# A Genetic Study of Cleft Lip and Palate in Utah

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AN EXCELLENT genetics study on cleft lip and palate was carried out in Denmark by Fogh-Anderson (1942), and although the results were confirmed by studies in Canada (Fraser, 1955; Curtis, Warburton, and Fraser, 1961), there is need for large studies in other populations. No such study has been carried out in the United States. Cleft lip and palate appear to be etiologically heterogeneous (Fraser, 1955) and comparative studies in different populations would be one way of evaluating the over-all importance of genetic and nongenetic components. The purpose of the present paper is to report the results of a genetic study of congenital clefts of the lip and palate in Utah. The results of an analysis of certain nongenetic variables will be reported later. This study is part of a general investigation of various types of congenital malformations in Utah, taking advantage of a population that is predominantly Mormon and therefore relatively stable in the area. Strong family-ties and an interest in genealogical records facilitate genetic research among the Mormon people.

## INCIDENCE OF CLEFT LIP AND PALATE

No data have been published on the incidence of congenital clefts of the lip and palate in any segment of the Utah population. Nursery records on file in the Latter-day Saints Hospital in Salt Lake City, Utah, were used to determine the incidence among live births occurring in the hospital during the years 1951-1961. The great majority of patients entering the hospital are Caucasian. This hospital is the largest in the state of Utah. About 23 per cent of the total births in the state occurred in this hospital during 1951-1961. When a newborn infant is taken into the nursery an entry is made in a record book of any observed congenital malformation. During the period 1951-1961, a total of 59,650 infants were registered in the nursery. A cleft of the lip or palate was recorded for 90 of these infants, giving an observed incidence of 1 in 662 (1.51 per thousand live births). The 90 cleft cases were classified as follows: cleft lip, 24; cleft lip and palate, 50; isolated cleft palate, 16.

Even though all cleft lip and cleft lip and palate cases might have been detected, isolated cleft palate cases could have been overlooked. Among a sample of surgical cases in Utah (see table 1), the numbers of cleft lip, cleft lip and palate, and isolated cleft palate cases approximate a 1:2:1 ratio. Fogh-Anderson (1942) has concluded that the real figures for the three groups at birth in Denmark are very close to 25 per cent, 50 per cent, and 25 per cent. Using the 1:2:1 ratio as a guide, allowance for missed isolated cleft palate cases can

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TABLE 1. CLASSIFICATION OF PROPOSITI

| Type of Cleft | Number | % | % Female | % Male |
|---|---|---|---|---|
| Cleft Lip | 128 | 23.1 | 36.7 | 63.3 |
| Cleft Lip and Cleft Palate | 290 | 52.5 | 26.9 | 73.1 |
| Isolated Cleft Palate | 135 | 24.4 | 52.6 | 47.4 |
| Total | 553 | | | |

be made by increasing the number from 16 to 24, which is equal to the number of cleft lip cases. This gives an adjusted total number of 98 cleft cases, and an adjusted incidence of 1 in 609 (1.64 per thousand live births). The adjusted incidence is probably closer to the true incidence among the 59,650 live births.

### PROPOSITUS-STATISTICAL GENETICS STUDY

The names of 1,116 cleft cases were obtained from surgical records made available by physicians in the state of Utah. A total of 317 were from areas inconveniently located from Salt Lake City, Utah, and were removed from the study. With the aid of city directories, telephone books, and church records, an attempt was made to obtain a current address for each of the remaining cases. This method failed to locate 243 cases. The homes of the remaining 556 cases were then visited and one or more of the family members (usually the mother of the cleft case) was interviewed in order to obtain information of epidemiological interest. The study required extensive traveling throughout the state of Utah and adjacent regions of Idaho, Nevada, and Wyoming. Cooperation on the part of the family members was excellent. Although some were hesitant to supply information when first contacted, complete refusal to cooperate was only encountered in the relatives of three cleft cases. Upon completion of the study, information was available on the families of 553 cleft cases.

During the ascertainment of cleft cases and family histories, clefts of the lip and palate were considered as one group. Only upon completion of the study were the cases classified as cleft lip (symbolized by CL), cleft lip and cleft palate (symbolized by CLCP), and isolated cleft palate (symbolized by CP). No selection was made for or against cleft cases with other anomalies. Some of the propositi were already deceased when the family history was obtained.

The classification of the 553 cleft cases (propositi) as to type of cleft is shown in table 1. Even though cleft lip and cleft palate occur more often together than separately, the frequency of the three types in the sexes is one type of evidence (Fogh-Anderson, 1942) that isolated cleft palate is etiologically distinct from cleft lip with or without cleft palate. Both CL and CLCP occur more frequently in males than females, while CP is more common in females.

Evidence that CP is a genetically distinct disorder from CL and CLCP comes from a study of the frequency of these disorders in the relatives of the propositi. Information was obtained on the following classes of relatives: siblings, parents, children, grandparents, aunts, uncles, nieces, nephews, and first cousins. The data are summarized in table 2. The frequency of CL and CLCP is appreciable in the relatives of both the CL and CLCP propositi, but the frequency of CP

in these relatives is small. The situation is reversed in the relatives of the CP propositi: CL and CLCP occur at a low frequency, but the frequency of CP is appreciable. This phenomenon can be studied objectively by comparing the observed percentage of cleft cases at birth among the living and deceased relatives of the propositi with expected percentages derived from the nursery record data on file in the Latter-day Saints Hospital. For the CP the adjusted percentage is used. It is assumed here that the percentage of cleft cases among live births in this hospital represents the percentage occurring among live births in the general population. Since this assumption may not be justified the derived values represent only crude expected (risk) values for the general population.

Among the relatives of the propositi with CL there is a significant increase in the frequency of both CL and CLCP, but not CP, over the frequency expected in the general population. The same situation prevails for the relatives of the CLCP propositi. Among the relatives of the CP propositi, CL and CLCP are present at the level of frequency expected in the general population, but the frequency of CP is increased significantly.

These data point out that CL and CLCP should be considered as one disorder, which can be symbolized by CL(P). This is done in table 3. The observed frequencies of CL(P) and CP in the relatives of the CL(P) and CP propositi are compared with expected frequencies. It is clear that among the relatives of the CL(P) propositi, there is a significant increase of CL(P), but CP is occurring at a frequency expected in the general population. Among the relatives of the CP propositi there is a significant increase of CP, but not of CL(P).

TABLE 2. TYPES OF CLEFTS IN RELATIVES* OF PROPOSITI

| Propositi | Total No. of Relatives | Relatives: Cleft Lip | | Cleft Lip and Palate | | Isolated Cleft Palate | |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % |
| Cleft Lip | | | | | | | |
| Observed | 5,726 | 20 | 0.349 | 28 | 0.490 | 2 | 0.035 |
| Expected† | | 2.3 | 0.040 | 4.8 | 0.084 | 2.3 | 0.040 |
| Cleft Lip and Palate | | | | | | | |
| Observed | 13,585 | 42 | 0.309 | 82 | 0.604 | 6 | 0.044 |
| Expected† | | 5.5 | 0.040 | 11.4 | 0.084 | 5.5 | 0.040 |
| Isolated Cleft Palate | | | | | | | |
| Observed | 5,863 | 4 | 0.068 | 2 | 0.034 | 27 | 0.460 |
| Expected† | | 2.4 | 0.040 | 4.9 | 0.084 | 2.4 | 0.040 |

* See text for classes of relatives.
† See text for expected values.

TABLE 3. TYPES OF CLEFTS IN RELATIVES* OF PROPOSITI

| Propositi | Total No. of Relatives | Relatives: Cleft Lip With or Without Cleft Palate | | Isolated Cleft Palate | |
|---|---|---|---|---|---|
| | | Observed | Expected† | Observed | Expected† |
| Cleft Lip With or Without Cleft Palate | 19,311 | 172 | 24.0 | 8 | 7.8 |
| Isolated Cleft Palate | 5,863 | 6 | 7.3 | 27 | 2.4 |

* See text for classes of relatives.
† See text for expected values.

The frequency of CL(P) in the various classes of relatives of the propositi with CL(P) is shown in table 4. The observed percentage in each class is increased over the percentage found in the general population. The frequency of CP in the various classes of relatives of the CP propositi is shown in table 5. Again, when the number of relatives in a given class is large enough to be meaningful, the observed percentage is larger than the percentage found in the general population.

## DISCUSSION

If two populations exhibited about the same incidence of congenital clefts of the lip and palate but differed in the frequency of responsible genetic and nongenetic factors, studies similar to the present one in each population might demonstrate the differences. For example, in the population where nongenetic factors were of prime importance, fewer familial aggregations of cases might be noted. The results of the present study and those carried out in Denmark and Canada are remarkably similar, suggesting a similarity of etiological factors in the populations. It would be informative to compare the results of studies carried out in low and high incidence populations.

The results of the present study support unequivocally the conclusions of Fogh-Anderson (1942) that CL and CLCP are due to the same genetic mechanism, which is different from the one giving rise to CP. The lip develops during the fifth to eighth week of gestation and the palatal region about the ninth week (Canick, 1954). A mechanism altering the first developmental process may secondarily affect the second; but the second process may be altered

TABLE 4. FREQUENCY OF CLEFT LIP WITH OR WITHOUT CLEFT PALATE IN THE RELATIVES OF PROPOSITI WITH THIS DISORDER

| Relative | Total No. | No. of Cases | % |
|---|---|---|---|
| Siblings | 1,410 | 65 | 4.61 |
| Parents | 836 | 17 | 2.03 |
| Children | 164 | 7 | 4.27 |
| Grandparents | 1,715 | 6 | 0.35 |
| Aunts and Uncles | 4,164 | 29 | 0.70 |
| Nieces and Nephews | 832 | 7 | 0.84 |
| First Cousins | 10,240 | 41 | 0.40 |
| Unrelated (General Population) | | | 0.12 |

TABLE 5. FREQUENCY OF ISOLATED CLEFT PALATE IN THE RELATIVES OF PROPOSITI WITH THIS DISORDER

| Relative | Total No. | No. of Cases | % |
|---|---|---|---|
| Siblings | 431 | 11 | 2.55 |
| Parents | 270 | 4 | 1.48 |
| Children | 46 | 4 | 8.70 |
| Grandparents | 540 | 1 | 0.18 |
| Aunts and Uncles | 1,267 | 4 | 0.32 |
| Nieces and Nephews | 162 | 0 | 0.00 |
| First Cousins | 3,147 | 3 | 0.09 |
| Unrelated (General Population) | | | 0.04 |

independently of the first. Although this genetic conclusion may be true in general, there is one noteworthy exception. In some families, fistula labii inferioris congenita is associated with cleft lip and palate. The mode of inheritance of the syndrome appears to be that of a single autosomal dominant gene (Van Der Woude, 1954). Some individuals with the gene may show CL, CP, and fistulae of the lower lip, while others possessing the gene may show a combination of two, one, or none of the traits. In these families CP may occur in the same sibship with CL or CLCP. This is evidence that in some cases a single genetic mechanism may interfere with either or both of the above mentioned developmental processes.

Evidence for the role of non-genetic factors in cleft occurrence comes from the observation of discordance for CL(P) and CP in the majority of MZ twins (Metrakos, Metrakos, and Baxter, 1958) and a slight maternal age effect for CL(P) (MacMahon and McKeown, 1953). The inducibility of clefts in experimental animals by vitamin deficient diets (Warkany, Nelson, and Schraffenberger, 1943; Nelson, Wright, Baird, and Evans, 1957), cortisone injections (Fainstat, 1954), and many other agents (Fraser, 1962), is perhaps further evidence that some clefts in man may have an environmental component. Although no viral agent has been definitely incriminated, Pleydell (1960) has reported a slightly increased incidence in urban areas as compared with rural areas in England, which may be attributable to a higher risk of infections in the more densely populated areas. This needs further testing.

All existing information suggests that CL(P) and CP are etiologically heterogeneous. In some cases a polygenic mechanism may be acting, perhaps of the type shown for polydactyly in guinea pigs by Wright (1934), while in others the genetic mechanism may be a single gene as shown for the syndrome consisting of fistulae on the lower lip and cleft lip and palate. Teratogenic agents interacting with genetic mechanisms would add further complexity to the etiology.

If CL(P) and CP can be determined by single genes, polygenes and non-genetic factors, then sporadic case families and multiple case families should be prevalent in a population. An attempt to demonstrate these families objectively can be made by comparing the frequency of families with 0, 1, 2, 3, 4 or 5 cleft cases, other than the propositus, with expected frequencies assuming that the probability of a cleft in the other family members, for one or more reasons, is low, random, and uniform from family to family. In tables 6 and 7, the frequency of families showing 0, 1, 2, 3, 4, or 5 other cases of CL(P) and CP are compared with the Poisson distribution using the arithmetic means of the observed distributions. The observed and generated distributions are not homogeneous. For example, in table 6, it is noted that 305 of the families of the CL(P) propositi showed no other case of CL(P). The expected number is 277. At the other end of the distribution, three families showed four other cases where the expected number of families is 0.3, and one family showed five other cases where the expected number is 0.0. Although there is a slight bias in this analysis because multiple case families have the highest likelihood of being ascertained, the results suggest, nevertheless, that sporadic case families and multiple case families are occurring at an increased frequency. Similar conclu-

TABLE 6. DISTRIBUTION OF CLEFT LIP WITH OR WITHOUT CLEFT PALATE CASES IN THE FAMILIES OF 418 PROPOSITI WITH THIS DISORDER

| No. of Cases of Cleft Lip With or Without Cleft Palate in Families (excluding propositi) | Observed No. of Families | Expected No. (Poisson Distribution) $\bar{x} = 0.4115$ |
|---|---|---|
| 0 | 305 | 277.0 |
| 1 | 75 | 114.0 |
| 2 | 22 | 23.5 |
| 3 | 12 | 3.2 |
| 4 | 3 | 0.3 |
| 5 | 1 | 0.0 |
| 6 | 0 | 0.0 |
| Total | 418 | 418.0 |

TABLE 7. DISTRIBUTION OF ISOLATED CLEFT PALATE CASES IN FAMILIES OF 135 PROPOSITI WITH THIS DISORDER

| No. of Cases of Isolated Cleft Palate in Families (excluding propositi) | Observed No. of Families | Expected No. (Poisson Distribution) $\bar{x} = 0.200$ |
|---|---|---|
| 0 | 118 | 110.5 |
| 1 | 11 | 22.1 |
| 2 | 2 | 2.2 |
| 3 | 4 | 0.2 |
| 4 | 0 | 0.0 |
| 5 | 0 | 0.0 |
| 6 | 0 | 0.0 |
| Total | 135 | 135.0 |

sions are reached for the CP families (table 7). Consequently, CL(P) and CP may be strongly heritable in some families through the action of a dominant gene, less heritable in others through the interaction of polygenes and non-genetic factors, and may appear as phenocopies in still other families.

## CONCLUSIONS

1. The incidence of congenital clefts of the lip and palate among 59,650 live births in the Latter-day Saints Hospital in Salt Lake City, Utah, was observed to be one in 662, or 1.51 per thousand live births.

2. The results of this study support the hypothesis that genetic components exist for these anomalies. A statistical analysis of the families of 553 propositi demonstrates that cleft lip (CL) and cleft lip with cleft palate (CLCP) have a genetic component in common, which is different from the one predisposing to isolated cleft palate (CP).

3. Sporadic case families and multiple case families occur at a frequency in the population supporting the hypothesis that congenital clefts of the lip and palate are etiologically heterogeneous.

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