Abnormal Morphology of the Soft Palate: II. The Genetics of Cleft Uvula

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Cleft uvula was recently reported to be present in one of every 75 individuals examined in an adult Caucasian population of 9,701 individuals (*9*). This frequency of occurrence is approximately 30 times greater that that of the more severe, but apparently related defect: isolated cleft of the secondary palate (*2, 5, 12*). Nevertheless, despite the apparent similarity between these malformations, their etiologic and genetic relationships have not been clearly investigated. Moreover, since the frequency of occurrence of these two defects appears to differ markedly and, since it has been hypothesized that cleft uvula is a minor manifestation of severe cleft palate (*1, 11*), the need to compare these relationships becomes even more apparent.

Therefore, this study was designed primarily to investigate the genetic pattern of the transmission of cleft uvula in order to compare this with the transmission of severe cleft palate. A secondary purpose of the investigation was to determine the prevalence of severe cleft palate and other congenital anomalies in the families of cleft uvula probands (individuals with cleft uvulae).

Methods and Materials

All probands demonstrating cleft uvula in a previous frequency study (*9*) were contacted for participation in this study. Fifty-four cleft uvula probands were selected. All of these probands who agreed to participate had at least one parent residing within 30 miles of our facilities who was available for examination. Forty-one subjects had uvulae bifurcated up to one-fourth of the total length, eight subjects had uvulae bifurcated from one-fourth to three-fourths of the total length, and five showed bifurcations of from three-fourths to the total length of the uvula. The families of these probands who were available for examination included 101 parents and 97 siblings.

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A control group was comprised of students randomly selected from those who were examined by the University of Minnesota Health Service during a specific period of time. This group was composed of 49 individuals and 93 parents and 107 siblings who were also available for examination. All examinations were carried out as previously described (*9*). All uvulae were directly visualized during the examination.

Results

Of the 101 parents of probands examined, a total of 19 (18.9%) demonstrated various degrees of cleft uvula as shown in Table I. A total of 25% of the maternal parents and 12.2% of the paternal parents exhibited some form of uvular cleft. The frequency of cleft uvula for the 97 siblings examined is shown in Table II. Eighteen siblings from 10 different families were found to demonstrate cleft uvula, a frequency of 18.6%.

The parents and siblings of the probands were also examined for congenitally missing or pegged permanent maxillary lateral incisors. Fourteen individuals with congenitally missing permanent maxillary lateral incisors were found. Two cases of osteogenesis imperfecta were also noted in one family.

TABLE 1. Prevalence of cleft uvula in parents of probands demonstrating cleft uvula.

No. of Proband Families / Sex of Probands	Maternal	Paternal	Prevalence of Cleft Uvula in Parents Observed
31 / 18 ♂ 13 ♀	normal	normal	0/62
11 / 5 ♂ 6 ♀	cleft	normal	11/22
2 / 1 ♂ 1 ♀	cleft	not observed	2/2
3 / 2 ♂ 1 ♀	normal	not observed	0/3
5 / 3 ♂ 2 ♀	normal	cleft	5/10
1 / 1 ♀	not observed	cleft	1/1
1 / 1 ♂	not observed	normal	0/1
Total 54 / 30 ♂ 24 ♀	13/52 (25%)	6/49 (12.2%)	19/101 (18.9%)

TABLE 2. Proband siblings demonstrating cleft uvula according to family size and incidence of parental uvula.

		No. of families	No. of sibs / family	Sibs with cleft uvula
normal parents	siblings of female probands	6	1	0
		4	2	0
		2	3	0
		1	4	0
		1	5	2 ♂
	siblings of male probands	10	1	2 ♀ 1 ♂
		7	2	0
		1	3	1 ♂
	total	32		6/57 (10.5%)
one parent with cleft uvula	siblings of female probands	3	1	0
		2	2	1 ♀
		1	3	0
		1	4	4 ♀
		1	5	3 ♂
		1	8	2 ♂ 1 ♀
	siblings of male probands	4	1	0
		1	2	0
		1	3	0
		1	4	1 ♂
	total	16		12/40 (30.0%)
Total sibs of all probands		48		18/97 (18.6 %)

Each proband family was also questioned regarding the presence of cleft lip and/or cleft palate in the not present but immediate family (grandparents, parental sibs, and their families). Five cases of cleft lip or cleft lip-cleft palate combinations and five cases of isolated cleft palate were noted in this biased sample.

Among the control group of 49 families, four cleft uvulae were noted; that is, one of the four had a relative with cleft palate. None of the families in the control group had more than one member affected with cleft uvula.

Discussion

The high frequency of cleft uvula in parents and siblings of affected probands strongly suggests the presence of hereditary factors in the

transmission of this congenital defect. In some cases, both the parents and the siblings demonstrated clefts of the uvula. In other cases, the parents but not the siblings showed this defect and, in still other cases, the siblings but not the parents were affected.

If a trait is genetically determined and follows an autosomal dominant inheritance pattern, 50% of the children of the affected heterozygote parent should demonstrate that trait. However, if there is limited penetrance, the manifestation of the trait in the parent or the offspring may be considerably reduced and still follow the criteria required for autosomal dominant inheritance.

If it is hypothesized that cleft uvula is inherited as an autosomal dominant trait with about 40% penetrance, it could be expected that of 50 families having a cleft uvula proband, 40% or 20 parents would demonstrate a similar defect. Analogous findings should also be observed in the other children of these parents.

In this study, a total of 101 proband parents were examined and 19 individuals (18.9%) demonstrated cleft uvula. Similarly, 18 of the 97 siblings examined (18.6%) also demonstrated cleft uvula. Both of these findings are compatible with the hypothesized 20% incidence produced by autosomal dominance with 40% penetrance.

If cleft uvula is a true palatal cleft, it should follow the hereditary pattern of severe cleft palate. Fogh-Anderson (*5*) and Fraser (*6*) have both reported that severe isolated cleft palate is a simple autosomal dominant trait with limited penetrance and some sex limitation to the female. The mode of transmission hypothesized for cleft uvula in this study is compatible with this mode of transmission reported for severe cleft palate. It should be pointed out, however, that no sex limitation has been demonstrated in the transmission of cleft uvula.

Fogh-Anderson (*5*) also reported a 1.8% frequency of cleft palate in the siblings of affected probands with normal parents. In this study, 10.5% of the siblings of cleft uvula probands with normal parents also demonstrated cleft uvula. Furthermore, Fogh-Anderson (*5*) reported a 17% frequency of cleft palate in the siblings of probands with cleft palate parents. A similar analysis of our results indicated that 30% of the siblings of cleft uvula probands with parents similarly affected also demonstrated cleft uvula. The increases in cleft uvula frequency noted in both instances in this study may be due to the small sample size when compared to the Fogh-Anderson data.

Other possible methods of cleft uvula transmission aside from autosomal dominance must also be considered. One conceivable entity is conditioned dominance in which the gene may act as either a recessive or a dominant. Cleft lip and cleft lip-cleft palate have been reported to be transmitted in this manner when inherited (*5*). The absence of a pure 50% frequency figure called for in the autosomal dominant pattern could be explained in this manner if cleft uvula is carried in this form of

genetic transmission. It is also possible that cleft uvula may be due to the interaction of two or more genes and that no single mechanism can accurately be singled out.

The role of environmental agents should also be considered in the induction of cleft uvula, however, in this study no provision was made to elicit extrinsic pre-natal factors common to the individuals demonstrating cleft uvula. On the other hand, one cleft uvula was noted to have resulted post-natally during a tonsillectomy operation.

When the families of probands were examined for congenital anomalies other than cleft uvula, an apparent increased prevalence of defects was noted. At the time of examination of the parents and siblings of the probands, the family was questioned regarding anomalies in other relatives. An affirmative statement to these inquiries resulted in a special attempt to observe the other anomalies. Therefore, due to this biased sampling procedure, the frequency of other congenital anomalies must be based on the estimated number of relatives of the 54 families observed. Using such a projection, this phase of the study included nearly 1,500 individuals (*10*). Based on this population total, the five cases of cleft lip and cleft lip-cleft palate observed are slightly higher than the usual reported frequency of one in 500 to 1,000 individuals (*5*). Isolated cleft palate was noted in five individuals also, with this frequency markedly higher than the usual reported frequency of one in 2,000–3,000 individuals (*2, 5, 12*).

Only the 252 probands, parents, and siblings were examined for pegging or aplasia of the permanent maxillary lateral incisor. Seventeen of these individuals demonstrated this trait giving a frequency of 6.13% as compared to a normal frequency of 1.78% (*8*).

The presence of two cases of osteogenesis imperfecta in these family studies poses another interesting question. Many syndromes or groups of congenital malformations, such as osteogenesis imperfecta, include severe cleft palate as one of the malformations. In some instances, however, cases have been reported who demonstrated many of the diagnostic features of particular syndrome without the expected severe cleft palate. In view of the lack of emphasis that has previously been placed on uvular examination and the potential etiologic relationship of severe cleft palate and cleft uvula, such cases should be examined carefully for uvular clefts. This concept is further substantiated by the reports of several workers who have observed the presence of cleft uvula in several other syndromes which normally manifest severe cleft palate (*3, 4, 7, 13*).

Summary

The parents and siblings of 54 cleft uvula probands were examined for cleft uvula and certain other congenital malformations. Nineteen of the 101 parents (18.9%) and 18 of 97 siblings (18.6%) demonstrated this anomaly. The observed frequency of this defect in the parents and

siblings of the affected probands is consistent with a transmission pattern of autosomal dominance with limited penetrance similar to that reported for isolated cleft palate. An apparent increase in the frequency of isolated cleft palate and pegging or aplasia of the permanent maxillary lateral incisor was also noted in this population.

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