THE RELATIVE EFFECTS OF PATERNAL AND MATERNAL AGE IN DOWN'S SYNDROME

BY L.S. PENROSE, M.D.*

This article, which appeared in J. Genet. 2009 Apr; 88(1): 9-14, was retypeset in 2015 by James Hanley. Rather than the terminology of the 1930's, it uses one of the terms suggested by Dr. Penrose and the other signatories to the 1961 letter to the Lancet (April 8, p.775). Some of them suggested that the term be changed to "Langdon-Down anomaly", or "Down's syndrome or anomaly" or "congenital acromicria". Several of them believed that was 'an appropriate time to introduce the term "trisomy 21 anomaly".' See the 2011 article 'Fifty years of evolution of the term Down's syndrome.' in the Lancet [Rodríguez-Hernández ML, Montoya E., July 30; 378(9789) : 402].

It has long been known that Down's syndrome children are frequently born to elderly parents, and practically every observer, who has recorded any large number of cases, has come to the conclusion that either the age of the parents at the birth of the child or ultimogeniture is an aetiological factor[1] The present communication is not concerned with the problem of how far order of birth may be an accessory causative factor, but is confined to consideration of the relative effects of paternal and maternal age.

In the human species ages of the parents are so closely correlated that it is difficult to separate the effects of the two elements. Hitherto attempts maternal age is of more aetiological importance than the paternal age. For example, a serious attempt to solve the problem was made in 1927 by Van der Scheer[2], who compared the relative percentages of 316 Down's syndrome children born at various maternal ages with the percentages of normal children born to mothers of equivalent ages in a very large series of families gathered from the general population. The resulting ratios showed a very marked increase in the incidence of affected childen as the age of the mother increased, and also a similar, though not quite so marked, rise of the incidence with increasing paternal age.

In studying the effects of parental age on certain characteristics in inbred stocks of guinea-pigs, Wright[3] was able to demonstrate that the age of the

* *Research Medical Officer, Royal Eastern Counties' Institution for Mental Defectives.*

1 Thurstone, L.L. and Jenkins, R.L.: *Order of Birth, Parent-Age and Intelligence*, pp. 73-5 and 110-13, Univ. of Chicago Press, 1931.

2 Van der Scheer, W.M.: "Beiträge zur Kenntnis der Mongoloiden Missbildung," *Abhand. a. d. Neur., Psychiat. und Psychol.* Heft 41. Berlin: S. Karger, 1927.

3 vVright, S.: "Effect of age of parents upon characteristics of the Guinea-pig," Amer. Nauralist, 60 (1926), pp. 552-9.

dam was an essential factor in the production of white coat colour and also of polydactyly. He found, for example, the correlation of age of dam and proportion of white in the offspring to be +0.190 ± 0.015. The correlation of age of dam and proportion of polydactylous offspring was -0.370 ± 0.018. In the case of white coat colour, the ages of the dam and sire were identical, and so no conclusion as to their relative effects could be reached. But in respect of polydactyly, which, it is to be noted, was most frequent when the dam was young, the use of the technique of partial correlation enabled him to show that the effect of the age of the sire was negligible, after eliminating the effect of the age of the dam.

The present writer has attempted a similar treatment of 150 families of the human species containing Down's syndrome among the children. Every family included was visited personally and, among other things, the ages of the parents at the birth of each child was carefully recorded: miscarriages and all individuals in whom a diagnosis of normality or Down's syndrome could not be made with certainty were excluded. No obvious disparity was observed between the ages of the parental pairs, which were distributed in a manner resembling that found by pooling all married couples in the general population, thus:

			Census	
	150 families		1911	1921
		%	%	%
Husband older	94	62.8	62.9	63.5
Husband and wife, same integral age	25	16.7	13.1	12-5
Wife older	31	20.7	24.0	24.0

The following results were obtained from the data summarised in Table I :

(i) Correlation between maternal age and incidence of Down's syndrome $= +0.362 \pm 0.032$.

(ii) Correlation between paternal age and incidence of Down's syndrome $= +0.294 \pm 0.034$.

(iii) Correlation between paternal age and maternal age $= +0.829 \pm 0.012$

The partial correlation between maternal age and Down's syndrome, found by eliminating paternal age, is $+0.221$, and that between paternal age and Down's syndrome, found by eliminating maternal age, is -0.011. Since the families contain 727 children, the standard deviation of these partial coefficients is less than 0.04. The result suggests that the age of the father is insignificant as an aetiological factor. But the partial correlation technique involved is open to certain objections, partly on account of the hypothetical nature of the variable Down's syndrome - normal. It is not, however, necessary to use this technique to demonstrate the various points, and the following method is at once clearer and more precise.

Having already calculated the correlation coefficient (iii) from Table I, the following two regression equations are easily obtained:

(iv) Regression of father's age (p) on mother's age (q) (based on 727 products) :
$P = (0.944)q + 4.304$. (Standard deviation of $P = 4.315$.[4])

(v) Regression of mother's age on father's:
$Q = (0.726)p + 7.120$. (Standard deviation of $Q = 3.787$.[5])

The following mean ages of fathers and mothers were also obtained from the pooled families:

Mean age in years of mother at birth of

154	Down's syndrome	(qD)	=	37.253	± 6.553
573	Normals	(qN)	=	31.249	± 6.242

Mean age in years of father at birth of

154	Down's Syndrome	(qD)	=	39.383	± 7.786
573	Normals	(qN)	=	33.830	± 7.253

It will be seen in the first place that the difference between the mean ages of the mother at the births of Down's syndrome and Normal children respectively is 6.004 years and the standard error of this difference equals

$$\sqrt{\frac{6.552^2}{154} + \frac{6.242^2}{573}} \text{ or } 0.589.$$

It is obvious that maternal age is of significance because the difference is ten times the standard error.

From the regression equation (iv) we find that the most likely paternal age at the birth of Down's syndrome children (given the maternal age as fixed) is 39.471, i.e. $0.944qD + 4.304$. Similarly, the most likely paternal age of normals (given the maternal age as fixed) is $0.944qD + 4.304$, which is 33.803. The expected difference between the father's average for Down's Syndrome cases and for normals is, therefore, 5.667 years and the actually observed value $(pD - pN)$ is 5.553 years. The standard error of the expected mean value of the father's age for Down's syndrome cases will be $4.315/\sqrt{154}$ or 0.348, and the corresponding error for normals will be $4.315/\sqrt{573}$ or 0.180. The standard error of the difference between these two expected mean paternal ages is, therefore, $\sqrt{0.348^2 + 0.180^2}$ or 0.392 year. The difference between the expected 5.667 years and the observed 5.553 years is 0.115 year, which is less than half the standard error and therefore quite insignificant, since it is very likely to be due to random sampling.

By using the regression equation (v) in a similar way – this time keeping paternal age constant – we find that the expected difference between average maternal age for Down's syndrome cases and for normals, respectively, is 4.032 years (see Table II). The observed difference (which has already been discussed) is 6.004 years. The difference between observed and expected mean values is 1.972 years, with a standard error, worked out again in the same way as above, of 0.341 year. The difference is nearly six times the standard error and therefore the odds are enormously against its being due to sampling.

4 $\sigma_P = \sigma_p\sqrt{1 - r_{pq}^2} = 7.711\sqrt{1 - 0.829^2} = 4.315$.

5 $\sigma_Q = 6.769\sqrt{1 - r_{pq}^2} = 3.787$.

Mean age	Observed value (a)	Expected value (b)	Difference (a-b)
pD	39.383	39.471 ± 0.348	-0.088
pN	33.830	33.803 ± 0.180	+0.027
pD − pN	5.553	5.668 ± 0.392	- 0.115
qD	37.253	35.712 ± 0.305	+1.541
qN	31.249	31.680 ± 0.158	-0.431
qD − qN	6.004	4.032 ± 0.341	+1.972

There can be little doubt, judging from these results, which confirm those obtained by the partial correlation technique, that the father's age is an insignificant factor in the aetiology of Down's syndrome, the emphasis being entirely on the age of the mother. This conclusion helps to justify the method of analysis of sibships containing Down's syndrome children applied by the present writer in a previous article.[6]

Though the material on which this argument is based may appear at first sight to be small in quantity, I believe it to be very accurate. In human genetics it is extremely difficult for one person to investigate a sufficient number of families to give significance to such results in a reasonable time. I have been fortunate in having had the assistance of Miss D.E. Newyyn and Dr M Gunther, who collected a great part of the material. I also wish to thank Dr G.F. Cobb for his kind assistance in supplying several family histories, and the Essex and Suffolk Voluntary Associations for Mental Welfare and also the London County Council for supplying us with accessory information. I am also much indebted to Miss H.L. Brown and Miss J. Bedwell for their help in analysing the data. I have also to thank the Medical Research Council and the Darwin Trust for financial assistance.

In this paper 150 sibships, containing each at least one Down's syndrome child, have been analysed with respect to the relative aetiological importance of paternal age and maternal age. The results indicate that paternal age is not a significant factor, while maternal age is to be regarded as very important.

6 "On the interaction of heredity and environment," *J. Genetics*, 25, No. 3, 407-22, April, 1932.

Summary of data

150 Families

N = Normal; D = Down's

Maternal Age (q)

Paternal age (p)

	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	N	D
17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
18	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.
19	.	.	1	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	.
20	.	.	2	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	1
21	.	.	1	2	2	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	6	.
22	.	.	.	1	4	3	.	1	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	8	2
23	.	.	2	1	1	2	3	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	8	2
24	.	.	.	.	2	3	4	5	2	1	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	16	2
25	.	.	.	1	2	.	4	6	7	4	4	.	2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	27	3
26	.	.	.	3	2	2	3	2	3	5	1	3	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	24	1
27	.	.	.	.	.	1	3	3	2	5	7	1	1	1	2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	23	3
28	.	.	.	.	.	1	3	5	.	4	8	2	3	4	.	4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	28	6
29	1	.	.	.	.	.	2	1	3	1	3	3	6	2	1	2	1	.	.	.	.	.	.	1	.	.	.	.	.	.	.	25	2
30	.	1	.	.	.	.	.	2	3	4	2	5	4	5	1	1	1	2	1	.	.	.	.	.	1	.	.	.	.	.	.	31	2
31	.	.	1	.	1	.	1	.	4	3	4	3	3	6	7	3	4	1	2	.	.	.	.	.	.	.	.	.	.	.	.	39	4
32	.	.	.	1	.	.	.	1	.	1	1	2	1	5	4	6	2	2	1	.	.	.	1	.	.	.	.	.	.	.	.	26	2
33	.	.	.	.	1	.	1	1	.	.	2	3	5	4	3	1	5	1	1	2	.	1	.	.	.	.	.	.	.	.	.	28	3
34	.	.	.	.	1	.	.	.	.	1	.	.	.	5	.	5	8	5	2	1	1	2	.	.	1	.	.	.	.	.	.	30	2
35	.	.	.	.	.	.	.	.	.	1	.	.	1	1	3	3	4	6	10	4	3	3	1	.	.	.	.	.	.	.	.	33	7
36	.	.	.	.	.	.	1	2	.	.	2	.	.	.	6	2	3	3	4	5	1	3	.	2	.	.	.	.	.	.	.	32	2
37	.	.	.	.	.	.	.	1	.	.	.	.	1	.	1	2	6	2	5	2	9	2	2	1	1	1	.	.	.	.	.	27	9
38	.	.	.	.	.	.	.	.	1	1	.	.	2	.	.	1	2	2	2	4	5	4	1	2	2	.	.	.	.	.	.	21	8
39	.	.	.	.	.	.	.	1	.	2	1	.	.	.	1	.	2	4	6	2	2	2	7	1	.	1	1	.	.	.	.	25	8
40	.	.	.	.	.	.	.	.	.	.	.	1	.	.	1	1	.	1	3	1	.	2	3	4	3	2	1	1	.	.	.	17	7
41	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	1	.	.	1	2	.	.	3	4	4	1	1	.	.	.	.	10	8
42	.	.	.	.	.	.	.	.	.	.	.	.	1	1	.	.	.	2	.	.	2	6	2	3	3	2	.	1	.	1	.	9	15
43	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	1	.	1	3	1	3	3	4	3	2	.	.	.	11	11
44	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	1	.	1	2	3	5	1	3	1	2	.	.	.	11	9
45	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	2	1	.	1	1	2	.	1	1	1	.	3	3	3	2	.	15	7
46	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	1	1	1	2	1	1	.	4	4
47	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	2	.	.	.	.	.	1	5	.	.	2	1	.	7	6
48	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	1	1	.	.	2	1	1	1	1	.	.	2	1	6	6
49	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	1	1	.	2	4	1
50	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	.	.	.	.	1	1	.	.	.	.	4	.
51	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	1	.	1	1	.	.	.	1	.	3	2
52	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	.	.	.	.	.	1	1	.	2	2
53	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	1	1	.	.	.	.	.	.	.	.	1	2
54	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	1	.	.	2	.	.	3	1
55	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	1	1	1
56	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	1	.	.	.	.	1	1
57	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	1	.
58	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	.	.	.	2
59	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	1	.
N	1	2	5	8	13	11	22	31	25	31	31	22	30	36	32	32	35	27	35	21	21	22	21	16	10	9	6	5	8	4	3	573	
D	.	.	2	1	3	2	3	1	.	3	4	2	1	.	2	2	6	7	9	5	9	11	10	13	15	16	8	7	4	5	1		154