Cleft Lip and Cleft Palate: A Genetic Study

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A fundamental approach to any human hereditary problem is concerned with identifying those individuals in a population who carry a gene for a given affliction but who do not clearly demonstrate the described phenotype for that gene. This implies that accurate definition of phenotype must precede all other considerations.

Many families display a definite hereditary tendency to have cleft lip and palate individuals but do not show a specific mode of inheritance for these conditions. One reason for this discrepancy is probably an inadequate designation and definition of the phenotype for a clefting gene or genes. Such varying phenotypes may result from either or both of the following conditions: a) minor anatomical discrepancies in the area of the lip and palate which represent modification of gene action by environment or other genes in the genome, and b) genetic heterozygosity in which an individual displays minor anatomical discrepancies which designate him as a "carrier" of the gene for cleft lip and palate.

The purpose of this study was to identify and to determine the prevalence of a number of orofacial variations which are possible incomplete manifestations of gene action. This would permit better definition of the phenotype of cleft lip and palate and thereby help to clarify any role these microforms might play in delineating a specific mode of inheritance.

Experimental Procedure

METHOD AND MATERIALS. A total of 11 families with more than a single occurrence of cleft lip with or without cleft palate, hereafter referred to as CL, CLP, and/or isolated cleft palate, hereafter referred to as CP, was studied. A total of 138 individuals was examined, representing first and second degree relatives and first cousins of the proband. If there was at least one other affected parent, sibling, or first cousin of the proband, the family was included for study. The purpose of selecting families with such closely related affecteds was to minimize the pos-

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sibility of selecting a family with multiple sporadic (that is, nongenetic) occurrences. Pedigrees were constructed through interviews of parents or close relatives, using standard techniques. All reported clefts among relatives were verified by individual examination, hospital records, and photographs.

Once the pedigree was constructed, specific individuals were selected to be examined clinically and radiographically. This selection was made for individuals who had no overt clefts, but who, according to the pedigree, and the proposed genetic hypothesis, had a high probability for being carriers of a gene for clefting. For example, an affected grandfather and grandson would make mandatory a careful examination of the father—or mother as the case may be—for the genetic hypothesis. Similarly, the presence of affected first cousins dictated examination of the common blood relatives (aunts, uncles).

Observations. The following orofacial variations were looked for in the selection of subjects: a) bifid uvula, b) raphé of the upper lip, c) notching of the alveolus, d) mandibular lip pits, e) commissural lip pits, f) asymmetrical nasal shape, and g) malformed or missing central lateral incisors. Selection of these tissue variations was based upon anatomic location in relation to the cleft, embryologic association both in time and space, and previously reported association with the clefting process (*8, 10, 11, 13, 19, 20, 21, 25, 26*). The conditions were noted and recorded on 35 millimeter Kodachrome film.

In addition to the previously listed orofacial variations, hypertelorism was also looked for as an incomplete manifestation of gene action (*7, 23*). Both ocular and orbital hypertelorism were evaluated, the former by soft tissue measurements and the latter by measurement on roentgen cephalometric PA headplates. The following measurements were made: a) innercanthal distance, b) outercanthal distance, c) intercorneal distance, d) skeletal interorbital distance, and e) occipital-frontal circumference. Canthal index was used to indicate interocular distance and circumference-interorbital index was used to indicate interorbital distance.[1] Skeletal interorbital measurements were made using the landmarks described by Gerald and Silverman (*14*).

In order to obtain comparative interorbital measurements, a group of 71 Caucasians of both sexes with a negative history of familial clefting, and ranging in age from 4 to 22 years, was selected from patients and students at the Indiana University School of Dentistry. These measurements were compared with those obtained from the unaffected individuals in the cleft lip and palate families. These results were further

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[1] $\text{Canthal index} = \dfrac{\text{inner canthal}}{\text{outer canthal}} \times 100.$

$$\text{Circumference-interorbital index} = \frac{\text{inner canthal}}{\text{occipital-frontal circumference}} \times 100.$$

compared to normal values for the canthal and circumference-interorbital indices published by Gunther (*15*) and the orbital measurements of Currarino and Silverman (*7*) and Johr (*17*), and Morin and others (*22*).

STATISTICAL ANALYSIS. In evaluating the frequency of the occurrence of each orofacial variation, a chi-square contingency test was used to compare the frequency of the various conditions with that reported for the general population.

The statistical analysis used in determining significant differences between ocular and orbital measurements of the control group and the noncleft relatives took into account the variables of age, sex and the relationship to the proband (coefficient of relationship). The observed orofacial variations and ocular and orbital measurements were coded, placed on punch cards, and analyzed with an IBM 7040 computer.

A preliminary analysis of the ocular and orbital measurements showed that many of the measurements were highly correlated and that a meaningful analysis between measurements for the relatives of the proband in families with a history of clefting and those for the control group could not be obtained if each of the measurements was treated as a separate variable. In addition, many of the orbital and ocular measurements vary with age and possibly with the sex of the individuals (*7, 16, 17*). Therefore, it was necessary to include the age and sex variables when comparing the two groups. Multivariate procedures were considered most appropriate in analyzing such data. Specifically, a step-wise multiple regression analysis (*18*)[2] was used, with group membership (that is, the control group and the group of relatives of the proband) as the dependent variable while the seven ocular and orbital measurements were used as the independent variables. Since the dependent variable is dichotomous (yes or no for group membership), this procedure is identical to a discriminant analysis for two groups.

In order to correct for differences attributable to the effects of age and sex on these measurements (independent variables) within the two groups, age, sex, and age-squared were used as control variables. The rationale for the use of age-squared as a control variable was based on the fact that these measurements do not change linearly with age but rather increase at a decreasing velocity resulting in a curvilinear curve which reaches a plateau at a specific age (*7, 17*).

Results

Figures 1, 2, and 3 show the pedigree symbols and the pedigrees of each of the families studied. Families are referred to by the initials of the proband, as indicated in the figures.

Table 1 summarizes the frequency of lip and palatal defects noted in these 11 families. There were eight probands with cleft lip or cleft lip

[2] BIMED-03R step-wise regression program, UCLA, Los Angeles, California.

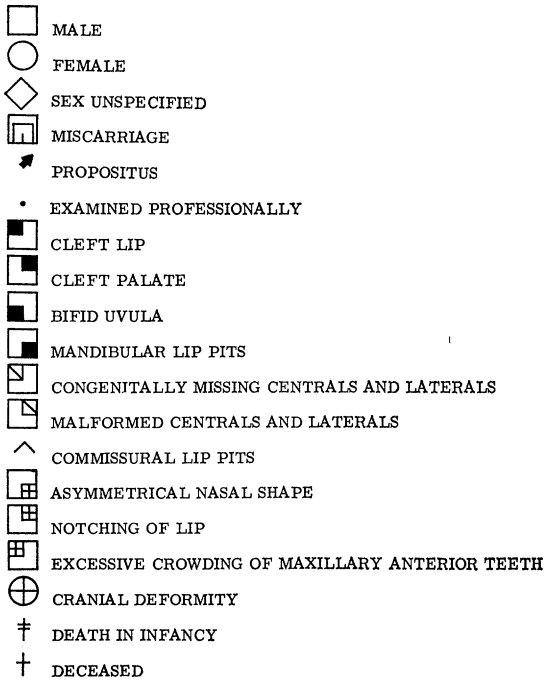

FIGURE 1. Pedigree symbols.

and palate and three with cleft palate. A total of 20 additional affected individuals in the eight families with CLP probands was noted; three with CL, eight with CLP, and nine with CP. In the three remaining families in which the proband had CP, there were four additionally affected individuals, three with CP and one with CLP.

Table 2 summarizes the frequency of occurrence of the various orofacial variations observed in the relatives of cleft lip and palate probands. The data are grouped according to relationship of relative to the proband.

The frequency of bifid uvula in the relatives of probands was compared to the reported frequency of bifid uvula in the general population (*21*); the difference was significant. It is apparent then that the sample of 11 families included in the present study was not a random sample of the general population with regard to the prevalence of bifid uvula. An equal distribution of the trait among males and females was noted (see sex ratio, Table 2). Interestingly, four of the 11 families studied contained one individual with bifid uvula and two families had more than one.

Seven individuals, occurring in two of the 11 families of this study (excluding probands), demonstrated mandibular lip pits, making a total of nine affected individuals. The occurrence of mandibular lip pits in the general population is rare; Červenka and others (*5*) estimate it at

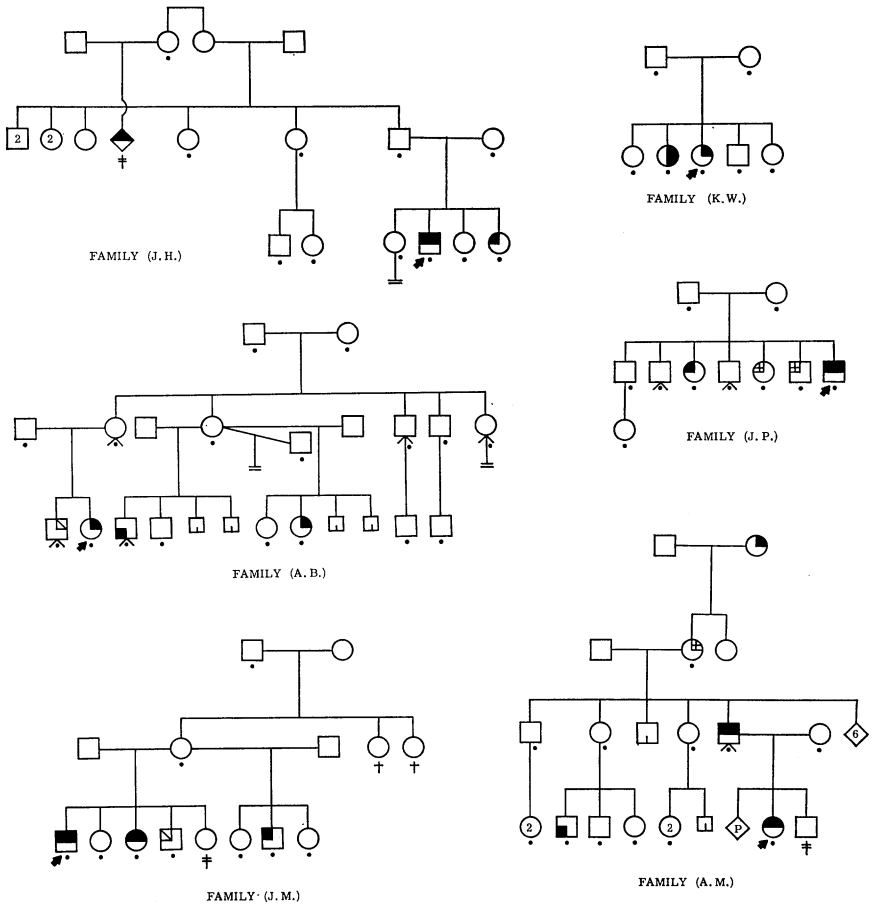

FIGURE 2. Family pedigrees for J. H., K. W., A. B., J. P., J. M., and A. M. (See legend, Figure 1.)

1:75,000–1:100,000. Six of the individuals affected with mandibular lip pits in this study belonged to one family (family D. C.).

When the frequency of commissural lip pits in this study was compared to that observed by Baker,[3] no significant difference was found. Seven of the 11 families (63.7%) demonstrated this type of lip pit, and males were affected approximately twice as often as females.

Three individuals had congenitally missing maxillary lateral incisors. Two of the three individuals had siblings with cleft lip and cleft palate. The difference between the frequency in this study and that which has been reported in the general population, 1.05% (*5*), was found to be significant at the 5% level. Since this is a condition which has been reported to be a dominant trait itself, the significance of this finding is

[3] Personal communication, Lt. Col. B. Baker, D.D.S., M.S.D., Chanute Air Force Base, Illinois.

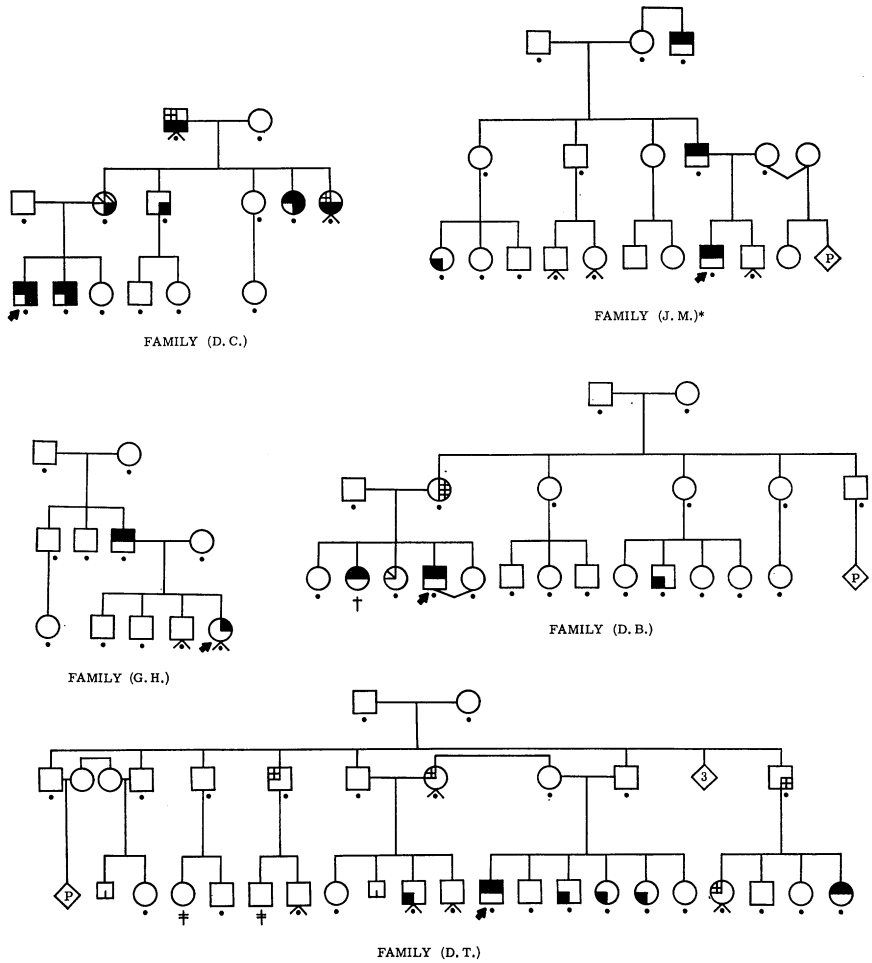

FIGURE 3. Family pedigrees for D. C., J. M., G. H., D. B., and D. T. (See legend, Figure 1.)

TABLE 1. Type of clefting defect observed in the 11 families of probands with cleft lip and cleft palate (CLP), cleft lip alone (CL), and cleft palate alone (CP).

type of cleft in proband	*number of probands*	*type of cleft in affected relatives*			*total number affecteds*
CLP	8	8	3	9	28
CP	3	1	0	3	7

questionable. In addition, Woolf and coworkers (*27*) have published data indicating that missing maxillary lateral incisors is not a microform of CLP.

Of the three individuals in the present study who had malformed

TABLE 2. The frequency of occurrence of facial and oral defects in relatives of probands with cleft lip and/or cleft palate. For each defect, the number of normal (N) and affected (A) individuals is shown according to relationship to proband (see headings) and by sex ratio.

discrepancy	*parents, siblings*		*grandparents, aunts, uncles*		*first cousins*		*double first cousins*		*sex ratio, affected*		*total number individuals*		*total number families*
	N	A	N	A	N	A	N	A	F	M	N	A	
bifid uvula (a)	44	3	35	2	33	4	2	1	5	5	114	10	4
mandibular lip pits	55	2	34	5	39	0	3	0	4	3	131	7	2
commissural lip pits	50	7	34	5	34	5	1	2	6	13	119	19	7
notching of alveolus (a)	47	0	37	0	37	0	3	0	0	0	124	0	0
raphé of upper lip (a)	46	1	36	1	37	0	3	0	2	0	122	2	2
asymmetrical nasal shape (a)	46	1	36	1	37	0	3	0	1	1	122	2	2
malformed maxillary central & lateral incisors (a, b)	45	2	37	0	33	1	3	0	2	1	109	3	3
congenitally missing maxillary central & lateral incisors (a, b)	42	3	30	0	34	0	3	0	2	1	109	3	3
excessive crowding of maxillary anterior segment (a, b)	43	2	26	4	33	1	3	0	5	2	105	7	3

(a) Cleft lip and cleft palate relatives were not included.
(b) Edentulous relatives were not included.

TABLE 3. Frequency of facial and oral discrepancies in relatives of probands with cleft lip and cleft palate when grouped together. For each defect, the number of normal (N) and affected (A) individuals is shown according to relationship to proband.

grouping	*parents*		*siblings*		*individuals with more than one manifestation*	*totals*	
	N	A	N	A		N	A
bifid uvula, commissural lip pits	32	4	39	25	4	71	29
bifid uvula, cleft lip and palate	40	8	56	36	—	96	44
bifid uvula, cleft palate	20	2	26	15	—	46	17
commissural lip pits, bifid uvula, cleft lip and palate	45	6	41	31	6	86	37

TABLE 4. Step-wise regression analysis on combined data of the control group and the relatives of probands. A history of clefting membership was used as the dependent variable and age, age-squared, sex, ocular and orbital distances as the independent variables.

variable	*partial regression coefficient (b)*	*standard error of regression coefficient*	*increase in R^2 in per cent*	F
age	0.002	0.001	14.66	4.7889**
circumference interorbital index	0.000	0.000	5.03	15.3896**
sex	0.112	0.068	1.31	2.7037
innercanthal	−0.000	0.000	1.22	0.0491
skeletal interorbital	−0.000	0.000	0.91	5.1120*
canthal index	−0.000	0.000	0.67	4.0163*
age-squared	−0.000	0.000	0.49	1.0228
outercanthal	NI†	—	—	0.0020
occipital-frontal circumference	NI	—	—	0.0389
intercorneal	NI	—	—	0.0984
total			24.29	

† Not included in equation.
* Significant at 0.05 level of confidence.
** Significant at 0.01 level of confidence.

maxillary lateral incisors, none belonged to the same family. This frequency was not statistically different from that in the general population, 2.7% (*21*).

Two families (D. B. and A. M.) presented a single individual with a raphé of the upper lip, one of whom also had an asymmetrical shape of the nares (family D. B.). Both of these individuals were parents of

at least one child with cleft lip and cleft palate. One other individual had an extreme discrepancy in symmetry of the nares but with no apparent oral deformity (family D. T.). He was both father and uncle of children affected with cleft lip and cleft palate. Finding these three subjects with such visible defects tends to support the concept that individuals may carry the gene for cleft lip and palate without demonstrating a cleft. This hypothesis is further strengthened by the fact that all three of these individuals have had at least one child with cleft lip and cleft palate.

Notching of the maxillary alveolar process, as described by Fukahara and Saito (*13*), was observed in none of the 138 subjects examined. The two individuals who had a raphé of the upper lip had no apparent alveolar involvement but were parents of children with cleft lip and cleft palate.

Examination of Single Facial and Oral Discrepancies for Specific Hereditary Patterns. Since commissural lip pits, mandibular lip pits, and bifid uvula displayed a high prevalence among individuals in the families of this study, an examination for a specific mode of inheritance was attempted for each entity.

One family (D. C.), in which six of the seven subjects with mandibular lip pits were observed, demonstrated an autosomal dominant mode of inheritance for this condition. Furthermore, by including cleft lip and palate in the pedigree, the occurrence of the triad of mandibular lip pits, cleft lip, and cleft palate, seemed to be due to a single dominant gene with variable expressivity. This confirms the reports of Van der Woude (*26*) and Červenka and others (*6*). Commissural lip pits appeared to be an autosomal dominant trait with reduced penetrance. However, the sex ratio of this trait was approximately two-to-one in favor of males (Table 2).

No definite hereditary pattern for bifid uvula was found. In one family (D. T.) the condition appeared to be transmitted as a dominant trait with reduced penetrance, but occurrence in the other families was sporadic.

Examination of Multiple Facial and Oral Discrepancies for Specific Hereditary Patterns. As previously noted, some of the proposed "microforms" did not make a discernible hereditary pattern alone. An attempt was made to make combinations of the most commonly occurring traits with cleft lip and cleft palate and to analyze these conditions as though they were all manifestations of clefting gene action.

As indicated in Table 3, four different combinations were attempted. When a segregation analysis was performed upon the affected and unaffected individuals in the sibling population, a 39-25 normal-to-affected ratio was observed for bifid uvula and commissural lip pits, while a 41-31 normal-to-affected ratio was demonstrated for the triad of

commissural lip pits, bifid uvula, and cleft lip and triad of commissural lip pits, bifid uvula, and cleft lip and cleft palate. The similarity of these attained ratios suggested autosomal dominance with approximately 80% penetrance. When this mode of inheritance was applied to the individual pedigrees, autosomal dominance with reduced penetrance was apparent in each instance.

When bifid uvula was considered together with cleft lip and cleft palate, a 56:36 normal-to-affected ratio was observed, while the grouping of the bifid uvula and isolated cleft palate gave a normal-to-affected ratio of 26:15. Both of these ratios suggested autosomal dominance with approximately 70% penetrance.

Ocular and Orbital Measurements. One hundred sixty-six individuals contributed complete information. Of these, 66 were from the control group.

Table 4 summarizes the results obtained in the step-wise regression analysis. Considering all of the variables measured in this study, 24.29% of the total measurement variation was accounted for by the independent variables. The increase in R^2 for each independent variable is the increased reduction in the proportion of variation in the dependent variable due to the addition of the independent variable.

Differences between the two groups were significant for three of the ocular and interorbital measurements even when these independent variables were regressed upon age. The canthal index was significantly smaller in the cleft group than in normals. The circumference-interorbital index was significantly larger in relatives of probands and the skeletal interorbital distance was significantly smaller in relatives of probands than in normals. Collectively, these results suggested that relatives of cleft lip and cleft palate probands may be somewhat hypoteloric rather than hyperteloric as was originally hypothesized.

The significant differences in these measurements between the two groups could not be related to the degree of genetic relationship between the relative and proband. Such a correlation to the degree of relationship is commonly used as the true test of hereditability and it is possible this observed lack of correlation is related to the size of the population studied.

Discussion

In previous studies of cleft lip and palate, the relatives of affected individuals have been largely ignored. Partially as a result of this a variety of modes of inheritance for the two conditions have been proposed. It should be noted that the possibility of "gene carriers" for the cleft lip-palate trait has never been adequately explored. Recently, Fukahara and Saito (*13*) have demonstrated possible "microforms" or incomplete manifestations of cleft lip and cleft palate in Japanese populations.

In order to evaluate such "microforms", a deliberately biased sample was used in the present study. Only families displaying a familial tendency for cleft lip and/or cleft palate were selected for study, thereby increasing the probability of finding individuals carrying "clefting genes" but who are not cleft themselves.

The various soft tissue discrepancies observed were found to be highly suggestive as criteria for "gene carriers" in at least three families (D. C., D. B., and A. M.). In each of these families, an individual who was in a direct line of descent for the clefting trait, but who had no cleft himself, had one or more of the orofacial discrepancies looked for in this study.

One mother (in family D. B.) exhibited a raphé of the upper lip coincident with an extreme asymmetry of the nostril of the same side. She bore two cleft lip and palate children. This subject clinically resembled a number of patients presented by Fukahara and Saito (*13*) as gene carriers for the clefting trait. The paternal grandmother in family A. M. had notching of the lip and had a cleft son and granddaughter. These findings strengthen Fukahara and Saito's observations on gene carriers for the cleft lip and cleft palate trait.

In two other families (J. H. and J. P.), the cephalometric headplates revealed unusual variations in the nasal floor (a notching of the floor in the other of two affecteds in family J. H.) and in the nasal septum and walls (hypoplastic and displaced inferior concha in the father of two affecteds in family J. P.). Perhaps these findings are related to the clefting process but the relationship is unknown.

Since the minor facial and oral abnormalities mentioned in this study were not observed in each expected instance, it seems reasonable to conclude that there may be additional significant orofacial alterations which are manifestations of the clefting process.

After reviewing the literature, it was difficult for the authors to believe that mandibular lip pits, cleft lip, and cleft palate were inherited independently of each other. The results of this study strengthen the hypothesis of Van der Woude (*26*) and Curtis and Walker (*8*): that the triad of cleft lip, cleft palate, and mandibular lip pits appears to be due to a single dominant gene with variable expressivity. The most recent publication of Červenka and associates (*6*) supports the single locus hypothesis for this triad, although those authors suggested that family heterogeneity observed with respect to both type of cleft and sensitivity of gene expression may be due to modifying genes at other loci or even different mutant alleles at the same locus.

Fogh-Andersen (*11*) and Fraser (*12*) have proposed that CL,CLP is a different genetic entity from CP. Thus, if a proband had CP, affected relatives were also much more likely to have CP than CL,CLP. Furthermore, both investigators suggested that most cases of CL,CLP were due to the same gene. If one considers bifid uvula as a mild form of

CP, the foregoing theories are supported by data accumulated in the present study (Table 1). In families where the proband had both cleft lip and cleft palate, the relatives were afflicted significantly more often with CL,CLP than with CL alone. When families exhibited a proband with CP, the preponderance of CP to CL,CLP in relatives was three to one.

If bifid uvula is a true manifestation of a palatal cleft, it should follow the hereditary pattern of CP. In this study, the combination of CP and bifid uvula produced an inheritance pattern which resembled an autosomal dominant gene with 70% penetrance. It should be noted, however, that in two of the three families with a CP proband (A. B. and K. W.) the proband did not show any orofacial discrepancies. The transmission of the bifid uvula trait contained no apparent sex-linkage or sex limitation and this agreed with Meskin and associates (*20*) who have proposed that, as clefts of the palate become less severe, sex affinity for the female decreases; since bifid uvula is considered the mildest manifestation of CP, no female sex predilection was expected and none was observed.

When bifid uvula and CL,CLP were considered as a single trait, an autosomal dominant hereditary pattern was again noted. This finding somewhat confounds the relationship of bifid uvula to the CL,CLP trait which is considered separate from CP. Perhaps the occurrence of bifid uvula may be due to the interaction of two or more genes and no single mechanism is readily discerned.

Commissural lip pits appeared to be occurring independently of the condition of cleft lip, or cleft palate, or both, and demonstrated an autosomal dominant pattern by itself. This confirmed the findings of Everett and Wescott (*10*).

Since the use of selected facial and oral discrepancies as incomplete manifestations of cleft lip and/or cleft palate only partially clarified the hereditary hypothesis of lip and palate clefting, comparison of these results with reports of other authors is warranted. The results presented here demonstrate that CL,CLP in a small number of families exhibits autosomal dominance with varying degrees of penetrance. This is not in accord with the studies of Fogh-Andersen (*11*) and Fraser (*12*) but does conform with Rank and Thomson's observations (*24*).

The interorbital measurements obtained from clinical and radiographic examination are interesting. A number of investigators (*2, 9, 23*) have observed individuals with cleft lip and cleft palate who exhibited hypertelorism. It has been suggested that the simultaneous occurrence of these anomalies indicates developmental retardation of the cranio-facial structures, and may be attributed to gross discrepancies in growth pattern of the sphenoid bone (*1, 2*).

One family (D. B.) displayed overt hypertelorism among the parents and siblings and in this family the condition itself appeared to have a

dominant mode of inheritance, a situation already described by Bojlén and Brems (4). However, this finding was an exception for the families studied, and, in fact, the data analysis showed the canthal index and skeletal interorbital distances to be significantly smaller in relatives of children affected with CL,CLP. The meaning of these findings is not clear at this time, but if subsequent studies prove the difference to be real, it might ultimately provide a basis for selecting "gene carriers". However, the significant differences in the ocular and orbital measurements between the two groups could not be related to the degree of relationship to the proband, the ultimate test of hereditability.

Assuming that hypotelorism was present in relatives of cleft individuals, an explanation is very difficult. The developmental and anatomical discrepancies of hypotelorism include premature closure of the metopic suture with hypoplasia of the ethmoid region. These factors produce associated changes in the frontal bone and medial portions of the orbit. The orbits then assume an oval or egg shape with the longer axis extending upward and medially from the inferolateral margins. The medial orbital walls are almost vertical with loss of the usual medial convexity. Careful examination of the headplates of the individuals in this study did not show any deviation of the medial convexity of the orbital wall from the normal.

Summary

Eleven families with multiple occurrences of cleft lip and palate (138 individuals) were examined for various oral-facial discrepancies which might be used as incomplete manifestations of clefting gene action. The discrepancies looked for included bifid uvula, mandibular lip pits, commissural lip pits, raphé of the upper lip, notching of the alveolus, asymmetrical nasal shape, congenitally missing and malformed maxillary central and lateral incisors, and excessive crowding of the anterior segment of the maxillary arch. In addition, ocular and orbital measurements were compared between the relatives of cleft individuals and a control group of similar age. In this instance, a total of 166 individuals was compared. The ocular measurements suggested that relatives of individuals with clefts may be hypoteloric, instead of hyperteloric as hypothesized. When the oral-facial variations were used as evidence of manifestation of gene action, the pedigrees of these 11 families strongly suggested an autosomal dominant mode of inheritance with reduced penetrance for both cleft lip and palate and isolated cleft palate traits.

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