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Facial Morphology as an Indicator of Genetic Predisposition to Cleft Lip and Palate

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It is clear that heredity plays a major role in the genesis of cleft lip and palate, although the mode of inheritance remains unresolved [1–5]. Falconer [6] and Carter [7] have proposed a multifactorial threshold model for inheritance of some congenital diseases including clefts of the lip and palate. Recently this model has received support from several authors, particularly for cleft lip with or without cleft palate [8–11].

Trasler [12] suggested that variation in susceptibility to cleft lip among certain strains of mice might be related to variation in embryonic face shape. A pilot study by Fraser and Pashayan [13] using soft tissue measurements and physio-prints indicated that the parents of children with cleft lip with or without cleft palate tended to have a longer interocular-to-chin dimension, wider dizygomatic diameter, underdeveloped maxillae, fewer ovoid face shapes, and more thin upper lips than the control group. Coccaro et al. [14], using measurements from lateral cephalometric radiographs, concluded that parents of children with cleft lip with or without cleft palate have less convex faces with a tendency toward mandibular prognathism and have shorter vertical and horizontal measurements of the upper face than the control group. Niswander et al. [15], using a smaller sample from the population reported here, showed increased interorbital distance in parents of cleft children.

Collectively, these studies suggest that the parents of children with cleft lip and palate might have some morphological features different from the rest of the population. However, some differences exist in the findings of the studies reported to date. Although they did not directly measure it, Fraser and Pashayan's [13] study did not support the finding of a shorter upper facial height in the experimental group as revealed in the study of Coccaro et al. [14]; rather, they found longer interocular-chin measurements, suggesting the converse. Also the former study did not show the increased interorbital distance as indicated by Niswander et al. [15].

Using a larger sample and controlling for sex and dental status, we attempt here (1) to reexamine whether there are significant features of facial morphology

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characteristic of parents of offspring with cleft lip and/or cleft palate and (2) if so, to investigate whether these features relate to genetic predisposition.

SUBJECTS AND METHODS

The majority of subjects used in the present study were parents of children under treatment or study at the Lancaster Cleft Palate Clinic. All were Caucasian. They consisted of two experimental and one control group: (1) parents of children with cleft lip with or without cleft palate, and CL(P) group; (2) parents of children with isolated cleft palate, the CP group; and (3) parents of children without any deformity, the Lancaster control group. An additional set of control cephalograms was made available through the courtesy of Dr. James Harris from the family studies conducted in the Orthodontic Clinic of the University of Michigan School of Dentistry. This represents a fourth group which we designate the Michigan control group. The number of individuals in each group is shown in table 1.

TABLE 1

SAMPLE SIZE

	Fathers	Mothers
Lancaster control	56	58
CL(P)	92	131
CP	49	75
Michigan control	65	67

Lateral and posterior-anterior cephalograms were available for each individual. Tracings of each film were made on frosted acetate; X and Y coordinates for 65 landmarks recorded on these tracings were transferred to data cards using a Gerber digitizer. Values for all variables were computed from the coordinates of the various landmarks.

The cephalometric techniques differed slightly between Lancaster and Ann Arbor in film-subject-source distances. Even though resultant differences in magnification were arithmetically corrected, variation in technique represents a potential source of bias. In addition to possible technical biases, there likely are ethnic differences which may affect facial morphology and complicate interpretation of our results. It is difficult to assess precisely the degree of ethnic difference between the groups. However, the Ann Arbor sample is entirely Caucasian and on the basis of surnames quite heterogeneous as expected in a large university community. In excess of half the Lancaster sample is of German or Swiss extraction.

Twenty measurements were recorded for each subject based on the reference points and lines listed in table 2 (see also fig. 1).

All bilateral landmarks have been midplaned. This procedure was carried out by drawing the profiles and marking the landmarks on each profile. The midplane for each landmark is taken as the point midway between each of the bilateral landmarks. The location of these reference points and lines and the 20 variables derived from them are shown in figure 1.

Initially, all distributions were inspected for evidence of multimodality and tested for normality. The four different groups were compared by performing t tests on each variable within each sex. Although this method establishes the significance of differences in mean values between groups for each variable, it provides no information on the underlying biological components in the original variables or on the interrelationship of groups. For

TABLE 2

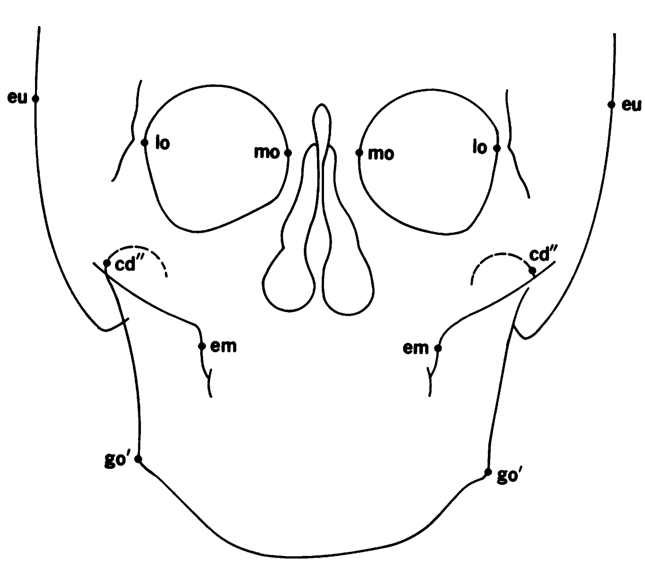
REFERENCE POINTS AND LINES

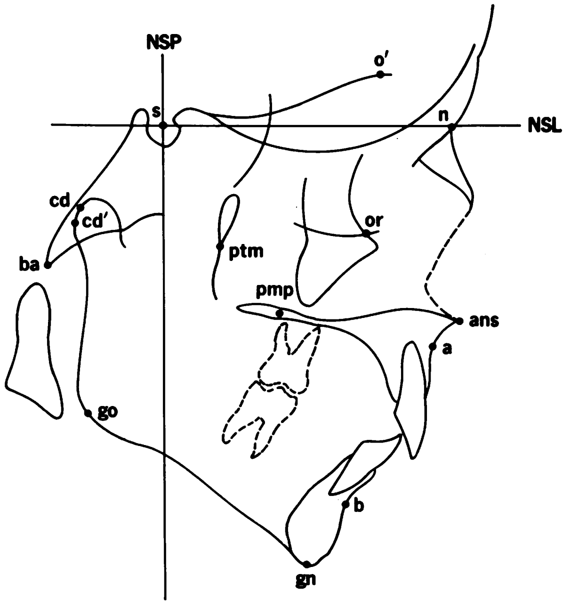
Symbol	Definition
a	A point. Most posterior point on anterior profile of maxilla.
ans	Anterior nasal spine. Most anterior point on profile of maxilla.
b	B point. Most posterior point on anterior profile of symphysis.
ba	Basion. Most posterior-inferior point on profile of clivus at anterior margin of foramen magnum.
cd	Condylion. Most superior-posterior point located on profile of mandibular condyle.
cd′	Most posterior point located on profile of condyle.
cd″	Most lateral point on condyle on frontal view.
em	Ectomolare. Most medial point on lateral contour of maxilla.
eu	Euryon. Most lateral point on cranial outline.
gn	Gnathion. Most anterior-inferior point on profile of mandibular symphysis.
go	Gonion. Most posterior-inferior point (halfway around curve) between posterior and inferior border of mandible.
go′	Gonion in frontal view. Located at gonial angle midway between outlines of mandibular ramus and body.
lo	Lateral orbitale. Most lateral point on orbital rim.
mo	Medial orbitale. Most medial point on orbital rim; this landmark drawn at superior limit of lacrimal fossa and does not include medial margin of this fossa.
n	Nasion. Point at junction of nasal and frontal bones; most anterior point on nasal-frontal suture.
NSL	Nasion-sella line. Line joining n and s.
NSP	Nasion-sella perpendicular line. Line perpendicular to nasion-sella line through s.
o′	Orbital roof. Point on profile of cerebral surface of orbital roof farthest from nasion-sella line.
or	Orbitale. Most inferior point on profile of orbital rim.
pmp	Posterior midpalate. Vertical midpoint in profile tracing of hard palate in region of second permanent molar.
ptm	Pterygo-maxillary fissure. Most inferior point on profile of pterygo-maxillary fissure.
s	Sella. Center of sella turcica.

this purpose, multivariate techniques including factor analysis and Q-mode similarity correlation combined with principal-component analysis were employed.

For factor analysis, correlation matrices were obtained for each sex from pooled samples of all three Lancaster groups (Lancaster control, CL[P], and CP). The first seven principal components obtained from the correlation matrix were rotated by means of the oblique rotation for simple loadings [16]. Factor scores for each individual were determined, and mean factor scores for each of the three cleft types for each sex were calculated and compared using t tests.

Distance analyses on two different data sets were done using a Q-mode similarity correlation [17] combined with principal-component analyses. One of the sets consisted of the CL(P), CP, Lancaster control, and Michigan control groups. Analysis of this data set provides information on the interrelationship of study groups and control groups and on the difference between the two control groups. The other data set consisted of the CL(P), CP, Lancaster control, severe CL(P) (24 fathers and 35 mothers of children with bilateral cleft lip and palate), and mild CL(P) group (23 fathers and 37 mothers of children with unilateral cleft lip only). The latter two groups were derived from the total CL(P) group. This analysis tests whether severity of the cleft shows a positive association





VARIABLES

1. eu-eu
2. lo-lo
3. mo-mo
4. cd″-cd″
5. em-em
6. go-go

VARIABLES

7. n-s
8. cd-gn
9. n-gn
10. o′-NSL
11. or-NSL
12. ans-NSL
13. pmp-NSL
14. go-NSL
15. ptm-NSP
16. a-NSP
17. cd′-NSP
18. n-s-ba angle
19. a-n-b angle
20. cd′-go-gn angle

FIG. 1.—Landmarks identified on frontal and lateral cephalograms and the variables derived from them

with change in facial characteristics, as might be predicted if facial features reflected genetic predisposition or liability in the sense of Falconer [18].

The Q-type correlations have been employed in numerical taxonomy [19–23]. Whereas the usual (R-type) correlation involves pairs of characters over n individuals or groups, Q-type correlations relate pairs of individuals (groups) over a set of standardized characters. Rohlf and Sokal [24] suggested that correlation should be employed whenever most of characters used were measurements of different parts of an organism. Sokal and Sneath [17] also recommended correlation as the best overall technique to compute similarity for numerical taxonomy.

We also computed several other measures of resemblance for the groups under study. These included Penrose's size and shape components of the coefficient of racial likeness [25] and Mahalanobis's generalized distance [26]. None gave results any more enlightening or interpretable than the correlation and principal-component analysis presented here.

The correlations between groups were obtained by Spearman's sum of variables method:

$$r_{pq} = \frac{Bpq}{\sqrt{N_p + 2Wp}\sqrt{N_q + 2Wq}},$$

where Bpq is the sum of all correlations between members of group p with group q, Wp and Wq are the sums of all correlations within members of the first and second group, respectively, and N_p and N_q are the number of members in each group. (More detailed explanations of this procedure have been published [17, 21].) The final results were obtained by reducing the coefficient matrix to a two-dimensional map depicting the relationship through the projection onto principal components, in which the latent vectors were normalized so that

$$\Sigma c_{ir}{}^2 = lr,$$

where lr is the rth latent root and c_{ir} is the rth normalized latent vector.

RESULTS

The mean, standard deviation, and standard error of each of the 20 characters for the Lancaster control group are listed by sex in table 3. Table 4 gives the difference between the means of the Lancaster control and the other groups.

CL(P)–Lancaster Control

Fathers. Of the 20 variables, seven show significant differences. In all dimensions relating to craniofacial width except eu-eu, the CL(P) means are greater than the Lancaster control means. The differences, however, are significant only for the lateral orbital (lo-lo) dimension. Four dimensions expressing facial height, namely, n-gn, or-NSL, ans-NSL, and pmp-NSL, are significantly smaller in the CL(P) group than in the control group. The a-n-b angle is significantly smaller in the CL(P) group than in the control group, indicating reduced convexity of the facial profile in the cleft group. This difference is significant at the .01 level. The cd′-go-gn angle is also significantly less in the CL(P) group than in the control group.

Mothers. The CL(P) and Lancaster control groups are significantly different in only three dimensions: mo-mo, go′-go′, and pmp-NSL. As found for fathers, five of

TABLE 3

MEANS AND STANDARD ERRORS OF LANCASTER CONTROL GROUP

	Fathers		Mothers	
	Mean	SE	Mean	SE
1. eu-eu	156.83	0.879	151.49	0.722
2. lo-lo	98.22	0.527	95.12	0.385
3. mo-mo	25.96	0.281	24.13	0.296
4. cd″-cd″	127.67	0.765	120.48	0.627
5. em-em	62.74	0.538	59.33	0.458
6. go′-go′	105.45	0.752	95.12	0.657
7. n-s	74.57	0.502	70.69	0.404
8. cd-gn	128.63	0.822	117.14	0.787
9. n-gn	133.45	1.137	120.77	0.771
10. o′-NSL	14.30	0.239	13.98	0.237
11. or-NSL	29.44	0.297	27.36	0.308
12. ans-NSL	58.41	0.364	53.55	0.428
13. pmp-NSL	53.06	0.351	48.44	0.328
14. go-NSL	93.93	0.769	83.69	0.697
15. ptm-NSP	14.06	0.392	13.97	0.386
16. a-NSP	65.99	0.671	61.80	0.522
17. cd′-NSP	22.69	0.481	20.22	0.440
18. n-s-ba	128.24	0.740	130.18	0.683
19. a-n-b	2.86	0.379	2.95	0.407
20. cd′-go-gn	125.34	0.958	123.06	0.774

NOTE.—56 fathers, 58 mothers.

the six dimensions expressing craniofacial width are larger in the CL(P) mothers than in the control mothers. For those dimensions which express facial height, the CL(P) mothers (again like the fathers) tend to be smaller than the controls. Only the pmp-NSL difference is significant. Likewise, the a-n-b angle is less in the CL(P) group than the control group, but the difference is not significant.

CP–Lancaster Control

In both sexes, three of the 20 measurements show significant differences but not for the same variables. However, the differences generally tend to be in the same direction for all variables. The trend of the differences between the CP and control group is similar to that seen in the CL(P)-control comparisons. Thus, those measurements reflecting facial width tend to be larger in the CP groups, while at the same time the upper face is reduced in height. A tendency for relative mandibular protrusion in the CP parents is indicated by their smaller a-n-b angles

Lancaster Control–Michigan Control

Statistically significant mean differences are seen in 16 of the 40 comparisons. Although those which reach statistical significance are somewhat different in the two sexes, there tends to be agreement between sexes in the direction of the differences. It is of interest to note that in both mothers and fathers, outer orbital distance is less in the Lancaster control than in the Michigan control. Similarly,

TABLE 4

Differences between Means of Groups

	CL(P)–Lancaster Control		CP–Lancaster Control		CP–CL(P)		Michigan Control–Lancaster Control	
	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers	Mothers
1. eu-eu	—0.796	—1.417	—0.987	—1.798	—0.191	—0.382	0.553	0.270
2. lo-lo	2.167**	0.716	0.952	0.595	—1.215	—0.121	1.684*	1.938**
3. mo-mo	0.806	0.709*	0.175	0.612	—0.631	—0.098	—0.173	—0.631
4. cd″-cd″	0.322	0.808	0.508	0.865	0.186	0.057	1.916	2.155*
5. em-em	0.963	0.948	1.442	1.573**	0.479	0.625	1.028	1.425*
6. go′-go′	0.448	1.858*	0.369	2.373**	—0.079	0.515	0.170	2.354**
7. n-s	0.793	0.818	1.173	0.669	0.380	—0.149	1.478*	0.560
8. cd-gn	0.062	1.255	1.814	2.320*	1.753	1.064	—1.832	—0.743
9. n-gn	—2.949*	—0.810	—1.355	0.299	1.594	1.109	—5.249**	—0.506
10. o′-NSL	—0.040	0.409	0.025	0.547	0.065	0.137	—0.192	0.817*
11. or-NSL	—0.930**	—0.233	—0.624	—0.104	0.305	0.129	—0.831*	—0.217
12. ans-NSL	—1.449*	—0.218	—0.665	0.404	0.785	0.531	—1.432*	—0.788
13. pmp-NSL	—1.340**	—0.940*	—1.030*	—0.727	0.310	0.213	—2.027**	—1.210*
14. go-NSL	—0.421	—0.044	0.465	—0.362	0.886	—0.318	0.400	—1.048
15. ptm-NSP	0.712	0.232	2.119**	0.440	1.406**	0.209	1.842**	0.731
16. a-NSP	0.190	1.006	1.354	0.555	1.164	—0.451	1.068	0.165
17. cd′-NSP	—0.773	—0.058	—1.419	—0.480	—0.646	—0.423	—0.597	—1.146*
18. n-s-ba	1.127	—0.547	—1.420	—0.335	—2.548**	0.212	1.548	—0.973
19. a-n-b	—1.479**	—0.494	—1.146*	—0.686	0.334	—0.192	—0.192	0.222
20. cd′-go-gn	—2.460*	0.341	—1.284	1.200	1.175	0.860	—6.964**	—2.293*

* $P \leqq .05$.
** $P \leqq .01$.

upper face height is significantly greater in the Lancaster control than in Michigan. Thus two of the findings relating to the CL(P) groups are duplicated in the Michigan control.

Factor loadings, eigenvalues, and the percentage of variance explained are presented for all fathers and mothers in tables 5 and 6, respectively. In general, there

TABLE 5

FACTOR LOADINGS FOR FATHERS*

	I Facial Height	II Ramus Height	III Inter-orbital Distance	IV Cranial Base Angle	V Gonial Angle	VI Facial Convexity	VII Vertical Orbital Position
1. eu-eu	...	...	...	...	...	...	...
2. lo-lo	...	...	—.76	...	...	...	...
3. mo-mo	...	...	—.92	...	...	...	...
4. cd″-cd″	...	...	...	...	...	...	...
5. em-em	...	.24	—.23	...	—.28	...	.23
6. go′-go′	...	...	...	...	...	...	...
7. n-s	...	...	...	...	...	...	...
8. cd-gn	...	.61	...	.28	...	—.27	...
9. n-gn	.74	...	...	...	.25	...	...
10. o′-NSL	...	...	...	...	...	...	.91
11. or-NSL	.59	...	...	...	...	...	...
12. ans-NSL	.78	...	...	...	...	...	...
13. pmp-NSL	.69	.23	...	—.24	...	...	...
14. go-NSL	.27	.63	...	...	—.34	...	...
15. ptm-NSP	—.29	.29	...	—.48	...	...	...
16. a-NSP	—.29	.42	...	—.24	...	.31	...
17. cd′-NSP	...	.26	...	.89	...	...	...
18. n-s-ba	...	—.27	...	.74	...	...	...
19. a-n-b	...	...	...	...	...	.98	...
20. cd′-go-gn	...	...	...	...	.91	...	...
Eigenvalue	3.84	3.01	1.92	1.43	1.28	1.16	0.99
% Variance	19.20	34.30	43.90	51.00	57.40	63.20	68.20

* Values less than .2 are eliminated.

is good correspondence between the sexes for the factors obtained and the portion of total variance explained.

The differences of mean factor scores between all possible pairs of groups were tested by t tests. Not surprisingly, the results tend to parallel closely those of the univariate analysis. Significant differences occur only between CL(P) and control fathers for factor I (facial height), factor III (interorbital distance), and factor VI (facial convexity). We observe similar trends for the CL(P) mothers (facial height and convexity decreased, upper face width increased) when compared to the control mothers, but the differences are not significant. With the exception of maternal factor V (facial convexity), the CP groups tend to be intermediate between the CL(P) and control groups in those factors relating to facial height, width, and convexity.

The Q-mode correlations for all possible pairs of the four major groups are listed

TABLE 6

FACTOR LOADINGS FOR MOTHERS*

	I Facial Height	II Facial Depth	III Gonial Angle	IV Inter-orbital Distance	V Facial Convexity	VI Vertical Orbital Position	VII Cranial Base Angle
1. eu-eu	...	...	...	...	...	...	...
2. lo-lo	...	...	...	.76	...	...	...
3. mo-mo	...	...	...	.86	...	...	...
4. cd″-cd″	...	...	...	...	...	...	...
5. em-em	...	...	...	...	...	...	...
6. go′-go′	...	...	...	...	...	...	...
7. n-s	...	.80	...	.26	...	...	.20
8. cd-gn	.36	.30	...	...	—.59	...	...
9. n-gn	.84	...	.25	...	...	...	...
10. o′-NSL	...	...	...	...	...	.99	...
11. or-NSL	.60	...	...	...	...	—.31	...
12. ans-NSL	.71	...	...	...	.30	...	...
13. pmp-NSL	.66	...	—.26	...	...	...	—.25
14. go-NSL	.33	.21	—.44	...	—.35	...	...
15. ptm-NSP	...	.68	...	...	...	...	—.38
16. a-NSP	...	.78	...	...	...	...	...
17. cd′-NSP	...	...	...	...	—.20	...	.73
18. n-s-ba	...	...	...	...	...	...	.85
19. a-n-b	.21	...	...	...	.88	...	...
20. cd′-go-gn	...	...	.86	...	...	...	...
Eigenvalue	3.90	2.91	1.96	1.49	1.15	1.09	0.96
% Variance	19.50	34.00	43.90	51.30	57.10	62.60	67.40

* Values less than .2 are eliminated.

TABLE 7

Q-MODE CORRELATION COEFFICIENTS

	CONTROL					
	Michigan	Lancaster	CL(P)	CP	CL(P) SEVERE	CL(P) MILD
Michigan control	...	.495	.738	.647	...	...
Lancaster control	.571	...	.374	.586	.518	.149
CL(P)	.756	.765	...	.711	.846	.796
CP	.708	.813	.857	...	.638	.546
CL(P)-severe	...	.693	.876	.654	...	.613
CL(P)-mild	...	.647	.910	.751	.831	...

NOTE.—Fathers above diagonal, mothers below.

in table 7. Also included are the correlations for the severe and mild CL(P) subgroups with the other Lancaster groups. In general the correlations between groups are higher for mothers than for fathers, confirming the greater diversity of fathers' groups found in other analyses.

The first two principal components of the matrices considering the major groups

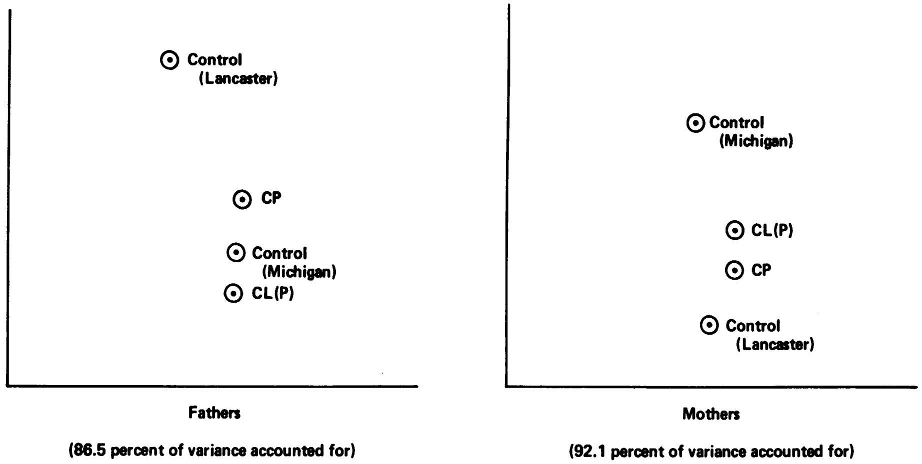


FIG. 2.—Group constellations of first two principal components of Q-mode similarity correlation matrix in fathers and mothers.

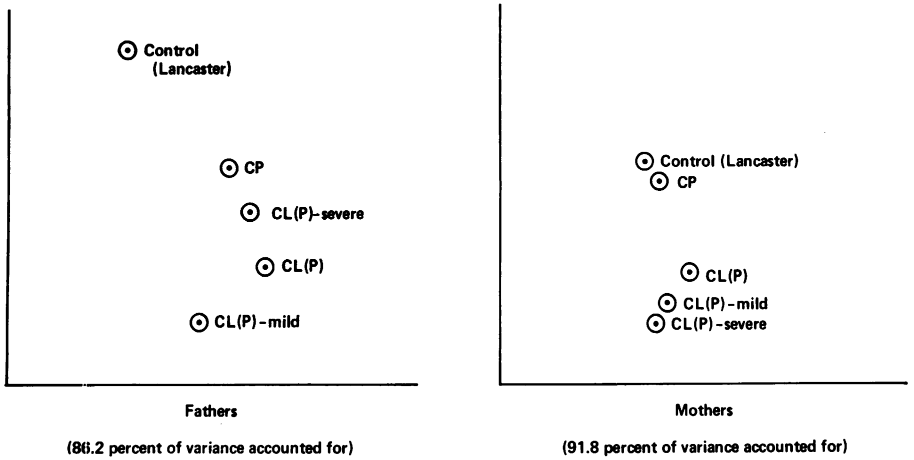


FIG. 3.—Group constellations of first two principal components of Q-mode similarity correlation matrix of five groups including the severe and mild cleft lip group in fathers and mothers. Mild = unilateral cleft lip without cleft palate; severe = bilateral cleft lip with cleft palate.

only are plotted in figure 2 for fathers and mothers separately. In figure 3 the first two principal components for each sex were plotted considering the most mild, most severe, and total CL(P) groups. The Michigan control group is not considered in the analysis.

DISCUSSION

The present findings for CL(P) are consistent with those of Coccaro et al. [14]. Thus, we find that parents of children with cleft lip and palate have less facial convexity, a tendency toward relative mandibular prognathism, and shorter vertical dimensions in the upper face. We do not find a decrease in horizontal dimensions of the upper face as reported in the earlier study. The decreased facial convexity was also a finding of Fraser and Pashayan [13]. These authors also reported significantly increased bizygomatic width and a higher proportion of individuals with wider interocular measurement in the experimental group. However, the mean interocular dimension was not significantly greater than that of the control group. In this regard, it is of interest to note that increased interorbital distance has been noted previously in children affected with cleft lip and palate [27–31]. Neither the present data nor that of Coccaro et al. [14] support the increased facial height of CL(P) parents reported by Fraser and Pashayan [13]. On the contrary, decreased facial height is seen, suggesting that this may be a chance finding in the Montreal study or may be related to the different techniques used.

Taken together, these three studies seem to offer strong evidence for an association between parental face shape and the occurrence of CL(P) among offspring. However, some caution is in order. In examining table 4, it is clear that the differences between the Michigan and Lancaster control groups are at least as great as those between the Lancaster control and cleft groups. The Michigan-Lancaster differences are presumably due to ethnic, socioeconomic, or other differences between the groups as well as to possible uncorrected technical variation in the radiographic procedures. The large Michigan-Lancaster difference is also apparent in the multivariate analysis of the data presented graphically in figure 2. For both sexes, the distance between the Michigan and Lancaster controls is as great or greater than that between the different groups obtained from Lancaster. We also pointed out earlier that several of the significant mean differences between Michigan and Lancaster are in the same dimensions for which the CL(P) group differs from the Lancaster control. One interpretation of this finding would be that it is the Lancaster control group which is unusual rather than the CL(P) group. However, the similarity of our results to those of the earlier studies tends to refute this.

Another consideration concerns the degree of severity of the cleft. According to the threshold model, the more severe the defect, the greater the liability. Hence we would hypothesize that the biggest deviations in face shape should occur among the parents of children with the most severe defect. Figure 3 demonstrates that this is not true. When the cases are subdivided into severe (bilateral CLP) and mild (unilateral CL) and plotted on the first two principal components of their Q-mode correlation matrices, for fathers the most severe cases are closer to the controls than the mild cases. For mothers there is no difference in distance from controls between the mild and severe cases. We repeated these analyses using midparent values rather than treating sexes independently. Under an additive model, we might expect a truer picture of the relationship using midparent values; however, no improvement was noted in the patterns of distance between groups.

By the multifactorial threshold hypothesis, we expect the groups to be ranked in the order of control, unilateral CL, and bilateral CLP, although it is not likely that the differences based on such crude severity rankings would be large.

When the means of the 20 variables were ranked, within sex, for these groupings (40 rankings), 11 were found to be in the order predicted while we expect 13 or 14 in this order by chance. However, when the specific measurements involved were examined, we found that for each sex the means for both medial and lateral orbital distances are in the order and direction predicted. The means of the variables reflecting upper face height did not consistently rank in the order predicted by the threshold model. Therefore, of those variables previously found significant, all those associated with interorbital distance support the hypothesis (i.e., four of four), while only one of six rankings for upper face height is in the proper order. Having specified the direction of the difference between study and control with the previous analyses, we would expect five of 10 rankings to be in this order by chance. Thus, in none of the analyses have we been able to find direct support for a genetic interpretation of the differences observed between the CL(P) and control groups. On the other hand, considering the magnitude of the differences involved and our relatively small samples, the power of these tests must be small and hence this can hardly be interpreted as strong negative evidence.

We are presently engaged in similar studies among unaffected identical cotwins of CL(P) and CP probands in the hope of obtaining more definitive results.

SUMMARY

The consistency of the present data with the findings of two previous studies suggests that there are detectable alterations in facial morphology in parents of children with cleft lip and palate. Such differences are certainly quite small, probably no greater than those which might ordinarily be found between two ethnically diverse samples obtained in geographically separate areas of the United States. The interpretation of these findings is not clear. We could obtain no direct support that these changes relate to or are part of a multifactorial genetic predisposition.

REFERENCES

1. Chung CS, Ching GHS, Morton NE: A genetic study of cleft lip and palate in Hawaii. II. Complex segregation analysis and genetic risks. *Am J Hum Genet* 26:177–188, 1974
2. Fogh-Andersen P: *Inheritance of Harelip and Cleft Palate.* Copenhagen, Busck, 1942
3. Woolf CM, Woolf RM, Broadbent TR: A genetic study of cleft lip and palate in Utah. *Am J Hum Genet* 15:209–215, 1963
4. Carter CO: The inheritance of common congenital malformations. *Prog Med Genet* 4:59–84, 1965
5. Fujino H, Tashiro H, Sanui Y, Tanaka K: Empirical genetic risk among offspring of cleft lip and cleft palate patients. *Jap J Hum Genet* 12:62–68, 1967
6. Falconer DS: *Introduction to Quantitative Genetics.* New York, Oliver & Boyd, 1960
7. Carter CO: The inheritance of congenital pyloric stenosis. *Br Med Bull* 17:251–254, 1961
8. Fraser FC: Hereditary disorders of the nose and mouth, in *Proceedings 2d International Congress of Human Genetics,* Rome, September 1961, vol 3, 1963, pp 1852–1855

9. Fraser FC: The genetics of cleft lip and cleft palate. *Am J Hum Genet* 22:336–352, 1970
10. Woolf CM: Congenital cleft lip: a genetic study of 496 propositi. *J Med Genet* 8:65–83, 1971
11. Bhatia SN: Genetics of cleft lip and palate. *Br Dent J* 132:95–103, 1972
12. Trasler DG: Pathogenesis of cleft lip and its relation to embryonic face shape in A/J and C57BL mice. *Teratology* 1:33–43, 1968
13. Fraser FC, Pashayan H: Relation of face shape to susceptibility to congenital cleft lip: a preliminary report. *J Med Genet* 7:112–117, 1970
14. Coccaro RJ, D'Amico R, Chavoor A: Craniofacial morphology of parents with and without cleft lip and palate children. *Cleft Palate J* 9:28–38, 1972
15. Niswander JD, Dutson H, Johnston MC, Mazahari M: Interorbital distance as an indicator of genetic predisposition for cleft lip and palate. Preprinted abstracts, general meeting of the International Association for Dental Research, Chicago, March 1971
16. Jennrich RI, Sampson PF: Rotation for simple loadings. *Psychometrica* 31:313–323, 1966
17. Sokal RR, Sneath PHA: *Principles of Numerical Taxonomy*. San Francisco, Freeman, 1963
18. Falconer DS: The inheritance of liability of certain diseases, estimated from the incidence among relatives. *Ann Hum Genet* 29:51–76, 1965
19. Michener CD, Sokal RR: A quantitative approach to a problem in classification. *Evolution* 11:130–160, 1957
20. Sokal RR, Michener CD: A statistical method for evaluating systematic relationships. *Univ Kansas Sci Bull* 38:1409–1438, 1958
21. Morishima H, Oka H: The pattern of interspecific variation in the genus *Oryza*: its quantitative representation by statistical methods. *Evolution* 14:153–165, 1960
22. Rohlf FJ: Correlated characters in numerical taxonomy. *Syst Zool* 16:109–126, 1967
23. Corruccini RS: Size and shape in similarity coefficients based on metric characters. *Am J Phys Anthrop* 38:743–754, 1973
24. Rohlf FJ, Sokal RR: Coefficients of correlation and distance in numerical taxonomy. *Univ Kansas Sci Bull* 45:3–27, 1965
25. Penrose LS: Distance, size and shape. *Ann Eugen* 18:337–343, 1954
26. Rao CR: *Advanced Statistical Methods in Biometric Research*. New York, Wiley, 1952
27. Psaume J: À-propos des anomalies faciales associées a des divisions palatines. *Sem Hop Ann Chir Plast* 2:3–11, 1957
28. Moss ML: Hypertelorism and cleft palate deformity. *Acta Anat* (Basel) 61:547–557, 1965
29. Dixon DA: Abnormalities of the teeth and supporting structures in children with clefts of lip and palate, in *The Causes and Natural History of Cleft Lip and Palate*, edited by Drillien CM, Ingram TTS, Wilkinson EM, Edinburgh, E & S Livingstone, 1966, pp 178–205
30. Aduss H, Pruzansky S, Miller M: Interorbital distance in cleft lip and palate. *Teratology* 4:171–182, 1971
31. Dahl E: Craniofacial morphology in congenital clefts of the lip and palate. *Acta Odontol Scand [Suppl]* 28:1–167, 1970