Paternal Age Effect for Cleft Lip and Palate

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A GENETIC STUDY of cleft lip and palate was carried out in Utah by Woolf, Woolf and Broadbent (1963a). The results support the conclusions of others (Fogh-Anderson, 1942; Fraser, 1955) that cleft lip with or without cleft palate, symbolized by CL(P), is genetically different from isolated cleft palate (CP). Although the propositi used in this genetic study were not collected primarily for this reason, the ages of their mothers were analyzed to determine if a parental age effect was evident. Maternal age was used as the measurement of parental age since comparative vital statistics data are readily available. A slight but statistically significant positive relationship was found between maternal age and CL(P), but not CP (Woolf, Woolf and Broadbent, 1963b). This supports the conclusion of MacMahon and McKeown (1953). Other investigators have presented data showing a significant relationship between maternal age and congenital clefts of the lip and palate (Phair, 1947; Loretz, Westmoreland and Richards, 1961). Fraser and Calnan (1961) have concluded that paternal age is more important than maternal age.

The present paper summarizes the results of a further study designed to determine if the parental age effect observed for the propositi with CL(P) is of paternal or maternal origin.

The CL(P) propositi were ascertained from surgical records in Utah. The ages of the parents at the birth of the propositi were obtained from medical records or at the time family members were interviewed. Ages of the parents were available for 411 of 418 propositi. As a control group, parental ages were obtained for 411 births occurring in the state of Utah during the years 1953-1960. Birth certificates were made available through the courtesy of Mr. John W. Wright, Director of the Bureau of Vital Statistics, Utah State Department of Public Health. The books containing the birth certificates for these years were opened randomly and the ages of the parents recorded. The control group may not be completely appropriate since the propositi were variable in age and were not all born in Utah during this period of time. However, this control group was used in the absence of a more suitable one.

The parental age data were placed in frequency distribution tables with the following classes: under 19, 20-24, 25-29, 30-34, 35-39, and over 40. A comparison of maternal ages is given in table 1. As compared with the control group, there is a deficiency of CL(P) propositi born to younger mothers and an excess born to older mothers. The chi square value calculated from this 6 x 2 contingency table (5 degrees of freedom) is highly significant ($\chi^2 = 16.9$;

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$P < 0.01$). Table 2 shows a similar comparison of paternal ages. The chi square value is also highly significant ($\chi^2 = 18.7$; $P < 0.01$).

Two covariance analyses were then carried out to test the hypothesis that the adjusted mean ages of the parents of the CL(P) propositi do not exceed those for the control groups. In the first analysis (table 3), maternal adjusted mean ages were compared. In the second analysis (table 4), paternal adjusted mean ages were compared. The probability of rejecting the hypothesis if it is indeed true (Type I error) was set at 0.05 in each analysis. On the basis of the F tests, the hypothesis should be accepted in the first analysis and rejected in the second analysis.

The group means before adjustment, adjusted group means, and differences between these means are given in table 5. Before adjustment, the mean ages of the fathers and mothers of the propositi are significantly higher than the mean ages of the respective control groups. After adjustment, the father's mean age is

TABLE 1. A COMPARISON OF THE AGES OF THE MOTHERS OF CL(P) PROPOSITI WITH CONTROLS

Age	Mothers of Propositi	Maternal Controls	Deviation
Under 19	22	52	—30
20-24	123	127	—4
25-29	119	101	+18
30-34	80	76	+4
35-39	49	46	+3
40 and over	18	9	+9
Total	411	411	

TABLE 2. A COMPARISON OF THE AGES OF THE FATHERS OF CL(P) PROPOSITI WITH CONTROLS

Age	Fathers of Propositi	Paternal Controls	Deviation
Under 19	4	8	—4
20-24	63	105	—42
25-29	135	118	+17
30-34	86	91	—5
35-39	74	56	+18
40 and over	49	33	+16
Total	411	411	

TABLE 3. COVARIANCE ANALYSIS. COMPARISON OF MOTHER'S AGES WHEN ADJUSTMENT IS MADE FOR FATHER'S AGES

Source of Variation	Deviations About Regression		
	Degrees of Freedom	Sum of Squares	Mean Square
Total	820	8,899.77	—
Within Groups	819	8,899.10	10.87
Difference for Testing Adjusted Group Means	1	0.67	0.67
$F = 0.67/10.87 = 0.06$			

TABLE 4. COVARIANCE ANALYSIS. COMPARISON OF FATHER'S AGES WHEN ADJUSTMENT IS MADE FOR MOTHER'S AGES

Source of Variation	Deviations About Regression		
	Degrees of Freedom	Sum of Squares	Mean Square
Total	820	11,071.92	—
Within Groups Means	819	11,024.78	13.46
Difference for Testing Adjusted Group Means	1	47.14	47.14*
	F = 47.14/13.46 = 3.50		

*Significant at 0.05 level

TABLE 5. A COMPARISON GROUP OF MEANS BEFORE AND AFTER ADJUSTMENT

Hypothesis: $\mu_1 \leq \mu_2$
Probability of a Type I error: 0.05

	Mothers of Propositi ($\bar{y}_1$)	Maternal Controls ($\bar{y}_2$)	Fathers of Propositi ($\bar{y}_1$)	Paternal Controls ($\bar{y}_2$)	Difference $\bar{y}_1 - \bar{y}_2$	Conclusions
Group Means	27.7	26.6	—	—	+1.1*	Reject hypothesis
	—	—	30.9	29.4	+1.5*	Reject hypothesis
Adjusted Group Means	27.1	27.2	—	—	−0.1	Accept hypothesis
	—	—	30.4	29.9	+0.5*	Reject hypothesis

*$t > +1.64$

still significantly higher, but the mother's mean age is actually lower than the control mean. It is concluded from these analyses that a paternal age effect exists for this anomaly.

DISCUSSION

Clefts can be induced in experimental animals by teratogenic agents (see Fraser, 1962). This observation plus the genetic data (Fraser, 1955; Woolf, Woolf and Broadbent, 1963a) suggests that clefts may be a manifestation of multiple genetic and non-genetic factors disturbing development. Evidence that at least one type of chromosomal abnormality results in cleft lip and palate is the occurrence of these anomalies in some individuals with Trisomy 13-15 syndrome (Lubs, Koenig and Brandt, 1961). Chromosomal aberrations may account for other cases.

Penrose (1962) has demonstrated a paternal age effect for the 21/22 type of Down's syndrome. He proposes that this is due to differential gametic selection with advancing paternal age. Relaxation of selection with advancing paternal age against those gametes containing a genetic or chromosomal mechanism predisposing to CL(P) might also explain the slight paternal age effect noted in this study.

Although differential gametic selection with increasing paternal age is an intriguing hypothesis, alternative hypotheses should be considered as well, such as differential mutation rate or accumulation of mutations with advancing paternal age. At the present, it is not possible to discriminate among these hypotheses.

SUMMARY

1. The ages of the parents at the birth of 411 propositi with cleft lip with or without cleft palate were compared with the ages of parents selected randomly from birth certificates. A parental age effect was demonstrated for this congenital anomaly. The risk of producing a child with this disorder is decreased in younger parents and increased in older parents.

2. Covariance analyses have shown that paternal age is of etiological importance.

3. Differential gametic selection with advancing paternal age is one explanation for the paternal age effect. However, differential mutation rate and accumulation of mutations with advancing paternal age should also be considered.

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