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Familial Recurrence-Pattern Analysis of Cleft Lip with or without Cleft Palate

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Summary

Cleft lip with or without cleft palate (CL/P) is a common congenital malformation with an incidence in European white populations of about 1/1,000. The familial clustering of CL/P has been extensively characterized, and epidemiological studies have proposed monogenic models (with reduced penetrance), multifactorial/threshold models, and mixed major-gene/multifactorial models to explain its inheritance. The recognition of an association between two RFLPs at the transforming growth factor alpha (TGFA) locus and CL/P supports a major-gene component to the etiology of CL/P. Risch has shown that the recurrence risk ratio λ_R (risk to relatives, vs. population prevalence) is a useful pointer to the mode of inheritance. Here we further develop the use of λ_R to analyze recurrence-risk data for CL/P. Recurrence risks for first-, second-, and third-degree relatives equate well with oligogenic models with as few as four loci. A monogenic/additive model is strongly rejected. The limited available twin data are also consistent with this model. A "major gene" interacting epistatically with an oligogenic background is shown to be a plausible alternative. Power calculations for a linkage study to map the CL/P major-risk locus suggest that a sample of 50 affected sib pairs will be adequate, but linkage to minor-risk loci will require very much larger samples.

Introduction

Nonsyndromic cleft lip with or without cleft palate (CL/P) is one of the most common serious craniofacial malformations, with an incidence of about 1/1,000 live births in European white populations. Familial clustering of CL/P is consistently found in different populations (for review, see Melnick et al. 1980) and supports the hypothesis that genetic factors are important in the pathogenesis of CL/P. Empiric recurrence risks for relatives are regularly used in genetic counseling.

There has been considerable interest in specifying a genetic model that predicts the familial patterns of recurrence of CL/P. The multifactorial/threshold (MF/T) model has been used to estimate the heritability of CL/P (Carter 1969; Cavalli-Sforza and Bodmer 1971, pp 553–565). Melnick et al. (1980) reviewed worldwide CL/P recurrence-risk data and found that both an MF/T model and a monogenic with random environment component model fitted poorly. More recently, Marazita et al. (1984) suggested a major-gene effect in a subset of Danish CL/P families. Chung et al. (1986) have applied complex segregation methods to analyze a series of Danish and Japanese CL/P families, and this led them to propose a major-gene model acting on a multifactorial background. Other epidemiological studies have supported this major-gene hypothesis (Marazita et al. 1986; Chung et al. 1989; Hecht et al. 1991).

Ardinger et al. (1989) have provided additional evidence to support a major-gene model for CL/P, after testing RFLPs detected by "candidate genes" (i.e., genes which might reasonably influence the pathogenesis of CL/P) in an association study. They found a significant association between CL/P and two RFLPs at the transforming growth factor alpha (TGFA) locus which maps to human chromosome 2p13. This phenotype-genotype association between CL/P and

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TGFA has been independently confirmed by Chenevix-Trench et al. (1991) in an Australian white population and by Holder et al. (in press) in the British white population.

Risch (1990*a*) has developed the use of the recurrence risk ratio λ_R which was first examined by Penrose (1953) and which is defined as the qualitative-trait risk to a relative of a proband vis-à-vis the population risk, to show how the pattern of λ_R across classes of relatives can be used to indicate the mode of inheritance. For example, for a monogenic trait, $\lambda_R - 1$ is halved for each subsequent degree of relationship (e.g., $\lambda_{\text{siblings}} - 1 = 2(\lambda_{\text{uncles}} - 1)$). This pattern of recurrence risks has been shown to persist in the presence of phenocopies or despite reduced penetrance.

It is interesting that the pattern of recurrence risks across relationships is identical for a homogenous or heterogeneous monogenic trait and for an oligo- or polygenic trait, provided that the risks attributed to the constituent loci act additively. When more than one gene acts epistatically (i.e., when the risks for each locus act multiplicatively), then the decrease in λ_R is more precipitate (e.g., for a large number of epistatic genes each with small effect, $\lambda_{\text{sibling}} \approx \lambda^2_{\text{uncle}}$). Hence, the pattern of recurrence risks across several classes of relationship can discriminate between additive and multiplicative models for the underlying genetic trait, and, in the case of multiplicative models, the number of genes determining the overall risk can be estimated. Here we describe a likelihood method which is used to fit several genetic models for the inheritance of CL/P, a common congenital malformation for which there have been conflicting views as to the mode of inheritance.

Methods

London Family Data

Carter et al. (1982) have published data from an extensive family study of CL/P collected through 424 probands treated at the Hospital for Sick Children, London, between 1920 and 1939. The recurrence risk to offspring of probands (K_o) was 32/1,015 (3.15% ± 0.56%) and the sibling recurrence risk (K_s) was 29/1,038 (2.79% ± 0.52%). These recurrence risks are not significantly different, and the dominance variance (V_D) is therefore assumed to be zero. The risk to the parents of probands was 10/848 (1.18% ± 0.37%), this risk is significantly ($P = .0035$) less than the pooled risk for offspring and siblings.

There were no significant differences in the recurrence risks for nephews and nieces (K_{NN} = 7/1,488 [0.47% ± 0.18%]), aunts and uncles (K_{AU} = 20/3,400 [0.59% ± 0.13%]) or grandchildren (K_G = 2/251 [0.8% ± 0.6%]). Data for these three classes of second-degree relatives were pooled for subsequent analysis. The proportion of affected first cousins was 13/4,744 (0.27% ± 0.08%). There was only one set of MZ twins in the present study who were discordant for CL/P.

Northern England Family Data

Bear (1976) has published results compiled from 208 CL/P probands collected between 1970 and 1974 after treatment in two hospitals in northern England. K_s was 7/575 (1.22% ± 0.46%); the risk to parents was not significantly different 13/646 (2.01% ± 0.55%) ($P = .37$). K_{AU} was 11/2,022 (0.54% ± 0.16%), and the recurrence risk for third-degree relatives (cousins) was 12/3,185 (0.38% ± 0.11%).

The recurrence risks for second- and third-degree relatives are consistent between the studies. The risks for first-degree relatives show substantially more variation: in London the risk to parents (1.18%) is significantly less than K_s or K_o (2.97%); in northern England the risk to parents (2.01%) was not significantly higher than the K_s (1.22%). Carter et al. (1982) suggested that reduced reproductive fitness would explain the reduced proportion of affected parents of probands treated between 1920 and 1939. Presumably the parents of the probands studied by Bear (1976) would have been treated in the 1950s and were at less reproductive disadvantage. We have chosen to pool all classes of first-degree relatives for this analysis. The population prevalence of CL/P was estimated as 0.1% for the London study (Carter et al. 1982) and as 0.096% for northern england (Bear 1976); 0.098% is assumed in the analysis.

Other Family Data

Recurrence-risk data collected in Denmark by Fogh-Andersen (1942), in the United States (Salt Lake City and Phoenix) by Woolf (1971), and in France (Paris) by Bonaiti et al. (1982) were also analyzed. Recurrence risks in first-, second-, and third-degree relatives and population incidence are summarized in table 2.

Recurrence-Risk-Ratio Analysis

Denote the population prevalence of a disease by K and the frequency of recurrence of the disease in a type

R relative as K_R. The recurrence-risk ratio for a type R relative is then defined as $\lambda_R = K_R/K$ (e.g., for first-degree relatives, $\lambda_1 = K_1/K$). If L loci (if $L > 1$, then the risks attributed to each locus act multiplicatively) each contribute to the overall risk ratio, then, as has been shown by Risch (1990*a*), $\lambda_1 = \lambda_{11}\lambda_{21} \ldots$, λ_{L1}, where λ_{i1} denotes the contribution of the ith locus. Similarly, the risk ratios for second- and third-degree relatives can be computed from λ_{i1} (Risch 1990*a*):

$$\lambda_2 = \left(\frac{1}{2}\right)^L \prod_{i=1}^{L} (\lambda_{i1} + 1);$$
$$\lambda_3 = \left(\frac{1}{4}\right)^L \prod_{i=1}^{L} (\lambda_{i1} + 3).$$

The $\log_{10}$ likelihood of observing the recurrence rate of disease in first-, second-, and third-degree relatives can be computed by assuming a binomial distribution of exactly x affected relatives of type R observed in a sample of n relatives of the proband with a proportion $\lambda_R \times K$ expected and is given by

$$\log_{10}L(\lambda_1, \lambda_2, \lambda_3) = \sum_{R=1}^{3} \log_{10}P[b(x;n,\lambda_R \times K)].$$

The $\log_{10}$ likelihood ratio (Z) is given by

$$\sum_{R=1}^{3} \log_{10}P\left[\frac{b(x;n,\lambda_R \times K)}{b(x;n,x/n)}\right].$$

Z is conveniently defined in that a perfect fit of predicted λ_R's to the data gives $Z = .0$. Z was maximized for each model (with L loci), by iterating λ_{i1} by using a program incorporating the NAG (Numerical Algorithm Group Ltd., UK) quasi-Newtonian optimization routine E04JAF; the number of variables was restricted by equally weighting the contribution of each separate locus in multilocus models (i.e., $\lambda_{i1} = \lambda_1^{1/L}$).

Results

Table 1 shows Z values computed for the pooled English data set for first-, second-, and third-degree relatives. These results are also shown graphically in figure 1. The fit of the recurrence-risk-ratio model improves markedly as L increases (i.e., relative odds for 1, 2, 3, and 4 loci are 1, 4,266, 20,893, and 28,184). The maximal likelihood estimate (MLE) of the number of loci is 4. An approximate confidence interval or "lod minus 1" support interval (Conneally et al. 1985) for L, each with equal effect, is computed as $2 \leqslant L \leqslant \infty$; models within the interval are not more than 10-fold less likely than the MLE L (i.e., that computed for 4 loci).

Table 1

Recurrence-Risk-Ratio Analysis of English CL/P Families

No. of Loci	λ_{i1}	λ_1	λ_2	λ_3	Z
0	8.29	8.29	8.29	8.29	−22.99
1	15.79	15.79	8.39	4.70	−4.65
2	4.45	19.82	7.43	3.47	−1.02
3	2.78	21.41	6.73	3.01	−.33
4	2.17	22.15	6.31	2.79	−.20
5	1.86	22.56	6.03	2.66	−.21
10	1.37	23.24	5.45	2.42	−.44
20	1.17	23.50	5.16	2.31	−.66
50	1.07	23.64	4.98	2.25	−.82
100	1.03	23.67	4.93	2.23	−.88
500	1.01	23.70	4.88	2.21	−.93
1,000	1.00	23.71	4.88	2.21	−.94

An additional likelihood ratio was computed assuming that the recurrence risk to first-, second-, and third-degree relatives are identical ("zero locus" model). This tests the hypothesis that the observed pattern of recurrence in relatives arose by chance and is overwhelmingly rejected ($Z = -22.99$); it is reassuring that virtually all this statistic (99%) is attributable to the four-gene multiplicative model.

A two-locus model was then fitted, allowing both λ_{11} and λ_{21} to vary independently; this model fitted marginally better than did the two-locus model constrained by $\lambda_{11} = \lambda_{21}$. Similarly, for three- and four-locus models, allowing λ_{11}, λ_{21}, and λ_{31} (and λ_{41}) to vary independently did not significantly improve the fit.

Another model was considered, in which λ_{11} was held constant and in which a single parameter ($\lambda_{21} = \lambda_{31} = \lambda_{41}$) was varied. This strategy is designed to estimate the largest plausible effect of a single locus acting on an oligogenic background, in other words to determine the largest "major-gene" effect. For a four-locus model, with $\lambda_{11} = 8.88$ and $\lambda_{21} = \lambda_{31} = \lambda_{41} = 1.32$, $Z = -1.20$; this model fits 10-fold less well than does the best-fitting model with four loci each with equal effect. The overall fitted λ_1 for this model is 20.3 ($\lambda_{11} \times \lambda_{21} \times \lambda_{31} \times \lambda_{41}$), so the major risk locus determines 8.88/20.3 = 44% of the recurrence-risk ratio. The relative contribution of the

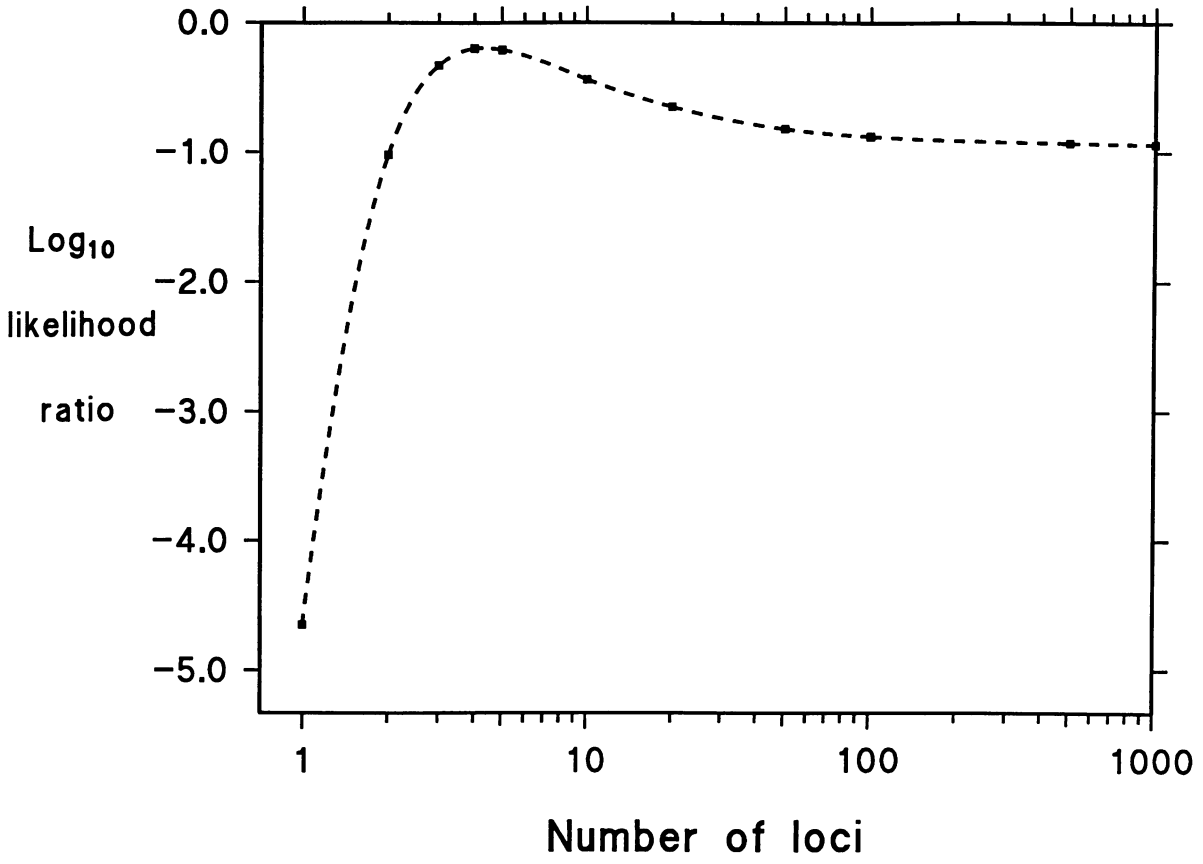

Figure 1 Log_{10} likelihood ratios displayed graphically, computed for combined English data set for models with 1–1,000 equally acting genes. Data points are connected by a dashed line for illustrative purposes.

major locus to the minor loci is $(8.88-1)$:(1.32^3-1) (i.e., 86% [7.88/(7.88 + 1.3)] of the "genetic" component of CL/P is determined by a single major locus).

A similar analysis was performed with data collected in Denmark (Fogh-Andersen 1942), in the United States (Woolf 1971), and in France (Bonaiti et al. 1982). In all three data sets, oligogenic models fitted substantially better than did a monogenic/additive model. Summary results (table 2 and fig. 2) show that for the Danish data, a 75-gene model fits 2.6×10^{12} times better than does the monogenic model, that for the U.S. data a 17-gene model fits 3 billion–fold better, and that for the French data a 7-gene model fits 700-fold better. Plausible "major genes" with 5-, 6-, and 12-fold λ_{11} were found for the Danish, U.S., and French data sets, respectively.

Finally, a joint analysis of all four data sets was performed, and a single λ_{i1} determined the pattern of recurrence risks in first-, second-, and third-degree relatives in the three populations. Overall there is substantial evidence to reject a single-gene model (1 vs. 8 loci; odds $1:[3 \times 10^{25}]$), the largest plausible major-gene effect was 4.9. For recurrence risk ratios, there was, however, significant evidence of heterogeneity between the four populations ($\chi^2_3 = 19.3$; $P = .00024$). This was estimated by computing the likelihood difference $([Z_{Denmark} + Z_{USA} + Z_{France} + Z_{England}] - Z_{joint})$, where each Z was computed for the appropriate MLE number of loci, which, when expressed as a $-2 \log_e$ likelihood difference is distributed as a χ^2 statistic with 3 df.

Discussion

We have shown here that the extensive published recurrence-risk data, which have previously been widely interpreted to be consistent with an MF/T pattern of inheritance, are equally compatible with an

Table 2

Recurrence-Risk-Ratio Analysis of CL/P in Four Populations

Population	K	λ_1 (N)	λ_2 (N)	λ_3 (N)	Z for Model With: No Genes[a]	One Gene[b]	MLE No. of Genes (no. of genes)[c]	Largest Plausible λ_{11}
Denmark.....	1.1/1,000	44.66 (1,140)	7.32 (5,343)	2.24 (7,703)	-33.02	-12.57	-.15 (75)	4.92
United States...	1.2/1,000	33.35 (1,574)	5.44 (4,747)	2.99 (11,698)	-30.55	-9.86	-.35 (17)	5.82
France.....	.82/1,000	36.84 (927)	5.18 (3,508)	4.52 (4,858)	-11.35	-3.91	-1.07 (7)	12.25
England	.98/1,000	22.53 (4,122)	5.70 (7,161)	3.22 (7,929)	-22.99	-4.65	-.20 (4)	8.88
Overall.....						-31.49	-5.97 (8)	4.71

[a] Assumes that familial clustering has arisen by chance.
[b] Computed for monogenic model
[c] Computed for best-fitting model with variable number of genes.

oligogenic model with perhaps as few as four genes. Our tests also show that a gene associated with 5–12-fold elevation of sibling risk vis-à-vis the population incidence is plausible. This strengthens the proposition of a major-gene effect in CL/P, a proposition suggested by both classical and complex segregation analysis (Marazita et al. 1984, 1986; Chung et al. 1986, 1989; Hecht et al. 1991) and which has received indirect support from the observation of an association to RFLPs detected by TGFA (Ardinger et al. 1989).

Inspection of figure 2 clearly shows that there is scant discrimination between oligogenic and polygenic models, in any of the data sets. For example, in the Danish sample of >14,000 relatives of CL probands, the best-fitting model with 75 loci only fits 12-fold better than does a 5-locus model. This reflects the low power of recurrence-risk analysis to distinguish polygenic (e.g., >20 loci) from oligogenic (e.g., ≤5 loci) models with typical sample sizes. Analytic problems would also result from genetic heterogeneity in the sense that CL/P is determined by a monogenic mechanism in some families and by a polygenic mechanism in others. A joint analysis of pooled families with a heterogeneous etiology would most likely result in an oligogenic model being proposed.

Apart from random sampling error, recurrence-risk analysis, in common with other family studies, is subject to nonrandom biases (e.g., ascertainment). For example, in the Carter et al. (1982) data set the risks to parents of probands were lower than the risks to offspring, which might be due to reduced fertility of severely affected individuals born and treated during the first 2 decades of this century.

Shields et al. (1979) have reported a study of CL/P in Danish twins. They computed a 36.4% (±14.5%) pairwise concordance rate for MZ twins and a 1.5% (±1.5%) concordance rate for DZ twins. The latter recurrence rate is lower but consistent with the contemporaneous first-degree-relative risks reported for the Danes (Melnick et al. 1977). Using the Danish summary data (Melnick et al. 1977), with $K = .0011$ and $K_1 = 3.8\%$, we compute $\lambda_1 = 34.4$, and, assuming that there are eight epistatic genes with equal effects (the best-fitting model from the joint analysis), we find that the recurrence-risk ratio associated with one of these genes (λ_{i1}) is 1.56. The recurrence-risk ratio for MZ twins (λ_M) (when one assumes $V_D = 0$) is given by $\lambda_M = [2(\lambda_{i1} - 1) + 1]^8 = 396$ (i.e., the pairwise concordance rate is $\lambda_M \times K = 44\%$), which is close to that reported by Shields et al. (1979).

A large body of recurrence-risk data have been collected for the Danish population. Melnick et al. (1977) have summarized the recurrence of CL/P in Denmark for 16,585 first-, second-, and third-degree relatives collected in a pioneering study by Fogh-Andersen (1942) and whose data have been updated by Bixler et al. (1971). As noted by Melnick et al. (1977), the recurrence rate drops off markedly from first-degree relatives (84/2,217 = 3.8%) to second-degree (47/7,316 = 0.6%) relatives but, paradoxically, increases in third-degree relatives (62/7,052) = 0.9%). This pattern is both inconsistent with the other data sets we have examined and incompatible with any of the genetic models investigated, and we have not attempted to analyze these data further.

There have been two mixed-model segregation analyses of the Danish CL/P family data (Marazita et

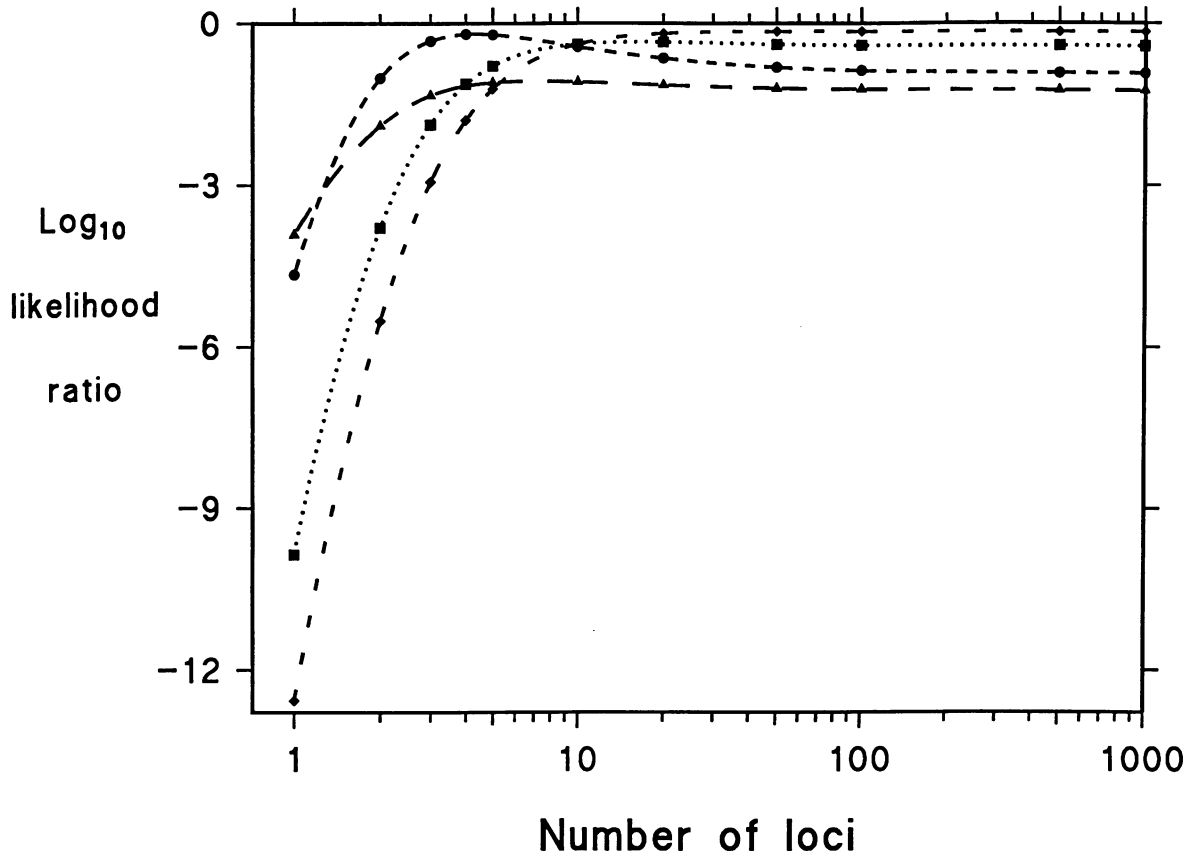

Figure 2 Log_{10} likelihood ratios computed for Danish (♦--♦), U.S. (■ . . . ■), French (▲— —▲), and English (●— —●) data sets for 1–1,000-locus models.

al. 1984; Chung et al. 1986). Marazita et al. (1984) found no support for a multifactorial threshold model but suggested the possibility of a major gene in at least some kindreds. They noted that 8 of 26 multigenerational families were consistent with autosomal recessive inheritance and that 3 of 26 showed a codominant pattern; the remainder were inconsistent with simple Mendelian models. Chung et al. (1986) concluded that the best-fitting model predicted a recessive major gene (with a population frequency of 3.5%) acting on a multifactorial background. They predicted that this major gene would account for about a third of Danish CL/P. We estimate that the largest plausible major-gene effect explains 35%, 55%, 90%, and 86% of "genetic" CL/P for the Danish, U.S., French, and English data sets, respectively.

There have been several epidemiological studies attempting to detect a "major gene" for CL/P in other populations. Chung et al. (1974) analyzed CL/P in a Hawaiian sample of families by using complex segregation methods but were unable to discriminate between alternative models. Mendell et al. (1980), in a study of North Carolina Caucasians, failed to reject a multifactorial threshold model. Marazita et al. (1986) have reported a mixed-model segregation analysis of the English multigenerational CL/P families collected by Carter et al. (1982). They were able to reject an MF/T model and demonstrated that a major locus acting on a multifactorial background gave a reasonable fit. Chung et al. (1986) found that a Japanese data set was best explained by multifactorial inheritance. Chung et al. (1989) analyzed Hawaiian families from several racial groups and found that the data were consistent with a major-gene/multifactorial model. Hecht et al. (1991) analyzed midwestern U.S. Caucasian families and showed consistency with a major-locus model.

Risch (1990*b*) has shown that the power of a pro-

posed study to detect linkage to a susceptibility locus underlying a complex genetic trait can be conveniently computed using the λ_R associated with the susceptibility locus. For the "largest plausible λ_{i1}" model for the English data set ($\lambda_{i1} = 8.88$), we estimate that 50 pairs of affected sibs would give an 83% chance of detecting linkage to a fully informative marker that shows no recombination with the disease locus. If the marker's PIC is only .5, then about twice the number of affected relative pairs will be needed to achieve the same power.

If three other loci equally contribute to the residual recurrence risk, then $\lambda_{21} = \lambda_{31} = \lambda_{41} = (\lambda_1/\lambda_{i1})^{1/3} = (22.52/8.88)^{1/3} = 1.4$. An affected-relative-pair linkage test would need 800 pairs of sibs for an 80% power to detect linkage with a completely informative marker with no recombination.

Kurnit et al. (1987) have proposed a stochastic genetic model in which chance and a single gene interact to explain the segregation of common malformations that cluster in families but recur less frequently than expected for a simple Mendelian trait. Using a model proposed by James (1971), Kurnit et al. (1987) derived, for a two-allele autosomal locus, equations to compute, in terms of gene frequency and genotype-specific penetrances, the probability of occurrence of an all-or-nothing trait in *n*th-degree relatives. The equations derived by Kurnit et al. (1987) and Risch (1990*a*) are both based on the same underlying model (James 1971), and it is therefore not surprising that identical patterns of recurrence in relatives are predicted by both methods.

Edwards (1969) has derived an equation (extending earlier work of Pearson [1990]) that computes the phenotypic correlation coefficient (ρ) from the population incidence of a threshold trait (i.e., K) and λ_R and that offers a good approximation and is simple to compute (see the Appendix). The correlation between various classes of relatives (ρ_R) can be used to estimate the heritability (h^2) (Cavalli-Sforza and Bodmer 1971, pp 553–565). If it is assumed that the h^2 estimates computed from the K_R in various classes of relatives should be equal, then it follows that the λ_R in any class of relatives can be computed from the correlation in first-degree relatives (ρ_1) and the population incidence (see the Appendix).

Likelihood ratios (computed in a manner analogous to those derived from estimating λ_{i1} by using Risch's equations) can be used to find the overall weighted estimate of ρ (and therefore h^2), as well as to measure the goodness-of-fit of the model to the recurrence-risk data. The model gave a good fit to the English ($h^2 = .72$; $Z = -.28$), Danish ($h^2 = .91$; $Z = -.85$), U.S. ($h^2 = .84$; $Z = -.61$), and French ($h^2 = .82$; $Z = -1.08$) data sets. These results are consistent with those reported in table 2, as the decrease in λ_R with degree of relationship, a decrease predicted by Edwards' model, is similar to that predicted by Risch's oligogenic model with five equally acting genes.

In conclusion, it is heartening, for those involved in molecular genetic studies that aim to identify genes involved in the pathogenesis of CL/P, that the extensive recurrence-risk data sets, which had been widely interpreted as providing evidence of a polygenic multifactorial trait, are consistent with a model with a major-gene effect contributing to about a third of CL/P and acting on an oligogenic background. We would note, however, that it seems unlikely that minor genes will individually contribute a risk of sufficient magnitude to be detected in an association or affected-relative-pair linkage study.

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Appendix

Edwards (1969) has extended and elaborated the work of Pearson (1900), to compute ρ from the incidences of a threshold character in relatives of a proband and in the general population. Edwards (1969) has suggested the following approximation, which is easy to evaluate:

$$\rho_R = \frac{.57\log_{10}\lambda_R}{-\log_{10}K - .44\log_{10}\lambda_R - .26}.$$

$\rho_R = H^2 r_R$ (Cavalli-Sforza and Bodmer 1971, pp 553–565), where r_R for first-, second-, and third-degree relatives is 1/2, 1/4, and 1/8, respectively. If it is assumed that the h^2 estimated from each K_R should be equal, then K_R's are given by

$$\lambda_R = \text{antilog}_{10}\left[\frac{2\rho_1 r_R(-\log_{10}K - .26)}{.88\rho_1 r_R + .57}\right].$$

A weighted estimate of the overall h^2 and a Z measuring the goodness-of-fit can be computed by iterating

ρ_1 (in a way analogous to estimating λ_{i1}) to fit the recurrence-risk data for first-, second-, and third-degree relatives.

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