Am. J. Hum. Genet. 49:674–681, 1991

Complex Segregation Analysis of Nonsyndromic Cleft Lip and Palate

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Summary

This study was undertaken to examine the inheritance pattern of nonsyndromic cleft lip with or without cleft palate (CL/P). Complex segregation analysis using the unified model as in POINTER and the regressive model as in REGD programs were applied to analyze a midwestern U.S. Caucasian population of 79 families ascertained through a proband with CL/F. In REGD, the dominant or codominant Mendelian major locus models of inheritance were the most parsimonious fit. In POINTER, besides the Mendelian major locus model, the multifactorial threshold (MF/T) model and the mixed model were also consistent with the observed data. However, the high heritability parameter of .93 (SD .063) in the MF/T model suggests that any random exongenous factors are unlikely to be the underlying mechanisms, and the mixed model indicates that this high heritability is accounted for by a major dominant locus component. These findings indicate that the best explanation for the etiology of CL/P in this study population is a putative major locus associated with markedly decreased penetrance. Molecular studies may provide further insight into the genetic mechanism underlying CL/P.

Introduction

Nonsyndromic cleft lip with or without cleft palate (CL/P) is a common, severe birth defect affecting 1/800–1/1,000 newborns (Fraser 1970). Familial recurrences have suggested a heritable etiology, but early studies did not identify a Mendelian pattern of inheritance (Fraser 1970; Carter 1976). The multifactorial threshold model was developed to describe the observed non-Mendelian recurrences of CL/P, as well as other common birth defects (Fraser 1970; Carter 1976). However, some study results did not fit the expectations of this model (Melnick et al. 1980). Dissatisfaction with the multifactorial model has led to reexamination of some population-based studies by using complex segregation analyses (Marazita et al. 1984, 1986; Chung et al. 1986). The results of these studies have indicated that, in at least some families, a major gene played an etiologic role and that genetic heterogeneity may be present. Recently, a number of multigenerational families have been described in which recurrence in families suggested autosomal dominant inheritance (de Paepe 1989; Temple et al. 1989; Hecht 1990). This latter finding was particularly striking in a population-based family study of CL/P in southeast Minnesota, in which 11 families were found to have CL/P following a pattern suggestive of autosomal dominant inheritance (Hecht 1990). The present study was undertaken to examine the pattern of inheritance in CL/P in a midwestern U.S. Caucasian population.

Methods

Seventy-nine families were ascertained through a proband diagnosed with CL/P at the Mayo Clinic/Foundation. CL/P at the Mayo Clinic/Foundation. CL/P probands were identified through the Mayo Clinic medical linkage registry which links medical records of four outside medical institutions also servicing Rochester and southeast Minnesota. The method-

Received March 15, 1991; revision received May 24, 1991.

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0002-9297/91/4903-0022$02.00

ology of the ascertainment has been described by Hecht et al. (1989). These probands represent virtually complete ascertainment of individuals with CL/P in southeast Minnesota during the years 1935–86 (Hecht et al. 1989). The family structure consisted of the proband, the proband's parents, and all of the proband's, proband's sibs', and proband's parents' descendants.

In order to test the hypothesis of a genetic basis for familial aggregation, it is necessary to employ analytic methods that model the transmission of genetic susceptibility. This is accomplished through the use of complex segregation analysis. In the present study, two alternative analytic strategies were employed. The first, regressive models, examines the correlation between relatives in terms of family data (Bonney 1986). The second, the mixed model (Elston and Stewart 1981; Morton and MacLean 1974), is based on variance components.

Regressive models represent an extension of conventional logistic regression. In brief, a regression relationship is formulated such that the phenotype of the individual (i.e., CL/P or no CL/P) is dependent on an unobserved "type" and other measured explanatory variables or covariates. These types are modeled such that they are dependent on the types of preceding relatives and therefore allow one to explicitly account for the interindividual correlations inherent in familial data. In the case of genetic susceptibility, these "types" can be modeled with the properties of genes and can be thought of as genotypes. As such, statistical tests can be constructed to evaluate whether the observed distribution of a given phenotype is consistent with an underlying genetic etiology.

Regressive models as implemented in the REGD module of the Statistical Analysis for Genetic Epidemiology (SAGE) computer package were used in the present study (SAGE version 2.0, copyright R. Elston). In this module the influence of genetic factors is assessed by utilizing the class A regressive model (Bonney 1986). In this model, risk (β) is assessed by the introduction of three types; aa, ab, and bb. Under genetic models these types are tested under the assumption of alternative Mendelian constraints. More specifically, genetic susceptibility is related to the segregation of two alleles (a and b) of a single locus. The risk-producing allele (a) is present in the population with frequency q. Genotypes (types) are transmitted from parent to offspring with Mendelian probabilities (τ). Sex was included as a covariate in all models.

The likelihood of a general unrestricted model is first calculated and then is compared with a variety of models with one or more parameters restricted. To test a hypothesis, minus twice the natural log likelihood ($-2\ln L$) of the general model is subtracted from $-2\ln L$ of the restricted model of interest. The difference is distributed asymptotically as a χ^2 with $n - k$ df, where n is the number of parameters estimated in the general model and k the number in the hypothesis tested. A series of eight models were tested against a general model in which all pertinent parameters were estimated, so that each of the eight models was a subset of the general model. The no-major-gene model assumes that the baseline risk is sex dependent but not influenced by type. The major gene model assumes that, besides the sex influence, there may be a major locus, with two alleles acting in either autosomal dominant, codominant, or recessive patterns. The "decreasing" and "arbitrary" models test the placement of the heterozygous genotype. Nongenetically determined type-specific risk or environmental models (τ's equal and $\tau = q$) were also tested.

Population birth prevalence of CL/P cannot be incorporated into the current version of REGD. This limitation may lead to an inaccurate parameter estimation if the latter is based only on observed data of a small sample. To overcome this, 15,384 individuals without families with five affected females and 10 affected males were included in the observed data in a second analysis (G. E. Bonney, personal communication). These numbers correspond to the sex-specific incidences of CL/P in the Caucasian population.

Familial clustering and transmission were also evaluated utilizing complex segregation analysis by assuming the mixed model of genetic susceptibility. This analysis was employed both for comparability to previous studies of CL/P and because alternative sources of familial correlation (e.g., multifactorial threshold, major locus with multifactorial threshold, etc.) are specifically evaluated. This analysis utilized the unified version of the mixed model of Morton and MacLean (1974), including both the modifications introduced by Lalouel and Morton (1981) and the transmission frequencies of Elston and Stewart (1971). For detailed discussion of the unified mixed model, see the work of Lalouel et al. (1983). In brief, the unified mixed model assumes that the total phenotypic variance can be decomposed into variance due to (*a*) a major locus (a single genetic factor), (*b*) a multifactorial component (multiple genes of small effect and/or environmental factors), and (*c*) residual random environment.

The unified model is formulated in terms of quanti-

tative traits but can be used for qualitative traits by defining, on an underlying continuous-liability scale, a threshold whose crossing results in affection. Liability is a measure of the risk of affection (morbid risk). To account for variation in the risk of affection for subsets of individuals, the threshold's relative position on the liability scale is shifted. Such an adjustment is equivalent to defining a different threshold for each risk class. In the case of CL/P, liability classes were defined based on sex. Analysis was performed utilizing the "Paris" version of the computer program POINTER (Lalouel and Morton 1981) obtained courtesy of S. Russell (Division of Biostatistics, Washington University, St. Louis), running on an MIPS 3240 UNIX workstation.

The unit of analysis in POINTER is nuclear families. As such, it is necessary to decompose multigenerational pedigrees into smaller units. Pointers to nuclear families without probands indicate how the family entered the study (Lalouel and Morton 1981). The model has five major parameters: q is the frequency of a putative gene for CL/P; d is the degree of dominance; h^2 is the heritability which measures multifactorial inheritance; t measures the major gene effect as the distance between two homozygotes; and τ is the transmission probability of the risk allele from heterozygous individual genotype Aa. Sex differences were incorporated into the model by using the incidence of CL/P at birth, .00064 for females and .0013 for males (Chung et al. 1989). Two of the 79 families had two probands each, but only one was used in all analyses. Among a total of 95 cases, 81 were identified as probands or index cases. An empirical ascertainment probability (Pi) of .853 based on the collected data was also incorporated into the model.

The models were tested in POINTER by the same likelihood ratio test as in REGD. Akaike (1974) information criteria (AIC) were applied to the data when more than one model fit the data, in order to determine which was the most parsimonious model. AIC = $-21nL + 2$(number of parameters estimated), where the model with the smallest AIC was considered the best.

Results

A total of 487 individuals from 79 families were studied (table 1). Within the 79 families, there were 116 nuclear families. There were 53 male and 26 female probands, demonstrating the expected male to female ratio of 2:1. Fifteen relatives with CL/P were identified in 12 families: two (19%) were children of probands; nine (56%) were parents; three (19%) were sibs; and one (7%) was niece/nephew (fig. 1).

Table 1

Descriptive Information about CL/P Families

Sex	No. of Individuals	No. Affected (%)	No. of Affected probands (% of total no. affected)[a]
Male.....	270	66 (24.4)	53 (80.3)
Female	217	29 (13.4)	26 (89.7)
Total	498	95 (19.5)	79 (83.2)

[a] One proband/family.

Table 2 shows the mating types for the 116 nuclear families. Of the matings, 98 (85%) were the result of normal father × normal mother. Males were affected twice as frequently in all of the mating types.

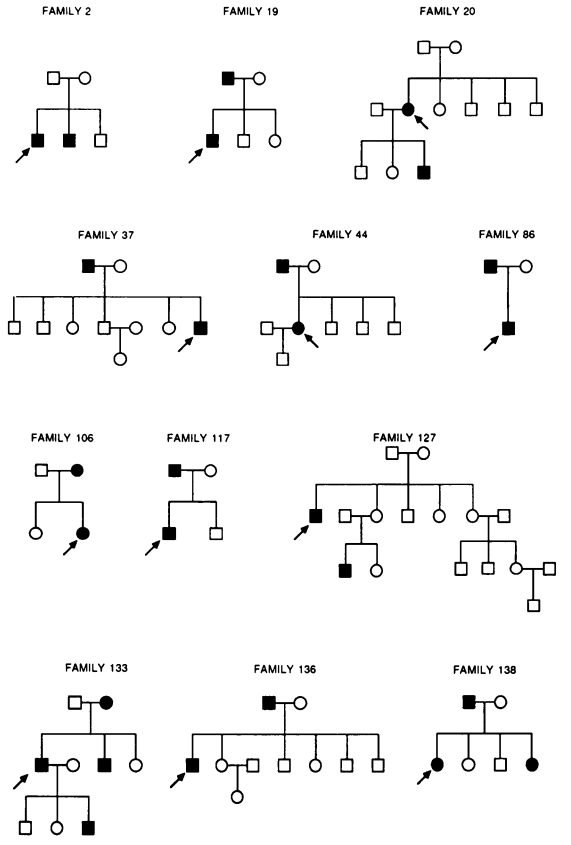

Figure 1 Pedigrees of 12 multiplex families demonstrating affected family members. Arrows indicate probands.

Table 2

Distribution of Mating Types of 116 Nuclear Families from 79 Pedigrees

Mating Type (no.)	No. of Affected Sons	No. of Affected Daughters
Normal mother × normal father (98)	50	23
Normal mother × affected father (14)	6	3
Affected mother × normal father (5)	2	1
Total (116)	58	27

The REGD (unadjusted data) and POINTER analysis rejected the no-major-gene and autosomal recessive major gene models ($\chi^2_{(df's = 4 \text{ and } 6)} = 11.03$ and $P < .05$ for both models in REGD; $\chi^2_{(df = 4)} = 38.1$ for the recessive model and $\chi^2_{(df = 2)} = 7.09$ for the sporadic model and $P = .00$ in POINTER), but neither program rejected the autosomal dominant and codominant major gene models ($\chi^2_{(df = 4)} = 2.9$ and $P = .60$ for both models in REGD; $\chi^2_{(df = 2)} = 0.46$ and $P = .80$ in POINTER (tables 3–5). REGD rejected τ's equal and τ's = q models, indicating that nongenetically determined type-specific risk models did not explain the observed familial aggregation of CL/P. The multifactorial mod-

Table 3

Complex Segregation Analysis Using POINTER on 79 Families Each with a CL/P Proband

Model	Value of Parameter								
	−2ln	df	χ^2	P	D	T	Q	H	τ_2
Sporadic	224.4922	4	43.5561	.00	[.0][a]	[.0]	[.0]	[.0]	[.5]
Multifactorial	182.1968	3	1.4573	.70	[.0]	[.0]	[.0]	.9311	[.5]
Recessive	189.2488	2	8.3127	.00	[.0]	2.5650	.0652	[.0]	[.5]
Dominant	181.3833	2	.4472	.80	[1.0]	2.6200	.0004	[.0]	[.5]
Codominant	181.3856	2	.4495	.80	[.5]	5.2430	.0004	[.0]	[.5]
Mixed	181.3797	1	.4436	.80	1.0000[b]	2.6120	.0004	.0064	[.5]
General	180.9361	. . .	0	. . .	1.0000[b]	2.3090	.0005	.0070[a]	.2940[a]

NOTE.—Liability for male = .00130; liability for female = .00064; π = .840 (79/94).

[a] Fixed initial value.

[b] Set at a bound by POINTER.

Table 4

Results from REGD on 79 Families with CL/P Proband

Model	Value of Parameter									
	−2lnL	df	χ^2	P	q(a)	βaa	βab	βbb	βsex	AIC
No major gene	129.3000	6	11.0278	.06	[1.0000]	−4.1433	−4.1433	−4.1433	1.3901	133.3000
Dominant	121.2074	4	2.9352	.60	.0004	.2818	.2818	−5.5424	2.4147	129.2074
Codominant	121.2075	4	2.9353	.60	.0004	6.1042	−.2814	−5.5415	2.4139	129.2075
Recessive	129.3000	4	11.0278	.025	.0000	4.7533	−4.1431	−4.1431	1.3900	137.3000
Decreasing	123.4473	3	5.1756	.15	.0001	29.8402	−2.4660	−11.4320	1.5523	133.4478
Arbitrary	121.2067	3	2.9345	.40	.0004	30.1000	−.2823	−5.5407	2.4131	131.2067
Equal τ_s[a] (.0424)	127.6041	2	9.3319	.01	.1065	−1.1639	−2.4273	−5.6756	1.6187	139.6041
τ = q	129.3000	3	11.0278	.01	.0002	−.7491	−.8544	−4.1583	1.4000	139.3000
General (τaa = 1.0000; τab = .0947; τbb = .0055)	118.2722		. . .[b]		.0066	33.8322	−1.2181	−32.8477	27.3533	136.5287

[a] Estimated along with other parameters in this model.

[b] −2lnL of general model served as background for χ^2 test.

Table 5

Results from SAGE-REGD on 79 Families with CL/P proband and 15,384 Simulated Individuals (five affected females and 10 affected males)

Model	Value of Parameter									
	−2lnL	df	χ^2	*P*	*q*(a)	βaa	βab	βbb	βsex	AIC
No major gene	440.8674	6	83.6048	.00	[1.0000]	−6.8922	−6.8922	−6.8922	1.0548	444.8674
Dominant	360.4909	4	3.2283	.55	.0012	2.1365	2.1365	−8.2657	1.1047	368.4909
Codominant	360.4925	4	3.2299	.55	.0012	3.9652	−2.1538	−8.2728	1.1110	368.4925
Recessive	415.5181	4	58.2555	.00	.0207	21.8750	−7.5403	−7.5403	1.1539	433.5181
Decreasing	360.4854	3	3.2228	.55	.0012	−.3493	−2.1466	−8.2698	1.1056	370.4854
Arbitrary	360.4854	3	3.2228	.55	.0012	−.3533	−2.1454	−8.2688	1.1052	370.4854
Equal τ_s[a] (.2410)	419.3160	2	62.0543	.00	.0118	−4.0977	−3.2789	−46.8977	1.0908	431.3160
τ = q	440.8674	3	83.6048	.00	.0000	−3.6703	−.0837	−6.8921	1.0548	450.8674
General (τaa = 1.0000; τab = .1930; τbb = .0011)	357.2626		. . .[b]	. . .	.0013	51.2578	−1.3578	−45.6711	1.5986	373.2626

[a] Estimated along with other parameters in this model.
[b] −2lnL of general model served as background for χ^2 test.

el in POINTER also fit the data. The decreasing and arbitrary models in REGD both fit the data and yielded estimated parameters equivalent to those in the autosomal codominant major gene model. χ^2 and AIC testing indicate that the best-fitting REGD models are autosomal dominant and codominant major gene models (tables 4 and 5).

As expected, the most parsimonious model did not differ between REGD analysis of the original data set and REGD analysis of the data set including individuals added to adjust the population incidence. However, differences in the parameter estimations were observed (tables 4 and 5). The autosomal codominant major gene model was selected to compare the specific parameters estimated in REGD and POINTER programs. Comparisons of the estimated allele frequencies and genotype-specific penetrances are shown in table 6. The incidence-adjusted data in the REGD programs produced estimates with narrower confidence intervals and more similar to the POINTER results.

Although 12 families had parent-to-child transmission of CL/P, when each family was examined in terms of contributions of likelihood to each model, only nine families contributed to discrimination be-

Table 6

Comparison of Some Parameters Estimated from POINTER and REGD under Codominant Model

Selected Parameter[a]	POINTER Estimates[b]	REGD (original data) Estimates (95% CI)	REGD (adjusted data) Estimates (95% CI)
q	.0004	.0004 (.0000, .0014)	.0012 (.0000, .0035)
Paa:			
M	.9860	.9998 (.5281, 1.0000)	.9938 (.8906, .9997)
F	.9740	.9978 (.4659, 1.0000)	.9813 (.8690, .9982)
Pab:			
M	.3260	.9367 (.0743, .9996)	.2611 (.0322, .7886)
F	.2450	.5699 (.0589, .9656)	.1040 (.0264, .3318)
Pbb:			
M	.0010	.0420 (.0006, .7501)	.0008 (.0001, .0065)
F	.0004	.0004 (.0005, .0299)	.0003 (.0001, .0009)

[a] P = penetrance: probability being affected for a given genotype.
[b] Point estimates used for comparison purpose.

tween the models (fig. 2). Five multiplex families (families 2, 20, 127, 133, and 138) supported the autosomal dominant and codominant major gene models. Four multiplex families (families 19, 37, 44, and 136) did not contribute to the autosomal dominant and codominant major gene model models but provided data that rejected the autosomal recessive major gene model. Three multiplex families (86, 106, and 117) did not contribute to any of the models.

Discussion

The results of the present study show that the dominant or codominant models with decreased penetrance best fit this data set. Discrimination between models was based on the following criteria: Both the MF/T model with an h^2 near 1 and the mixed model with a dominant major gene effect and an h^2 near zero were found to provide an explanation of familial clustering pattern. The high heritability estimate in the multifactorial model converges on zero in the mixed model in which the parameter estimates are close to the dominant model (table 3). This implies that most of the genetic variability in the mixed model could be accounted for by the single gene component. Complex segregation analysis of a population-based data set from Hawaii obtained similar results, but with a recessive mode suggested for the major locus (Chung et al. 1989).

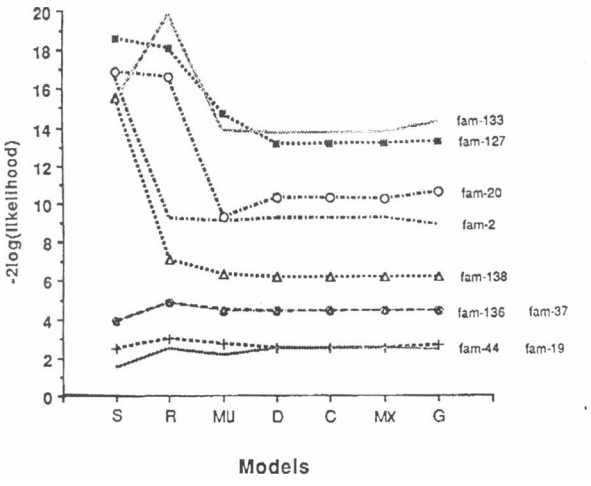

Figure 2 Likelihood distributions for nine multiplex families contributing to models. Families 2, 20, 127, 133, and 138 contributed to the autosomal dominant and codominant models. Families 19, 33, 44, and 136 did not contribute to the autosomal dominant and codominant models but contributed to the rejection of the autosomal recessive model. S = sporadic; R = recessive; MU = multifactorial; D = dominant; C = codominant; MX = mixed; G = general.

The autosomal dominant and codominant models in REGD and POINTER both explain the data equally well. There are only trivial differences between these two models when parameters are interpreted. The number of homozygotes (aa), on the basis of the estimated allele frequency (i.e., q) of .0004, is .00000016, or $1.6/10^7$ in the population. Thus individuals with an aa genotype would account for only 0.006% of CL/P cases and can be ignored, as we would not expect one case in our study population.

Penetrance in either the dominant or codominant models was markedly decreased, being 33% in males and 24% in females in POINTER, 26% in males and 10% in females in the dominant model (adjusted data), and 44% and 46% in males and females, respectively, in the codominant model (unadjusted data) in REGD. The decreased penetrance associated with this putative gene(s) provides the impression of irregular inheritance, as has been noted in large population studies). However, we have demonstrated that the best genetic explanation for CL/P in families is a dominant/codominant model with decreased penetrance. The factors influencing penetrance of this putative gene are unknown.

It is interesting that the results of the alternative models of segregation analysis are similar, which is not altogether unexpected. Demenais and Bonney (1989) and Demenais et al. (1990) have shown that, under a set of limiting assumptions, regressive models and the mixed model are algebraically equivalent. One practical difference in the analytic strategies entailed the use of population incidence data. Although complete ascertainment of cases can be achieved in defined populations, it is rare that the sample of collateral relatives and spouses is large enough to allow the incidence to be accurately estimated from within the data set itself. The mixed model, as implemented in POINTER, allows correction for this by the introduction of liability scores. No similar correction is available for the regressive model implemented in REGD. However, it was possible to add a collection of individuals, in the appropriate population proportions, to the analysis. Tables 4 and 5 show the results of model fitting with and without the correction. From tables 4 and 5 it can be seen that equivalent models were obtained. Table 6 presents a comparison of the parameter estimates from the mixed-model analysis, regressive analysis without adjustment, and regressive models with adjustment (when a codominant model is assumed). Ta-

ble 6 indicates that the pointer and adjusted REGD results are similar. However, substantive differences in parameter estimates are observed between the adjusted and nonadjusted REGD results. Such differences could have profound consequences if these risk estimates were used in a genetic counseling setting.

The results of the present study are consistent with three Danish population-based studies (Melnick et al. 1980; Marazita et al. 1984, 1986). These studies suggested that the MF/T model was not supported by population data and that a single gene may have an etiologic role in some families (Melnick et al. 1980; Marazita et al. 1984, 1986). Calculations of heritability were determined using the method of Falconer (1965), and model fitting used the method of Reich et al. (1972) and Kidd and Spence (1976). The heritability estimates from these early analyses suggested a significant dominant effect or a common sibling environmental component as an etiology.

The Danish data set was updated and expanded by Marazita et al. (1984). Pedigrees of these families varied from nuclear families to multigenerational pedigrees. Pedigree analysis of the 26 multigenerational families suggested autosomal recessive inheritance in eight families and codominant inheritance in three families. Fifteen families did not fit a simple genetic hypothesis. The multifactorial threshold model was rejected using the goodness-of-fit analysis. Classical and complex segregation analyses were consistent with a possible major recessive gene in a proportion of families. The data also suggested that CL/P was genetically heterogeneous. Genetic heterogeneity was also observed when two additional data sets from China and England were analyzed and compared with the Danish data (Marazita et al. 1986).

In contrast, another complex segregation analysis study compared the Danish and Japanese data. It found that a major gene best explained the Danish data, with heritability estimated at .97 (Chung et al. 1986). The best-fitting model was characterized by a recessive gene with $t = 2.7$ and gene frequency of .035. Further, it was estimated that among CL/P homozygotes only 29% of females and 39% of males showed the CL/P phenotype. This result is similar to the penetrance found in our study, i.e., 24% in females and 33% in males. That study also suggested that one-third of CL/P cases were accounted for by a major gene in that population. The similarity, with regard to penetrance, between our study results and those of Chung et al. may reflect the homogeneity of the two populations. However, we found no evidence of a recessive gene, as the autosomal recessive model was rejected in all analyses. Chung et al. (1986) also found that the multifactorial model, with a heritability estimate of .77, best explained CL/P in the Japanese population. This is in contrast to our heritability result of .93.

The genetics of other common birth defects, clubfoot, and neural tube defects have also shown a trend away from the MF/T model in favor of the major gene model (Wang et al. 1988). Complex segregation analysis in clubfoot and neural tube defects has shown that the mixed model with a major gene influence best explains the pattern of inheritance (Demenais et al. 1982; Wang et al. 1988). Those findings are in agreement with the findings of the present study.

In summary, the evidence from the present and other studies that apply complex segregation analyses to large CL/P populations give credence to the case reports suggesting that a major gene is responsible for a proportion of CL/P (Marazita et al. 1984; de Paepe 1989; Temple et al. 1989). This finding has important implications for genetic counseling, as some families may be at significant risk of recurrence while others are at very low risk. However, discrimination of the heritable form(s) of CL/P will rely on pedigree analysis until molecular studies provide new information.

Acknowledgments

We wish to thank Dr. Edward Lustbader for providing important advice on the use of POINTER and the family-by-family analysis, Owen Jiang for preparing the data for analysis, and Rose Sonlin and J. Lynn Grace for typing the tables. This work was supported in part by grant RO3 DE 09189-01 to J.T.H. and by grant DE08559 to K.H.B.

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