Sex-linked Cleft Palate*

Report of a Family and Review of 77 Kindreds

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Cleft palate, with or without cleft lip, is one of the more common congenital malformations in man (Fraser and Calnan, 1961). The frequency of facial clefts in Caucasians is about 1.5 per 1000 live births (Fogh-Andersen, 1942, 1963; Van der Woude, 1954; Neel, 1958; Rank and Thomson, 1960; Loretz, Westmoreland, and Richards, 1961; Milham, 1963; Kraus, Kitamura, and Ooe, 1963; Greene, 1963; Woolf, Woolf, and Broadbent, 1963; Greene, Vermillion, Hay, Gibbens, and Kerschbaum, 1964), and this condition comprises 7.5% of all congenital defects noted at birth (Kraus *et al.*, 1963). Using these figures, Greene (1963) estimated that in the United States nearly 6000 new cases of lip and palatal clefts occurred annually.

The incidence of clefts of the lip and palate varies among the different races. Mitani (1943) and Neel (1958) found the frequency to be higher in the Japanese (1.89–2.68 per 1000 live births). Ivy (1962) and Greene *et al.* (1964) found the frequency of facial clefts to be lower among American Negroes (0.22–0.55 per 1000 live births).

This paper describes the first reported family with cleft palate that manifests an apparent sex-linked pattern of inheritance. This study also includes an analysis of 77 other families studied in the Heredity Clinic of the University of Michigan from December 1941 through December 1964; they were ascertained through a facial cleft in the proband.

Case Report

The N family (HC 9046, Fig. 1) was referred to the Heredity Clinic at the University of Michigan after the birth, on May 8, 1964, of the proband, IV.4. At birth

it was noted that this male child had a wide midline cleft of both the soft and hard palate extending to the incisor foramen (Fig. 2). Other anomalies observed at this time included hypertelorism, strabismus, a median frontal prominence, an occipital protuberance, and low-set posteriorly rotated ears (Fig. 3A and 3B). An inclusion cyst of the penile meatus was also noted.

The older brother of the proband (IV.3) born on August 26, 1961, also had a large midline cleft palate that was repaired surgically at 17 months of age. At 32 months of age contrast radiographs of the genito-urinary system in this youngster revealed urethral obstruction. Vesical neck surgery was performed for urethral valves on April 27, 1964. Fig. 3C and 3D reveal the same phenotypic defects as noted above in his younger brother.

The mother (III.2) exhibited similar hypertelorism and the median frontal prominence seen in her sons (Fig. 3E and 3F). She manifested a prominent occiput and also had a soft cystic lesion of the scalp (3 × 3 × 2 cm.) at the occiput. Both the father (III.1) and an older female sib (IV.2) were normal. There was no known parental consanguinity. A maternal great-uncle (II.3) was found to have a repaired midline palatal cleft and also showed hypertelorism and a median frontal prominence. These findings led to the conclusion that

FIG. 1. Pedigree of family with apparent sex-linked recessive cleft palate.

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FIG. 2. Propositus, IV.4 (age 8 months), demonstrating midline cleft palate.

the great-uncle had a facial cleft probably based on the same genotypic constitution as the propositus and his brother.

A male second cousin (IV.20) was found to have a repaired unilateral (left) cleft lip and palate and did not have similar facies to the 3 affected individuals described above. He may represent a coincidental case of facial clefts. However, his anomalies may also be due to the same gene (as his great-uncle (II.3) and 2 second cousins (IV.3 and IV.4)) but influenced by different 'modifier' genes. Since he is related to the other affected individuals through 2 female ancestors (III.6 and II.5), the latter hypothesis is suggested.

Glucose-6-phosphate dehydrogenase (G6PD) assays in II.3, III.1, IV.4, and IV.20, showed normal levels of enzyme activity. Blood grouping studies, including Xg^a, were performed on II.2, II.3, III.1, III.2, III.6, IV.2, IV.3, IV.4, and IV.20. Electrophoretic mobility of the red cell enzymes G6PD and acid phosphatase, as well as haemoglobin of these family members, was normal. The blood grouping and electrophoresis of G6PD and acid phosphatase revealed no parental exclusion.

It was not possible to demonstrate any linkage between the above genetic markers and the clefts segregating in the family. Cytogenetic studies of the chromosomes of the peripheral leucocytes in these 9 subjects (II.2, II.3,

III.1, III.2, III.6, IV.2, IV.3, IV.4, and IV.20: 4 affected and 5 normal) revealed numerically and morphologically normal karyotypes. No apparent X autosome translocation could be discerned. Colour vision was not tested because of the young ages of the two affected brothers.

Review of Heredity Clinic Kindreds

From more than 9000 kindreds recorded in the Heredity Clinic of the University of Michigan, 33 were found to have one or more individuals with facial clefts. In 5 of these kindreds the facial clefts were found to be associated with lip pits and the

FIG. 3. A and B, propositus, IV.4 (age 8 months), demonstrating hypertelorism, strabismus, median frontal prominence, occipital protuberance, and low-set posteriorly rotated ears; C and D, older brother of propositus, IV.3 (age 3 1/2 years), demonstrating hypertelorism, strabismus, median frontal prominence (mild), occipital protuberance, and low-set posteriorly rotated ears; E and F, mother of propositus, III.2 (age 23 years) demonstrating hypertelorism and median frontal prominence.

TABLE

SEX OF PROPOSITI AND AFFECTED RELATIVES IN 77 KINDREDS WITH CLEFT LIP, WITH OR WITHOUT CLEFT PALATE (CL(P)), AND WITH CLEFT PALATE ALONE (CP)

	Male	Female	Total
52 <i>Propositi with CL(P)</i>			
Sporadic cases	14	13	27
Cases with affected relative(s)	16	9	25
Relatives with CL(P)	33	22	55
Relatives with CP alone	2	1	3
25 <i>Propositi with CP alone</i>			
Sporadic cases	9	9	18
Cases with affected relative(s)	3	4	7
Relatives with CL(P)	1	2	3
Relatives with CP alone	4	2	6
144 <i>Affected Individuals in 77 Kindreds</i>			
CL(P)	64	46	110
CP alone	18	16	34
Total	82	62	144

syndrome inherited in an autosomal dominant fashion (Van der Woude, 1954). These 5 kindreds and the present family (HC 9046) are excluded from this review of the Heredity Clinic Kindreds. The remaining 77 kindreds are summarized in the Table.

Of the propoiti with cleft lip with or without cleft palate, 49% (25/52) had a positive family history of facial clefts. In his study of 703 families, Fogh-Andersen (1961) found 37% of cleft lip with or without cleft palate propoiti to have a positive family history. Similarly, 28% (7/25) of the propoiti with cleft palate alone in the present report had a positive family history in contrast to the 19% found by Fogh-Andersen. The higher incidences of positive family histories in the present cases probably represents the ascertainment bias of a heredity clinic.

Cleft lip with or without cleft palate accounts for approximately 75% of the facial clefts in the general population and cleft palate alone for 25% (Spriestersbach, Spriestersbach, and Moll, 1962). Spriestersbach *et al.* (1962) have shown that clefts in the relatives of affected individuals are of the same type as the propoitus more often than would be expected from the general population figures. In the present study 95% (55/58) of the affected relatives of the cleft lip, with or without cleft palate, propoiti had either cleft lip alone or cleft lip and palate. Of the 9 affected relatives of the cleft lip propoiti, 6 (67%) had cleft palate alone. Although these numbers are too small for significant conclusions, the results are consistent with the findings of others.

Cleft lip, with or without cleft palate, is usually

found more commonly in males (65–70%), while cleft palate alone is more often reported in females (60–65%) (Fogh-Andersen, 1942; Greene, 1963). Among the present 77 kindreds, 58% of the 110 cases with cleft lip, with or without cleft palate, were males, while 47% of the 34 with cleft palate only were females. The alteration in the sex ratio in the cases with cleft lip, with or without cleft palate, is consistent with the findings of others but that of the cases with cleft palate alone is not. Again, however, the numbers are small.

Fig. 4 and 5 illustrate the pedigrees of the 32 kindreds with familial cases of facial clefts. Heredity Clinic cases HC 266, 366, and 8569 (Fig. 4) could be due to a sex-linked recessive mutant gene, as is postulated for the family reported above (HC 9046). Cases HC 309 (Fig. 5) 315, 593, and 6943 (Fig. 4) could represent sex-linked dominant inheritance with variable penetrance, though autosomal dominance cannot be ruled out.

At birth about 15–25% of all patients with facial clefts will have other associated malformations (Kraus *et al.*, 1963; Greene *et al.*, 1964). Spriestersbach *et al.* (1962), Jaworska and Poradowska (1963), and Greene *et al.* (1964) found that the associated malformations in facial cleft patients were significantly more numerous in patients with isolated cleft palate. In the present study 35 of 144 patients (24%) were found to have one or more associated anomalies. Of the 110 patients with cleft lip, with or without cleft palate, 20 (18%) were so affected while 44% (15 of 34) of the patients with cleft palate only had other malformations. Although the number of associated malformations is significantly higher in the cleft palate group ($\chi^2 = 9.055$, d.f. = 1, $p < 0.01$), a review of the types of malformations in the two groups did not appear to be different. Included in both groups were malformations in the skeletal, muco-cutaneous, central nervous, respiratory, and endocrine systems, as well as congenital heart disease. The group with cleft palate only included one patient with possible D or E trisomy syndrome, and the group with cleft lip, with or without cleft palate, included one chromosomally-proven trisomy D. Of the 20 patients of the latter group, with an associated anomaly, 10 were sporadic clefts and 10 familial (4 sibs, 2 sibs, 4 separate). In the group with cleft palate only, 11 of the 15 patients with an associated malformation were sporadic clefts and the remaining 4 familial (two sib pairs). The congenital urethral valves found in the brother of the propoitus are in keeping with the high incidence of associated malformations in patients with facial clefts, especially those patients with cleft palate only.

FIG. 4. Heredity clinic pedigrees, male propiti with cleft lip, with or without cleft palate (CL(P)) showing familial cases of facial clefts.

Discussion

Numerous studies have attempted to elucidate the role of heredity in the formation of human facial clefts (Fogh-Andersen, 1942, 1961; Metrakos, Metrakos, and Baxter, 1958; Rank and Thomson, 1960; Ramsey and Wynn-Williams, 1960; Loretz *et al.*, 1961; Spriestersbach *et al.*, 1962; Ivy, 1962; Greene, 1963; Greene *et al.*, 1964; Cervenka, 1963; Jaworska and Poradowska, 1963; Tretsvén, 1963; Woolf *et al.*, 1963; Woolf, Woolf, and Broadbent, 1964). Generally it is concluded that both groups exhibit different degrees of familial aggregation and that heredity is apparently much more significant in the group with cleft lip, with or without cleft palate, than in the group with cleft palate only. Little has been added to the genetics of facial clefts since Fogh-Andersen (1942) suggested that cleft lip, with or without cleft palate, was transmitted as an incomplete recessive trait with sex limitation to the male. In incomplete recessive traits the gene

generally occurs as a recessive, but under certain conditions the heterozygote is manifested. Fogh-Andersen states that the predominance of males is probably not due to the occurrence of sex-linked cases. Further, Fogh-Andersen felt that cleft palate alone was inherited as a simple autosomal dominant with decreased penetrance and sex limitation to the female. Only one Japanese study (Fujino, Tanaka, and Sanui, 1963) has found a significant increase in consanguinity, suggesting that recessive genes may play a role in facial clefts. Schull (1958), however, found no clear suggestion of recessive factors in the aetiology of facial clefts among offspring of consanguineous Japanese marriages.

Fraser (1955) suggested that specific genetic types of facial clefts should be sorted out from the heterogeneous categories. Van Der Woude (1954) described several families in which facial clefts associated with lip pits were inherited in an autosomal dominant fashion. Fraser and Calnan (1961)

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FIG. 5. Heredity clinic pedigrees, female propositi with cleft lip, with or without cleft palate (CL)(P), male and female propositi with cleft palate only (CP), showing familial cases of facial clefts.

pointed out that cleft palate seemed to occur with a remarkable frequency as a part of autosomal dominant syndromes, including those of Pierre-Robin and Treacher-Collins as well as in ectrodactyly.

The finding of facial clefts and chromosomal anomalies has been reported several times; however the only consistent association is noted in the D_1 -trisomy syndrome. In 9 of 13 cases, both cleft palate and lip were manifested, while one additional patient exhibited cleft palate alone (Smith, Patau, Therman, Inhorn, and DeMars, 1963). Cells cultured from the palatal mucosa of a patient with cleft lip and palate showed a modal number of 72 chromosomes (Gropp, Jussen, and Odunjo, 1964). No diploid or tetraploid cells were found and the

modal karyotype of this tissue was a triploid complement plus a triplicated supernumerary member of Group F. DeMyer, Zeman, and Palmer (1963) report a pair of sibs with alobar holoprosencephaly and median clefts of the lip and palate. The chromosomes of one of these sisters as well as another patient with the syndrome were normal. Numerous other karyotypic investigations of individuals with facial clefts have revealed no chromosomal aberrations.

The present family represents the first reported occurrence of human facial clefts exhibiting a probable sex-linked recessive mode of inheritance. In the 3 affected sibships there are 5 males, 4 of whom are affected, and 5 females, none of whom are affected (Fig. 1). If the inheritance pattern were autosomal recessive, the prior probability of

having 4 affected males, 1 unaffected male, and 5 unaffected females, among 10 offspring, 5 of whom are male, is 0.00341. The analogous probability if inheritance were sex-linked recessive is 0.154.

The facial clefts in this family could also be the result of an autosomal dominant gene with much reduced penetrance (50%), as proposed by Fogh-Andersen. One would also have to postulate a sex limitation in the male rather than in the female, as suggested by previous studies. It is felt that a sex-linked recessive gene is the most likely cause of the clefts in this family.

The hypertelorism, median frontal prominence, and occipital protuberance seen in the 2 affected males, their mother, and their affected great-uncle may be phenotypic expressions of pleiotropic effects of the abnormal gene. The failure of the palate to join and fuse in the midline may be secondary to an underlying bony abnormality of the skull. The skull, in effect, may be too wide. Fraser (1955) and F. C. Fraser (1965, personal communication) mentions the association between facial clefts and a wide head.

Summary

A family is presented with an apparent sex-linked recessive form of facial cleft. Chromosome studies on the 4 affected individuals and 5 normal family members were normal. Cases of clefts of the lip and palate seen in a heredity clinic from 1941 to 1964 are reviewed with an analysis of 77 kindreds.

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