Letters to the Editor

Am. J. Hum. Genet. 52:1270–1271, 1993

Genetic-Counseling Implications for Cleft Lip if an Autosomal Recessive Major Locus Accounts for All Cases

To the Editor:

Marazita et al. (1992) report the surprising finding that, for nonsyndromic cleft lip (with or without cleft palate) data, the autosomal recessive major-locus model fits best the available demographic and family data from Shanghai. Analyses of the type done by Marazita et al. have two main practical goals: (i) to lead to more accurate risks for genetic counseling in particular populations and (ii) to lead to eventual identification of underlying loci and their gene products and mechanisms of action. Whatever the consequences of their report for the second goal, which may indeed be considerable, they are silent about the first. They do not comment about recurrence risks in this population. Some readers of whom I am aware interpret their report as implying that, for individuals in the population studied, there is a 25% recurrence risk for nonsyndromic cleft lip.

I question this inference for several reasons. First, while of all models considered, the single-locus recessive model has the reported minimum Akaike Information Criterion (AIC), other models incorporating a multifactorial component actually fit the data better, if we judge by the reported χ^2 values. (The AIC is, in essence, a criterion based on parsimony. Conclusions based on this may be but are not necessarily correct.) Second, even if an autosomal recessive locus underlies all affected cases in this population, one cannot draw any inferences for genetic counseling, without appropriate data on or estimates of the sex-specific penetrances of the putative recessive disorder in this population. The estimated values of the variables which Marazita do report on imply a very wide range in penetrances and recurrence risks of the disorder, as I illustrate in table 1.

One may derive these values from Marazita et al.'s report of 279 affected (with a male/female sex ratio of 1.42) in 250,372 live births which have a sex ratio of 1.04. This implies a prevalence of 1.28/1,000 livebirths in males and 0.94/1,000 in females and that the male/female penetrance ratio is 1.28/0.94 = 1.37 = 1/0.73. Assuming a single-locus completely recessive disorder, the authors report an estimated gene frequency of .05 with a standard error (SE) of .08. (An SE larger than the estimate itself suggests a very wide range in the counseling implications of the putative model.) On the assumption that Hardy-Weinberg equilibrium and an autosomal recessive single-locus model apply, one may estimate (i) the associated sex-specific penetrance (e_i) and (ii) the recurrence risks (r_i) after birth of one affected offspring to unaffected parents, from equations in terms of the gene frequency (q) of the putative recessive at the hypothesized locus and the sex-specific disease frequency (d_i), where i = M for males and F for females:

$$q^2 = d_i/e_i\,; \tag{1}$$

$$r_i = e_i/4\,, \tag{2}$$

so

$$r_i = d_i/4q^2\,. \tag{3}$$

From the disease prevalences d_m and d_f given above, one may readily derive values of sex-specific penetrances

and associated recurrence risks after birth of a single affected child to unaffected parents, as a function of various values of gene frequencies within the range implied by the report by Marazita et al. (see table 1). For example, as the maximum penetrance (e_m) is 1.0, the maximum-likelihood estimate of the *minimum* putative allele frequency in this population is the square root of the disease prevalence in males, or .0358. A penetrance of 1.0 in males implies, of course, that the recurrence risk of an affected male after birth of a child of either sex to unaffected parents is 25% and that that of an affected female is about 18%, for a mean recurrence risk of almost 22%, much higher than 4%, which is usually cited in most European populations. But this is only the upper limit. The average recurrence risk if one assumes a gene frequency equal to the estimate by Marazita et al. *plus* 2 SEs (.21) is only 6/1,000, or 0.6%, much *less* than that counseled in European populations. (See table 1.) If, of course, one had a firm estimate of the empirically observed recurrence risk in this population, then one could derive from the equations above more precise estimates of the gene frequency and penetrances *on the assumption of the recessive model,* which may or may not be correct. An issue which has not been considered in the analysis is the possible selective embryonic and fetal loss of conceptuses with nonsyndromic cleft lip. Such loss (over and above reduced penetrance of alleles at a putative major locus) would lower the recurrence risk after birth of an affected individual, although this would also imply, if the population is in equilibrium, that there was some carrier advantage. There are too few data on prenatal selection (Hook 1988) to indicate how much effect, if any, this factor has on risk implications.

Ultimately, one must use empiric risk data for counseling until there are both (i) compelling proof for a putative simple model purporting to explain all genetic variation in a single population and (ii) firm estimates of variables such as penetrance if a single-locus model is established. Insufficient data are presented in the report to enable derivation of estimates for practical purposes. One hopes that the data may be deposited in readily available data banks or otherwise be made available, so they may be scrutinized and used by other investigators for such goals.

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Table 1

Variations in Recurrence Risk of Nonsyndromic Cleft Lip (With or Without Cleft Palate) after Birth of One Affected Offspring to Unaffected Parents on the Assumption of a Single Autosomal Recessive Locus with Varying Allele Frequencies[a]

	VALUE WHEN ALLELE FREQUENCY IS				
	.0358 (minimum)	.05[b]	.083[c]	.13[d] (+1 SE)	.21[e] (+2 SE)
Penetrance:					
Male	1.0	.51	.18	.076	.029
Female	.73	.37	.14	.056	.021
Recurrence risk of affected:					
Male	.25	.13	.05	.019	.007
Female	.18	.09	.03	.014	.005
Mean	.22	.11	.04	.016	.006

[a] Assuming prevalences of 1.28/1,000 live-born males, 0.94/1,000 live-born females, and other assumptions noted in the text.
[b] Point estimate reported by Marazita et al. (1992).
[c] Implied by recurrence risk of 4%, often cited in European populations (e.g., see Stevenson and Davison 1976, p. 244).
[d] Point estimate plus 1 reported SE.
[e] Point estimate plus 2 reported SEs.

References

Marazita ML, Hu D-N, Spence MA, Liu Y-E, Melnick M (1992) Cleft lip with or without cleft palate in Shanghai, China: evidence for an autosomal major locus. Am J Hum Genet 51:648–653

Hook EB (1988) "Incidence" and "prevalence" as measures of the frequency of congenital malformations and genetic outcomes: application to oral clefts. Cleft Palate J 25:97–102

Stevenson AC, Davison BCC (1976) Genetic counseling. Heinemann, London

0002-9297/93/5206-0028$02.00

Am. J. Hum. Genet. 52:1271–1272, 1993

Reply to Hook

To the Editor:

Hook (1993) queries the interpretation of the results of our study of cleft lip with or without cleft palate in Shanghai (Marazita et al. 1992) and suggests that the