Missing Maxillary Lateral Incisors: A Genetic Study

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A genetic study was carried out in Salt Lake City, Utah, to determine whether an anomaly of the maxillary lateral incisor is a microform of cleft lip or palate [1]. It was noted that the frequency of an anomaly of the lateral maxillary incisor is similar in the close relatives of propositi with cleft lip with or without cleft palate and control families consisting of parents and children. It was also observed that the frequency of facial clefts in the relatives of propositi with unilateral or bilateral missing permanent maxillary incisors is similar to that found in the general population. It was concluded from these results that a maxillary incisor anomaly is not a microform of cleft lip or cleft palate. Although the primary objective of the study was to investigate the microform status of an incisor anomaly, the study led to the collection of data that could be used to investigate the etiologic importance of genetics for anomalies of the maxillary lateral incisors. The purpose of this paper is to present these data.

MATERIALS AND METHODS

Using roentgenologic evidence as the basis of diagnosis, propositi with either unilateral or bilateral missing permanent maxillary lateral incisors were obtained from dental files in Salt Lake City, Utah. The study was sanctioned by the Salt Lake District Dental Society. Fieldworkers visited the homes of the propositi and obtained information on hypodontia of the permanent dentition, with specific emphasis on the maxillary lateral incisor, in the following relatives of 103 propositi: sibs, parents, grandparents, aunts, uncles, and first cousins. This often required several visits to the same home and/or interviews with different members of the family. None of the relatives was given a roentgenologic or clinical examination. Questionable cases were checked by using dental records, when available. Either an absent or a peg-shaped maxillary lateral incisor was considered an anomaly. The propositi are classified as to type of incisor anomaly in table 1.

The study was carried out in a population that is predominantly Morman and therefore relatively stable in the area. Strong family ties and an interest in genealogical records facilitate genetic research among Mormon people. However, regardless of the advantages of the population for studies of this type, the difficulty of determining whether a member of an older generation had a missing or peg-shaped permanent maxillary lateral incisor is often insurmountable. Genetic studies of this type lack reliability for members of previous generations and for those of remote relationship to the propositi. The goal of the present study was to obtain reliable data for the parents and sibs of the propositi and those segments of the families reported as having one or more individuals with a dentition anomaly. This procedure leads to an underreporting of cases in second- and third-degree relatives of the propositi.

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TABLE 1

PROPOSITI CLASSIFIED BY TYPE OF MAXILLARY INCISOR ANOMALY

Anomaly of Permanent Maxillary Lateral Incisor	Female	Male	Total (Frequency)
Missing bilateral	43	13	56 (54.4%)
Missing unilateral	17	6	23 (22.3%)
Missing one side, peg shaped other side	14	10	24 (23.3%)
Total	74	29	103

A total of 187 control families consisting of parents and children were obtained from Salt Lake City, Utah. An attempt was made to select them from the same socioeconomic level as the families of the propositi. The control families were studied in the same manner as the families of the propositi. In both the families of the propositi and the control families, children too young for permanent dentition were excluded from the study. No data were gathered on the third molars.

RESULTS

In 71 (69%) of the 103 families of the propositi, at least one of the specified relatives had a missing or peg-shaped permanent maxillary lateral incisor. This is a minimum value because of assumed underreporting of cases, especially in second- and third-degree relatives. The familial nature of the anomaly is shown by its relatively high frequency in the first-degree relatives of the propositi (see table 2). The frequency in their parents and sibs is 17.7%, as compared with 2.8% in the controls. The value for the controls, which apparently reflects the frequency in the general population, is slightly lower than the ones (3.3% and 3.0%) found by Grahnén [2] in two different Swedish groups. It is slightly higher than the value (1.78%) found by Meskin and Gorlin [3] in a group of students at the University of Minnesota.

Dominant inheritance with reduced penetrance has been proposed as one of the genetic mechanisms leading to hypodontia [2, 4]. When a trait is due to a completely penetrant autosomal dominant gene, the expected frequency of affected individuals

TABLE 2

TYPES OF ANOMALIES OF PERMANENT MAXILLARY LATERAL INCISOR OCCURRING IN PARENTS AND SIBS OF 103 PROPOSITI AND 187 CONTROL FAMILIES

Anomaly of Propositi	No. of Individuals	Unilateral Peg shaped (%)	Bilateral Peg shaped (%)	Unilateral Missing (%)	Bilateral Missing (%)	Missing and Peg shaped (%)	Total (%)
Missing bilateral	253	0.8	2.8	2.0	11.9	2.0	19.4
Missing unilateral	119	0.8	0.8	6.7	6.7	0.0	15.1
Missing and peg shaped	90	3.3	2.2	2.2	6.7	2.2	16.7
Total	462	1.3	2.2	3.2	9.5	1.5	17.7
Control families	918	1.0	0.6	0.1	1.1	0.0	2.8

is 50% in both the parents and sibs of the propositi. Although the frequency value will be reduced if the gene shows reduced penetrance, the value should be similar in parents and sibs if factors affecting penetrance are acting similarly in both generations. The data support the hypothesis that at least part of the genetic component consists of a dominant gene (or genes) showing reduced penetrance. The frequencies of an incisor anomaly in the parents and sibs of the propositi are 20.0% ($N = 195$) and 15.7% ($N = 267$), respectively. The difference is not statistically significant ($.30 > P > .20$). Evidence that the dominant gene responsible is not on the X chromosome comes from the observation that affected fathers transmit the condition equally to sons and daughters. Selecting families where the fathers of the propositi had the anomaly, and excluding the propositi in the calculations, results in values of 40.9% ($N = 22$) and 41.7% ($N = 35$) for the respective frequencies of affected sons and daughters.

The majority of the 71 families of the propositi with a positive history of an incisor anomaly attest to the etiological importance of a dominant autosomal gene. Representative pedigrees are shown in figures 1, 2, 3, and 4. These pedigrees also demonstrate that a gene causing an incisor anomaly tends to show reduced penetrance and variable expressivity. Missing or peg-shaped maxillary incisors are present both unilaterally and bilaterally in various members of these pedigrees. Although reduced penetrance, dominant mutation, or nongenetic factors may account for sporadic cases, it is also plausible that incisor anomalies in some families have a recessive or polygenic mode of inheritance. The 39 families with only the propositi reported as having an incisor anomaly as well as six families with only sibs affected support this conclusion.

The following results also support the hypothesis [2, 4] that a genetic relationship exists between a missing and a peg-shaped maxillary lateral incisor: (1) individuals are frequently encountered with a missing and a peg-shaped maxillary lateral incisor, as shown by 24 of the 103 propositi (table 1); (2) the frequency of the peg-shaped condition is increased in the first-degree relatives of the propositi (see table 2); and (3) families are encountered with the missing and peg-shaped conditions occurring in different members (fig. 3). Grüneberg [5] has demonstrated that a polygenic system determines the size as well as the presence or absence of the third molar in mice. A model can be imagined for man where in the presence of a dominant gene, genetic modifiers determine whether the maxillary lateral incisor is peg shaped or absent.

Genetic modifiers may account for much of the variation in expression among affected members of the same family and in different families. It is also likely that different alleles and mutations at different loci contribute to the variation. In some families (fig. 1), the affected individuals tend to have bilateral missing maxillary incisors. In other families, the affected individuals tend to be unilateral (right or left) for this condition, while in still others, both bilateral and unilateral cases are found (fig. 2). The affected individuals in some families often have peg-shaped maxillary lateral incisors (fig. 3). The tendency for concordance as to type of anomaly between propositi and family members is especially evident for bilateral missing lateral incisors, suggesting that a dominant gene segregating in some families acts in a very specific manner. For example, the propositi with bilateral missing maxillary

lateral incisors had 84 relatives who were either bilateral or unilateral for a missing maxillary lateral incisor; 64 (76%) of these were bilateral cases like the propositi. The propositi who were unilateral for a missing maxillary lateral incisor had 55 relatives who were either bilateral or unilateral for this tooth anomaly; only 29 (52%) of these relatives were bilateral for this missing tooth. The difference is statistically significant ($P < .01$). These data are summarized in table 3.

DISCUSSION

Based on the results of clinical and genetic investigations carried out in Sweden, Grahnén [4] concluded that "as there seems to be a connection between different regions, one cannot do a genetic study in a special region of the dentition, but must study the whole permanent dentition." The results of the present study do not com-

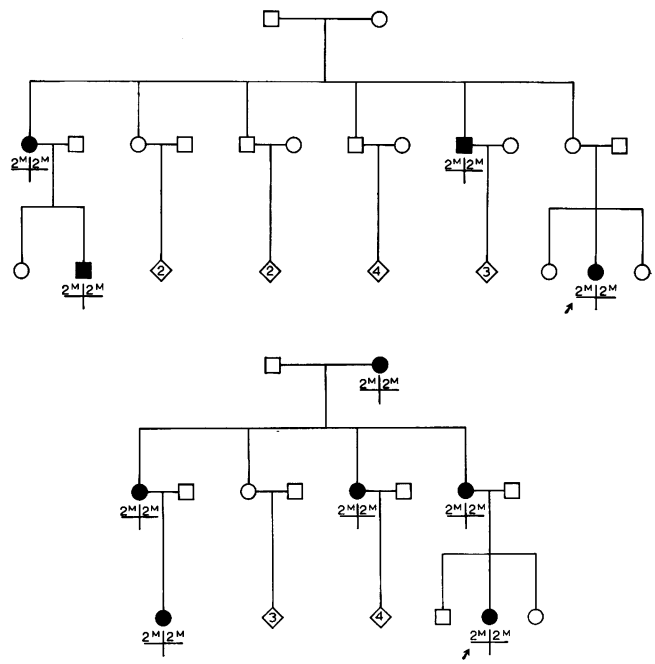

FIG. 1.—Pedigrees of families where affected members tend to be bilateral for missing maxillary lateral incisors. The propositus in each family is designated by an arrow. In these pedigrees as well as in those to follow, the symbols are interpreted as follows:

$\frac{2^M}{}\Big|\frac{2^M}{}$ = right and left maxillary lateral incisors missing;

$\frac{}{}\Big|\frac{2^M}{}$ = left maxillary lateral incisor missing;

$\frac{2^M}{}\Big|\frac{2^P}{}$ = right maxillary lateral incisor missing, left maxillary lateral incisor peg shaped;

$\frac{2^M}{2^M}\Big|\frac{2^M}{2^M}$ = maxillary and mandibular lateral incisors bilaterally missing.

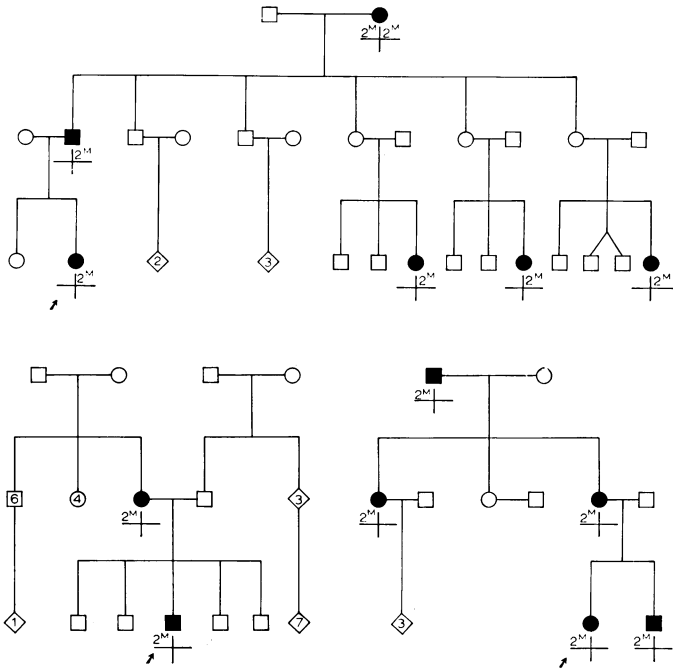

FIG. 2.—Pedigrees of families where affected members tend to be unilateral for a missing maxillary lateral incisor. It is of interest that affected members of the same family tend to show the same type of asymmetry (either right or left).

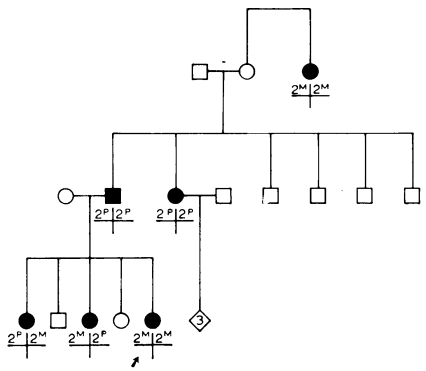

FIG. 3.—Pedigree of family where affected members show peg-shaped and/or missing maxillary lateral incisors.

pletely support this conclusion for the region of the maxillary lateral incisor. Grahnén [2] studied the parents and sibs of 171 propositi with hypodontia of one or more teeth. These family members showed extreme variation in regard to the type and extent of hypodontia. A large number of the relatives had multiple missing teeth. He concluded that in the majority of cases, hypodontia is primarily determined by dominant autosomal genes showing incomplete penetrance and variable expressivity, with the

TABLE 3

HYPODONTIA OF PERMANENT MAXILLARY LATERAL INCISOR IN RELATIVES (PARENTS, SIBS, GRANDPARENTS, AUNTS, UNCLES, FIRST COUSINS) OF 103 PROPOSITI

HYPODONTIA IN PROPOSITI	HYPODONTIA IN RELATIVES		TOTAL
	Bilateral Missing	Unilateral Missing	
Bilateral missing	64	20	84
Unilateral missing	29	26	55
	$\chi^2=7.2$ (Yates's correction), $P<.01$		

penetrance being high if the propositi had hypodontia of six or more teeth and being low if the propositi had hypodontia of five or fewer teeth.

Although family members with more than one missing tooth were occasionally encountered in the present study, the tendency was for the anomaly to be specifically of the maxillary lateral incisor. Only one family was encountered (see below) with members showing multiple missing teeth. The families investigated by Grahnén and those encountered in the present study differ, therefore, in regard to the number of individuals with multiple missing teeth. It appears that this difference is largely a function of ascertainment. Many different mutant genes and genotypes may upset the development of the permanent dentition [6]. Selecting propositi with generalized hypodontia would insure that they are genetically heterogeneous and would therefore result in a group of relatives showing varying types of hypodontia. Assuming that certain mutant genes act specifically on the development of maxillary lateral incisors, it is evident that selecting propositi with only a missing lateral incisor would increase the probability of their genetic homogeneity and the uniformity of their relatives in regard to this type of hypodontia.

Grahnén's own data [2] can be used to support the model that the development of the dentition is influenced by many different genotypes, some with a specific action and some with a more general action. Seventy-three of his 171 propositi had family histories of hypodontia. These 73 propositi can be classified as follows: (1) hypodontia of only the maxillary lateral incisor; (2) missing teeth including the maxillary lateral incisor; and (3) missing teeth other than the maxillary lateral incisor. Family members can be scored in a similar manner. The results are shown in table 4. It is noted that the type of hypodontia present in a propositus is the type that tends to occur in his relatives. It can be concluded from these data that some genotypes tend to result in agenesis of specifically the maxillary lateral incisor. Other genotypes tend to cause agenesis of multiple teeth including the maxillary lateral incisor; still others tend to cause agenesis of teeth other than this incisor. Propositi of the present study were selected on the basis of a dental record stating that the defect was a missing maxillary incisor. Further investigation revealed that five of the propositi had additional missing teeth; one of these had multiple missing teeth. It is of interest that only one

TABLE 4

TYPES OF HYPODONTIA OCCURRING IN FAMILIES (PARENTS AND SIBS) OF 73 PROPOSITI STUDIED BY GRAHNÉN [2]

HYPODONTIA IN PROPOSITI	NUMBER OF FAMILIES		
	Maxillary Lateral Incisor Only Missing Tooth in Any Member	Missing Teeth including Maxillary Lateral Incisor in Any Member	Missing Teeth Other than Maxillary Lateral Incisor in Any Member
Hypodontia of only the maxillary lateral incisor	10	4	1
Missing teeth including the maxillary lateral incisor	8	12	6
Missing teeth other than the maxillary lateral incisor	4	2	26

of the 103 families had members with multiple missing teeth, and the propositus of this family is the one with multiple missing teeth. The pedigree of this family is shown in figure 4.

Pedigrees showing an autosomal mode of inheritance for anomalies (missing and peg shaped) of the maxillary lateral incisors appear in the literature [7–9]. In many of these pedigrees, as in most of the pedigrees encountered in the present study, the mutant gene responsible seems to act quite specifically on the development of this one incisor. However, because of the existence of genetic heterogeneity there is a need for genetic studies where the concentration is not on the entire dentition or a single tooth, but on specific mutant genes in large families. Well-designed clinical studies of members of these families would supply answers to questions concerning gene specificity and therefore advance the important field of dentition genetics.

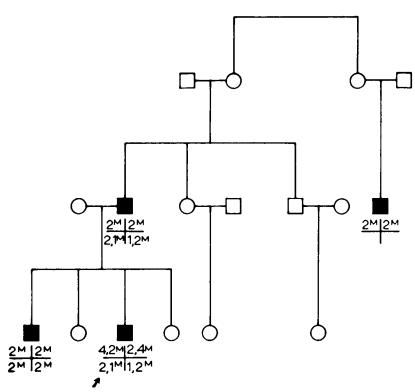

FIG. 4.—Pedigree of family where the propositus had multiple missing teeth (maxillary lateral incisors, maxillary first premolars, mandibular central and lateral incisors). Multiple missing teeth occurred in his brother and father.

SUMMARY

Propositi for a genetic study of missing maxillary lateral incisors were obtained from dental files in Salt Lake City, Utah. Family histories were obtained for 103 propositi with either bilateral missing incisors, unilateral missing incisor, or missing and peg-shaped incisors. The frequency of individuals with a missing maxillary lateral incisor was significantly increased in the parents and sibs of the propositi as compared with the frequency in parents and sibs of 187 control families. The frequency of individuals with peg-shaped maxillary lateral incisors was also increased in the first-degree relatives of the propositi, indicating that a genetic relationship exists between the missing and peg-shaped conditions of this incisor.

In 71 (69%) of the 103 families of the propositi, at least one first-, second-, or third-degree relative had a missing or peg-shaped maxillary incisor. The data support the hypothesis that at least part of the genetic component consists of a dominant autosomal gene (or genes) showing reduced penetrance and variable expressivity. It is also plausible that this trait has a recessive or polygenic mode of inheritance in some families.

A high degree of concordance exists between propositi and affected family members in regard to the type of incisor anomaly, especially if the propositi have bilateral missing maxillary lateral incisors. It is concluded that the development of the dentition can be altered by many different mutant genes and genotypes, some with a specific action involving the maxillary lateral incisor, and others with a more general action. Genetic modifiers may account for much of the variable expressivity among affected members of the same family and in different families. It is also likely that different alleles and mutations at different loci contribute to the variation.

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