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Maternal Effects in Human Cleft Lip and Palate

GLENN J. BINGLE[1,3] AND JERRY D. NISWANDER[2]

Maternal and paternal age effects for cleft lip have been previously demonstrated in both man and mouse [1–4]. However, maternal factors that effect the frequency of cleft lip with or without cleft palate (CL [P]) and teratogenically induced isolated cleft palate (CP) have only been demonstrated in mice, not in man.

Davidson et al. [5] demonstrated a developmental maternal effect on the frequency of CL through a series of back and reciprocal crosses involving the A/Jax and C57BL mouse strains. Employing additional crosses, Bornstein et al. [6] demonstrated that similar maternal effects in the CL/Fr strain were related to maternal uterine environment and were not of cytoplasmic origin. However, Fraser [7] has noted the as yet unexplained discrepancy with the results of ova transfer failing to confirm such maternal effects.

Ching and Chung [8], studying malformation frequencies from Hawaiian interracial crosses, found no evidence for a maternal effect in either CL(P) or CP. Similar findings were reported by Niswander et al. [9] in the American Indian. Fraser [10] reported a dizygous (DZ) twin concordance rate as high as 10% for both CL(P) and CP; this frequency was considerably greater than the established recurrence risk for sibs of affected probands and suggested the possibility of a maternal effect. More recently, in a large sequential birth twin series, Hay and Wehrung [11] reported DZ twin concordances similar to sib recurrence risk estimates. The discrepancy between these rates may have resulted from overreporting of concordant twins in nonsequential series.

Nance et al. [12] have recently advocated the use of half sibs, ascertained as the progeny of monozygous (MZ) twins, to test for the existence of maternal effects on congenital malformations. Janerich et al. [13] suggested using record linkage between birth and marriage records as a means of assembling a continuous series of half sibs. However, because of the rarity of MZ twins who produce a child with a facial cleft and because of the difficulty in obtaining a single population large enough for record linkage, we ascertained half sibships with clefts from the family history files of cleft lip and palate investigators.

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[1] Department of Medicine, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, Michigan 48202.

[2] Laboratory of Developmental Biology and Anomalies, National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland 20014.

[3] Present address: Division of Medical Genetics, Community Hospital, 1500 N. Ritter, Indianapolis, Indiana 46219.

If a major maternal effect exists and is etiologically important in facial clefting and if such an effect is not sporadic but persists from one pregnancy to another, half sibships ascertained through an affected proband will have a higher frequency of clefting when the mother is the common parent.

SUBJECTS AND METHODS

Family history and pedigrees were obtained from 16 investigators who had collected data to study the inheritance of CL and CP.* The geographic distribution of the populations varied widely. Pedigrees were obtained from clinic populations except for those obtained from the large Denmark Registry of Fogh-Anderson, those of S. Hay from birth certificates, those of C. Witkop from a study of a population isolate in North Carolina, and those of C. M. Woolf from hospital records. Over 8,000 pedigrees were screened for maternal and paternal half-sib relatives of each proband. Approximately 5% of the original proband families contained maternal or paternal half sibships, and often a pedigree contained both. Most half sibs were the progeny of other marriages, but a few were illegitimate.

Any proband about whom sufficient documentation was available to clarify the etiology of the cleft was deleted from the sample. Moreover, data from C. Witkop (55) were excluded entirely because of a high frequency of the dominantly inherited lip pit syndrome. Such exclusions, with this one exception, accounted for less than 5% of the original sample.

RESULTS

Data on half sibships and full sibships of 393 probands is given in table 1. Occurrences of CL(P) in maternal (.011) and paternal (.014) half sibships are nearly identical (table 1). The risks for paternal half sibs (.009) with regard to isolated CP probands are more than double the maternal (.004). Frequencies among the full sibs of these probands are .035 for CL(P) and .027 for CP, which is approximately three to eight times those for half sibs.

Another test of maternal effects can be obtained by comparing the frequency of affected maternal and paternal first cousins of propositi. Data on first cousins were only available from the Lancaster Cleft Palate Clinic. These are given in table 2 along with those of the series reported by Woolf et al. [16]. Neither the first-cousin nor half-sib data give evidence for a maternal effect.

DISCUSSION

The half-sib, twin, and first-cousin data presented no evidence of a specific maternal effect on the occurrence of CL(P) or CP. More data on half sibs might reveal a small maternal effect, but this methodology is incapable of revealing sporadic teratogenic effects.

Maternal half sibs (324) at risk for CL(P) were ascertained more often than paternal half sibs (203), and for isolated CP, only 104 paternal half sibs were available compared

* The following 16 investigators contributed their family data on facial clefting. (The number of pedigrees taken from each investigator is given in parentheses after their name.) J. C. Bear (17), Newcastle upon Tyne, England; David Bixler (44), Indianapolis, Indiana; C. S. Chung (26), Honolulu, Hawaii; P. Fogh-Anderson (6), Copenhagen, Denmark; F. C. Fraser (12), Montreal, Canada; Sylvia Hay (16), San Francisco, California; Gillian Ingall (14), Buffalo, New York; William Krogman (74), Lancaster, Pennsylvania; A. Donald Merritt (39), Indianapolis, Indiana; P. Moller (33), Birmingham, Alabama; J. V. Neel (12), Ann Arbor, Michigan; J. Sanders (6), Rotterdam, The Netherlands; Edward Shields (41), Indianapolis, Indiana; V. Wertelecki (12), Charleston, South Carolina; C. Witkop (55), Minneapolis, Minnesota; C. M. Woolf (24), Tempe, Arizona.

TABLE 1

FREQUENCY OF CL(P) AND ISOLATED CP IN MATERNAL AND PATERNAL HALF SIBS AND FULL SIBS OF AFFECTED PROBANDS

Subjects	Normal	Affected	Frequency
Half Sibs:			
Maternal CL(P)	342	4	.011
Paternal CL(P)	210	3	.014
Total	552	7	.013
Maternal CP	253	1	.004
Paternal CP	104	1	.009
Total	357	2	.006
Full Sibs:			
Cleft lip (P)	570	20	.035
Cleft palate	298	8	.027

with 250 maternal half sibs. This excess of maternal half sibs was probably the result of several factors. There was a high percentage of family histories obtained solely from the mother. This could bias the comparison between the maternal and paternal half-sib frequencies, if mothers report paternal half sibships more frequently when they know of affected individuals. Such a bias would spuriously elevate the recurrence frequency among paternal half sibs.

A differential parental age effect for either CL(P) or CP might distort the frequencies since each half sibship necessarily involves a common parent who is younger in one marriage. Although parental age effects have been reported for CL(P) [2], the data are still inconclusive as to whether the effect is predominately maternal or paternal.

A sex ratio distortion for both CL(P) and CP is well documented. CL(P) is more common in males, and CP is more common in females; however, there are exceptional populations [17]. We have no evidence in these data that the ratio of male to female probands (for either maternal or paternal half sibships) differs from expectation. The distorted sex ratio greatly limits testing for maternal effects with data collected from affected parents as the recurrence risk varies for children of the affected parent depending on whether the mother or the father is affected. These data include no instances of affected half sibs with affected parents.

TABLE 2

FREQUENCY OF CL(P) OR CP IN FIRST COUSINS OF CLEFT LIP OR ISOLATED CLEFT PALATE PROBANDS

Source	Type of Cleft	Relationship to Proband	No.	Frequency
[10]	CL(P)	Maternal cousins	5,807	.0027
	CL(P)	Paternal cousins	5,891	.0044
W. Krogman	CL(P)	Maternal cousins	2,003	.0059
	CL(P)	Paternal cousins	1,949	.0087
W. Krogman	CP	Maternal cousins	1,479	.0068
	CP	Paternal cousins	1,521	.0052

Because of the variation in racial incidence of CL(P), it would have been desirable to control for race in this data. The size of the sample, however, was too limited for such an analysis.

Since teratogens can produce CP or CL(P) in susceptible strains of mice [18, 19], four maternal half sibships with two affected half sibs were carefully reviewed for evidence of a responsible environmental factor. In one instance, there was a maternal history of epilepsy, and during both pregnancies, the mother was taking diphenylhydantoin sodium. A history of maternal epilepsy has been reported to be associated with a five to sixfold increase in risk of CL(P) [20]. However, in the other three instances, no factor was identified.

The pooled frequency in half sibs of .013 for CL with or without CP and .006 for CP is in agreement with a multifactorial hypothesis with the assumption that clefting is a genetic threshold characteristic. The pooled frequency of CL with or without CP in half sibs is 13 times the general population incidence of .001, approximately double that seen in third degree relatives and first cousins, and slightly more than half that of full sibs. In a heterogeneous population like this, a suitable control population does not exist.

The discrepancy between genetic backcross studies in mice [5] and results from blastocyst transfer [7] remains to be resolved; both studies are impossible in man. Demonstration of maternal effects in humans relies upon family, twin, or interracial cross studies which in turn depend on the meticulous collection of family histories and generous collaboration. Our data strongly suggest that a major maternal effect does not exist for human cleft lip and palate. The demonstration of a minor maternal effect will require information on more half sibships.

SUMMARY

To look for a persistent maternal effect on CL(P) and CP, 8,000 pedigrees were screened for half sibships, and data were pooled from 16 investigators. After excluding known genetic or cytogenetic diagnoses from the probands with facial clefts, a recurrence risk of .011 was obtained for CL(P) based upon 342 maternal half sibs. This was nearly identical to the risk of .014 based upon 210 paternal half sibs. CP proband frequencies of .004 for maternal half sibs and .009 for the paternal counterparts were also found. The lack of significant maternal effects in this data supports previously reported data from twin studies and from interracial crosses from Hawaii. The lack of maternal effect in human CL(P) and CP is in contrast to genetic data on clefting in mice.

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