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Paternal age effect in fibrodysplasia ossificans progressiva[1]

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SUMMARY Analysis by the method of Smith (1972) of birth order and parental age data collected from 38 of 42 patients with fibrodysplasia ossificans progressiva shows a significant paternal age effect. This finding among the sporadically occurring cases would support the proposition that this condition usually arises as a new dominant mutation.

Tünte *et al.* (1967) suggested that there was a paternal age effect in fibrodysplasia ossificans progressiva. We undertook a survey of patients with fibrodysplasia ossificans progressiva (FOP) to assess their clinical status. This study has been reported in detail elsewhere (Rogers and Geho, 1978). The data collected included complete information on parental age and birth order in 38 of 42 patients. This short communication is to report the confirmation of a paternal age effect using the method of Smith (1972).

Methods and results

The ages of the parents at the time of birth of the affected child and the birth order are shown in Table 1. The birth order was based on the number of children born to the mother, regardless of sire. The birth order of FOP patients is shown in Table 2, in comparison with their 'expected birth order' calculated from the 1960 US Census figures, which are derived in the same manner. Of the 42 patients, 38 provided complete data for analysis, by the method of Smith (1972), to determine the presence of direct maternal age, paternal age, and birth order defects. This analysis attempts, through conventional regression techniques, to estimate the effects of maternal age, paternal age, and birth order, after having accounted for linear relationships among these effects. The direct estimates of these effects reach statistical significance when they are greater than twice the standard error of the method.

The estimate of direct maternal age effect d_m was $0{\cdot}77 \pm 2{\cdot}96$ (2 SE). The estimate of direct paternal age effect d_f was $2{\cdot}87 \pm 2{\cdot}82$. The estimate of direct birth order effect d_b was $-0{\cdot}37 \pm 0{\cdot}62$.

Table 1 *Age of parents and birth order*

Patient no	*Father's age at birth of affected child*	*Mother's age at birth of affected child*	*Birth order*
1	27·75	27	1
2	32·08	27·67	2
3	—	—	4
4	33·67	32·75	6
5	23	21·67	1
6	36	22·58	1
7	33·33	25·83	1
8	44·50	39·50	5
9	32·67	31·50	5
10	26·92	23·50	1
11	27·92	28·75	3
12	20·50	19·83	1
13	36·75	28·58	1
14	31·08	32·83	1
15	21·17	17·75	1
16	47·83	36·83	3
17	23·75	16·50	1
18	20·42	17·83	4
19	27·50	21·33	3
20	30·75	28·08	4
21	45·75	36·75	5
22	37·25	25·83	2
23	33	30·50	4
24	—	—	2
25	45	40·50	3
26	29·42	24·92	1
27	—	24·42	2
28	34	27·17	2
29	37·75	26·67	3
30	39·75	39·33	6
31	29·58	25·42	1
32	25·42	23·67	4
33	42·92	35·42	4
34	28·17	27·92	2
35	22·17	19·42	1
36	39·45	37·75	3
37	42·75	35·83	5
38	43·33	40·58	4
39	28·58	28·33	1
40	39·08	32·75	1
41	34·42	29·83	1
42	—	24·50	2

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Table 2 *Birth order*

	Observed	*Expected*
1st born	16	10·53
2nd born	6	9·98
3rd born	6	7·73
4th born	6	4·80
5th born	4	2·59
6th born	2	1·37

Discussion

Birth order and parental age are liable to change with time. Comparing our population, born over many years, to a single year in the US Census data may introduce bias. The year 1960 was chosen as the median year of birth of our sample. However, it is likely that all three parameters, birth order, maternal age, and paternal age will change with time.

The results of direct estimate of paternal age effect shows that a significant effect remained after adjustment by the method of Smith (1972). The estimate d_f was more than twice its standard error, but no significant effect was detected either for birth order or maternal age. These data are set out in comparison with the data of Tünte *et al.* (1967) and US 1960 Census data in Table 3.

In the sample of Tünte *et al.* (1967), the mean age of fathers is considerably older than in our sample and the differences in mean ages of both parents are greater. In addition, the mean paternal age shows a greater departure from the reference population mean than maternal age or birth order. They used a mixed reference population from Denmark, Norway, England, and Japan.

Table 3 *Mean and standard deviation of paternal age, maternal age, and birth order*

	Paternal age	*Maternal age*	*Birth order*
Present study	32·9±7·6 (SD)	29·3±6	2·6±1·7
US Population (1960)	29·8±6·9	28·5±6·8	2·8±1·7
Data of Tünte *et al.* (1967)	37·2±7·2 (SD)	31·7±6	3·2±2

Advanced paternal age has been shown as a factor in a number of dominant conditions arising as new mutants (Jones *et al.*, 1975). The confirmation of a paternal age effect in FOP would support the proposal that it usually occurs as a new mutation. This feature would account for the lack of affected sibs. Low reproductive fitness accounts for the lack of reports of offspring.

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