean value of delta in each interval were calculated from the formula $m \pm 1.96$ (SEM), where m is the mean, and SEM, the standard error of the mean. The hypothesis of no paternal age effect predicts delta = 0; therefore, if the 95% confidence interval of delta excludes 0, this implies the existence of a paternal age effect, $P < .05$.

(2) Regression approach: For each temporal interval, a regression equation predicting the rate of Down syndrome as a function of maternal age was fit to the data. We then introduced a term involving paternal age into the regression equation and determined if there was a "statistically significant" increase in the fit of the equation to the data. We first fit an equation of the form $\ln[y/(1-y)] = a + b_1x_1 + b_2x_2$, where y is the rate, and x_1 and x_2 are functions of maternal age x as follows: $x_1 = x - 32$ if $x \leq 32$, and 0 otherwise, and $x_2 = x - 32$ if $x \geq 32$, and 0 otherwise. (This model results in about as good a fit to the observed data as those used in previous analyses of maternal age [14, 15].) We then calculated G^2, the likelihood ratio statistic (twice the log likelihood ratio) for the equation [16], and fit the data to the equation $\ln[y/(1-y)] = a + b_1x_1 + b_2x_1 + cz$, where z is paternal age and calculated G^2 for the second equation. The difference between the values of G^2 for these 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 introduction of a paternal age term significant at the .05 level. All analyses were by 1-year parental age interval.

RESULTS

The mean and standard error of the mean of delta for 1952–1963 is $+0.05 \pm 0.22$. The 95% confidence interval is -0.37 to $+0.48$; the mean case paternal age is 36.87, and comparison paternal age is 36.82. For 1964–1976, delta is to $+0.46 \pm 0.21$ (95% confidence interval = $+0.04$ to $+0.88$), and the mean case paternal age is 34.55, and comparison paternal age, 34.09. There is a negligible nonsignificant effect in 1952–1963, but for 1964–1976, the effect is significant at the .05 level.

We also analyzed two subintervals of the period 1964–1976 to determine if the paternal age effect was stronger in the latter half of the interval, consistent with a gradual secular increase with time. This was not the case, however. For the 283 cases born in 1964–1969, the mean and standard error of delta were +0.50 and 0.30. For the 209 cases in 1970–1976, these values were +0.34 and 0.32, respectively.

In table 1 appear the results of the regression analysis. For the second interval, there is a significant increase in the likelihood ratio statistic with the introduction of paternal age.

Because analyses by others had reported a paternal age effect only at age 55 and over [6, 7], we re-analyzed the data excluding men of this age to determine if the significance of the paternal age effect would diminish or disappear. In fact, evidence for a paternal age effect was enhanced after excluding this group. The change in the likelihood ratio statistic rose from 6.4 to 9.5, and the value of c, the coefficient of paternal age, from 0.024 to 0.032. While it is likely that this change is attributable to statistical fluctuation, it demonstrates that the overall effect is not derived exclusively from those fathers 55 and over.

DISCUSSION

The data for the years 1964–1976 provide evidence for a paternal age effect throughout the entire age range. In this respect, it differs from results that report evidence for an effect in men only 55 and over [6, 7], or those studies reporting no evidence for an effect [8–10, 17, 18]. It also differs, of course, from the results of the analysis of the years 1952–1963, in which there is only a negligible, nonsignificant trend.

An obvious possibility is that there are temporal and geographic fluctuations in the independent effect of paternal age upon rates, and this is responsible for the reported variation. Before this may be inferred, however, it must be shown that the positive results in 1964–1976 are incompatible with the observations in the other studies. As the 95% confidence intervals for the values of delta in the two intervals analyzed here overlap, the results in both are compatible with a paternal age difference of +0.04 to +0.48 years. While ascertainment is likely to be less complete in the earlier interval, we have no reason to expect this would obscure an effect

TABLE 1

RESULTS OF REGRESSION ANALYSIS

POPULATION	EQUATION* $\ln[y/(1-y)] =$	PARAMETERS a	b_1	b_2	c	G^2†	ΔG^2‡
1952–1963	$a + b_1x_1 + b_2x_2$	−7.026	0.053	0.262	...	703.28	...
	$a + b_1x_1 + b_2x_2 + cz$	−7.137	0.050	0.259	0.003	703.12	0.16
1964–1976	$a + b_1x_1 + b_2x_2$	−6.829	0.063	0.257	...	661.66	...
	$a + b_1x_1 + b_2x_2 + cz$	−7.671	0.041	0.236	0.024	655.26	6.40

*y = rate of Down syndrome, x_1 and x_2 are functions of maternal age as defined in MATERIALS AND METHODS, and z is paternal age.

†G^2 = likelihood ratio statistic [16] (see MATERIALS AND METHODS).

‡ΔG^2 = difference in G^2 between equations associated with introducing paternal age term.

of paternal age. Others have not reported a case-control comparison of this type, so one cannot make the same comparisons with data from other jurisdictions. (Sigler et al. [17] and Cohen et al. [18] have reported no evidence for paternal age effects in case-control studies in Baltimore, but the matching by maternal age in these studies does not appear to have been by 1-year intervals as in the analyses here.)

If differences between various data sets are attributable to statistical fluctuation, it is of interest to determine with what magnitude of effect the data available to date are compatible. Considering the two intervals analyzed here and three others [9], the 95% confidence intervals of the paternal age coefficient for the five data sets all overlap the values +0.006 to +0.017. Thus all are consistent with an increase of about 0.6% to 1.7% in the rate for each year of paternal age (independent of maternal age). This is a relatively small increase.

If the paternal age coefficient is assumed to be +0.010 (an intermediate value in the range consistent with all data sets), the regression equation is then: $\ln[y/(1 - y)] = -7.17041 + 0.05510x_1 + 0.22490x_2 + 0.01000z$, where y_1, x_1, x_2, and z are as defined above. As an illustration of the prediction of this equation, for 41-year-old women, whose overall rate of affected live births is 10.80 per 1,000, the rate is 9.50 per 1,000 if married to 31-year-old men, 10.50 per 1,000 if married to 41-year-old men, and 12.20 per 1,000 if married to 56-year-old men.

We do not suggest, however, that our estimates of the paternal age effects are precise, nor that the derived regression equations are the most appropriate for genetic counseling concerning a paternal age effect in future populations.

Lastly, it is of interest that, judging by maternal age-specific rates, the 1964–1976 live births represent to our knowledge the most "complete" large scale community sample of Down syndrome in which a paternal age effect has been sought. (The maternal age-specific rates are about the same as those observed in a Massachusetts study [15] and about 10% lower than those reported in a Swedish study [14].) Ascertainment was likely less complete for the 1952–1963 group, as well as for other groups in which no significant effect was reported [8–10]. It is conceivable, therefore, that some as yet undetected systematic loss has resulted in failure to find a significant paternal age effect in the latter studies.

In conclusion, several hypotheses may explain the discrepancies among the studies of paternal age effect to date: (1) there is a weak paternal age effect that, because of sampling fluctuation, is significant only in the 1964–1976 data set; (2) as yet unknown geographic, ethnic, and temporal factors affect the possible influence of paternal age, and such factors resulted in a significant effect in British Columbia in 1964–1976; (3) some as yet undetected methodological artifact associated with incomplete sampling of live births tended to obscure a paternal age effect in 1952–1963 British Columbia live births and in other studies that reported negative or nonsignificant trends; and (4) there is no paternal age effect, and statistical fluctuation is responsible for observed positive results.

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ADDENDUM

Since these data were presented at the 1980 American Society of Human Genetics meeting, I have received many queries as to how I interpret them with regard to genetic counseling and paternal age. There are obviously several alternatives. My own preference is ecumenical: to assume there is a single underlying distribution that is compatible with all the jurisdictions and temporal periods studied to date. This assumption, which, of course, may be erroneous, is consistent with about a 1% increase per year in rate with each year of paternal age, at any fixed maternal age. This suggests only a modest effect even if there are great differences in age. If for a 21-year-old woman married to a 21-year-old man the expected rate is .05/1,000, then if she is married to a 56-year-old man the expected rate is about 0.75/1,000. Similarly, if for a 26–26-year-old couple the expected rate is 0.7/1,000, then for a 56–26 couple it is 0.9/1,000; if for 31–31 it is 1.0/1,000, then for 56–31 it is about 1.3/1,000; if for 36–36 it is 2.9/1,000, then for 56–36 it is 3.5/1,000; if for 41–41 it is 10.3/1,000, then for 56–41 it is 12.0/1,000; and if for 46–46 it is 37.6/1,000, then for 56–46 it is 41.4/1,000. For intermediate ages, the predictions may be interpolated. Again these inferences depend on the assumption that this particular ecumenical model is correct. It will be of interest to test it against future data sets as they become available.

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