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A Genetic Study of Cleft Lip and Palate in Hawaii. II. Complex Segregation Analysis and Genetic Risks

C. S. CHUNG,[1] G. H. S. CHING,[2] AND N. E. MORTON[3]

In a population study of cleft lip with or without cleft palate (CL[P]) and isolated cleft palate (CP) involving interracial crosses in Hawaii, Ching and Chung [1] observed that the underlying factor for these conditions are acting additively without a clear-cut maternal effect. They considered the observation prima facie as consistent with the mode of multifactorial inheritance with threshold effect. However, a more critical test for discriminating alternative modes of inheritance must be made on family data, and the conclusion derived from the population incidences must be supported by such data. The present investigation attempts to discriminate specifically between the hypothesis of single locus with multiple parameters and that of quasi-continuity under multifactorial inheritance. Obviously, accurate estimates of recurrence risks depend on the degree of success of such a discrimination. The family data were derived largely from the same base population studied earlier [1]. The analytical method employed is that of Morton et al. [2].

MATERIALS AND METHODS

Of a total of about 1,200 probands ascertained in the previous study [1], we have been able to obtain adequate family information on 353 families or approximately one-third of the total number of probands ascertained. These probands represented liveborn CL(P) and CP cases with exclusion of recognized syndromes or possible chromosomal abnormalities. The mode of ascertainment was multiple so that a sibship could have multiple probands who were clinically verified. The CL(P) and CP cases were found in two sibships in the sample and were expected by chance based on the incidence in the general population; therefore, they were classified according to the cleft type of the proband while the individuals with the other type of cleft were considered "normal" for the purpose of segregation analysis. The family information was usually provided by the mother through interview. However, when neither mother nor father was available for interview, the proband himself or other close relatives furnished the necessary information.

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[1] Departments of Public Health and Genetics, University of Hawaii, 1960 East-West Road, Honolulu, Hawaii 96822. Address reprint requests to C. S. Chung.

[2] Department of Genetics, University of Hawaii, 1960 East-West Road, Honolulu, Hawaii 96822. Present address: School of Medicine, Tulane University, New Orleans, Louisiana 70112.

[3] Population Genetics Laboratory, University of Hawaii, 1980 East-West Road, Honolulu, Hawaii 96822.

The data obtained from the family included the following: (1) birth dates and places for father, mother, and all sibs of probands; (2) family pedigree including all parents, grandparents, uncles, aunts, first cousins, nephews, nieces, half-sibs, and children of probands with information on oral clefts; (3) name, sex, relation, and type of cleft of each affected relative; (4) parental consanguinity; and (5) race of each grandparent. As a partial verification of the data, the birth certificates of sibs of the probands were checked for sex, age, birth order, ages of parents, and congenital malformations. In general, the agreement between the two sources of data was good.

The analytical method used was complex segregation analysis [2]. According to the method, in general the probability of r affected among s sibs with h affected parents under incomplete selection is

$$P(r; s, h, \pi) = \frac{\binom{s}{r} [1 - (1 - \pi)^r] \sum_{j,k} \phi_{hjk} m_{jk}^r (1 - m_{jk})^{s-r}}{1 - \sum_{j,k} \phi_{hjk} (1 - m_{jk}\pi)^s}$$

where π is the ascertainment probability, ϕ_{hjk} is the probability of a mating of genotypes j and k where h of them is affected ($h = 0, 1, 2$), and m_{jk} is the risk of affection of the child from the mating type.

Under the two-allele, single-locus model, parameters t, d, and z are introduced to specify risks of three genotypes GG, GG', *and* $G'G'$. The risks are $t + z$, $td + z$, and z, respectively, where t is the penetrance of GG, d is the dominance of gene G, and z is the frequency of nonheritable cases so that $x = z/A$, where x is the proportion of sporadic cases [3] and A is the incidence in the general population. Using the theory of maximum likelihood, tests of hypotheses on parameters t, d, and z are made.

Under the model of multifactorial inheritance, the additive liability for a condition is assumed to be distributed normally with a threshold which determines affection [4]. The apparently sharp threshold imposed by Falconer [4] in the model was shown to be equivalent to the model of a cumulative normal risk function acting on genetic liability assumed to be normally distributed [5]. The distribution of genetic liability is polychotomized into a number of nonoverlapping classes, and the risk of affection for the mean of each class is calculated. Morton et al. [2] used 52 classes for this purpose. Having obtained discrete classes, the probability of a specific mating of genotypes (ϕ_{hjk}) and the corresponding risk of affection for the child (m_{jk}) can be calculated and are used for complex segregation analysis. The parameters in this model are population incidence (A) and heritability (T).

Under either model the probability of the $(s + 1)$st child being affected, after having r affected among s children, is specified [2] by

$$Q(r; s, h) = \frac{\sum_{j,k} \phi_{hjk} m_{jk}^{r+1} (1 - m_{jk})^{s-r}}{\sum_{j,k} \phi_{hjk} m_{jk}^r (1 - m_{jk})^{s-r}}.$$

These methods of complex segregation analysis are programmed on a CDC 3100 computer. The program (COMSEG) enables pooling of the results from cases with varying h (0, 1, 2) in testing hypotheses. Therefore, the results are over the cases with $h = 0$ and $h = 1$; no mating with $h = 2$ was observed.

RESULTS

Complex Segregation Analysis

Initially the probability of ascertainment (π) was estimated by the maximum-likelihood method separately for CL(P) and CP from the family data using the distributions of the number of probands per sibship and the number of ascertainments per proband [6, models 22 and 27]. The estimates of π over all racial groups were .903 and .819 for CL(P) and CP, respectively, and were homogeneous over the models. These values are lower than the estimates of ascertainment probability in the earlier study [1], which was limited to children born during a specified interval without inclusion of sibs born previously. The incidences used in the analyses were .00128 and .00078 for CL(P) and CP, respectively, which were obtained in the earlier study [1]. Table 1 shows the distribution of families by number of affected parents (h), sibship size (s), and number of affected sibs (r) for CL(P) and CP. Families with $s = 1$ are not included since these are uninformative for the analysis.

Table 2 gives the result of the complex segregation analysis for CL(P). Hypotheses to be tested were classified broadly into two classes, rank 1 and rank 2 [2];

TABLE 1

NUMBERS OF FAMILIES BY NUMBERS OF AFFECTED PARENTS (h), SIBS (s), AND AFFECTED SIBS (r) FOR CL(P) AND CP

No. Sibs (s)	No. Affected Sibs (r)	CL(P)		CP	
		$h = 0$	$h = 1$	$h = 0$	$h = 1$
2	1	35	0	12	1
2	2	2	0	0	0
3	1	45	1	26	0
3	2	3	2	0	0
4	1	40	0	23	1
4	2	1	0	1	0
5	1	22	0	13	0
5	2	3	1	1	0
6	1	16	0	8	0
7	1	15	0	4	0
7	2	3	0	0	1
7	3	2	0	0	0
8	1	7	0	7	0
8	2	1	0	1	0
9	1	9	0	7	0
9	2	1	0	0	0
10	1	1	0	0	0
11	1	2	0	1	0
12	1	0	0	1	0
12	2	4	0	0	0
13	1	1	0	2	0
13	2	0	0	1	0
14	1	0	0	1	0
15	1	0	0	1	0

NOTE.—CL(P) = cleft lip with or without cleft palate; CP = isolated cleft palate.

TABLE 2

TESTS OF TWO-ALLELE, SINGLE-LOCUS MODEL WITH THREE PARAMETERS FOR CL(P) BY COMPLEX SEGREGATION ANALYSIS

HYPOTHESIS	PARAMETERS FIXED			PARAMETERS ESTIMATED	LIKELIHOOD-RATIO	
	d	t	x		χ^2	df
Rank 1:						
Recessive:						
Complete penetrance ..	0	1	...	$x = 0.679$	49.44	83
No phenocopies	0	...	0	$t = 0.195$	37.76	83
Additive:						
Complete penetrance ..	½	1	...	$x = 0.532$	49.63	83
No phenocopies	½	...	0	$t = 0.216$	41.13	83
Dominant:						
Complete penetrance ..	1	1	...	$x = 0.003$	99.98	83
No phenocopies	1	...	0	$t = 0.00001$	185.17	83
Rank 2:						
Recessive	0	...	...	$t = 0.325$ $x = 0.359$	36.56	82
Additive	½	...	...	$t = 0.378$ $x = 0.372$	39.41	82
Dominant	1	...	...	$t = 0.190$ $x = 0.373$	39.42	82

under a rank-1 hypothesis, one parameter (t or x) was left to vary and was estimated, whereas two parameters (t and x) were estimated from the data under the rank-2 hypothesis. Rank-1 hypotheses of special interest for the present study were recessive ($d = 0$), additive ($d = 1/2$), and dominant ($d = 1$) inheritance with subclassification of complete penetrance or no phenocopies (sporadics) under each d value. Three special rank-2 hypotheses represent the three modes of inheritance ($d = 0$, $1/2$, and 1).

Among the nine specific hypotheses to be tested, the case of dominance with no phenocopies was found to fit the data least well judged from the unusually large value of the likelihood-ratio $\chi^2_{(83)}$ of 185.17. This suggests that there is no likelihood peak within the boundary values of t (0 and 1) under this hypothesis. Therefore, it is reasonable to conclude that this is an unrealistic hypothesis which should be eliminated from further consideration.

Of the remaining hypotheses, the likelihood-ratio χ^2's show that the rank-2 hypotheses do not fit the data appreciably better than the best fitting rank-1 hypothesis with the same d value except for the case of dominant inheritance. Under the mode of recessive inheritance, the rank-1 hypothesis with no phenocopies gave the likelihood $\chi^2_{(83)}$ of 37.76 with the estimated t value of 0.195, whereas the $\chi^2_{(82)}$ under the rank-2 hypothesis was 36.56 with the estimated parameters of $t = 0.325$

and $x = 0.359$. Under the mode of additive inheritance, the rank-1 hypothesis of no phenocopies gave rise to a $\chi^2_{(83)}$ of 41.13 with the estimate $t = 0.216$ compared to a $\chi^2_{(82)}$ of 39.41 under the rank-2 hypothesis with $t = 0.378$ and $x = 0.372$. Again, the hypothesis of dominant inheritance with complete penetrance under rank 1 fits the data least well.

The generally low χ^2 values observed are characteristic of distributions with small expected numbers [7]. However, the relative magnitude of χ^2 values and reduction in χ^2 for higher rank from lower rank hypotheses serve as useful criteria for comparison. According to the criterion specified [2], the likelihood-ratio χ^2 for a rank-2 hypothesis should be smaller than an alternative of lower rank by at least 4 before the hypothesis can be declared better than the alternative hypothesis. Applying this criterion, it can be concluded that the rank-1 hypotheses are equally well fitting as are the rank-2 hypotheses under the recessive and additive modes of inheritance. In view of this, the rank-1 hypotheses are much more appealing than those of rank-2 since they represent the simplest possible models under consideration. The hypothesis of recessive inheritance with no phenocopies with $t = 0.195$ yielded the smallest χ^2, whereas the next smallest χ^2 was obtained from the hypothesis of additive inheritance with no phenocopies with $t = 0.216$. The difference of 3.37 in the magnitude of the χ^2 values is not remarkable.

Table 3 shows the result of analysis of the CP family data. The situation here

TABLE 3

TESTS OF TWO-ALLELE, SINGLE-LOCUS MODEL WITH THREE PARAMETERS FOR CP BY COMPLEX SEGREGATION ANALYSIS

HYPOTHESIS	PARAMETERS FIXED			PARAMETERS ESTIMATED	LIKELIHOOD-RATIO	
	d	t	x		χ^2	df
Rank 1:						
Recessive:						
Complete penetrance ..	0	1	...	$x = 0.891$	19.11	105
No phenocopies	0	...	0	$t = 0.059$	11.50	105
Additive:						
Complete penetrance ..	½	1	...	$x = 0.819$	15.94	105
No phenocopies	½	...	0	$t = 0.070$	12.43	105
Dominant:						
Complete penetrance ..	1	1	...	$x = 0.011$	33.89	105
No phenocopies	1	...	0	$t = 0.00001$	108.73	105
Rank 2:						
Recessive	0	...	...	$t = 0.097$ $x = 0.437$	11.03	104
Additive	½	...	...	$t = 0.245$ $x = 0.692$	11.24	104
Dominant	1	...	...	$t = 0.123$ $x = 0.697$	11.24	104

appears fairly comparable to the case of CL(P), though in general the data seem to fit specific hypotheses better than in CL(P) as seen by the magnitude of the likelihood-ratio χ^2 values. As in the case of CL(P), the rank-1 hypotheses of dominant inheritance gave the poorest fit to the data.

Rank-2 hypotheses seem to exhibit no added attraction over the corresponding rank-1 hypotheses. The best fitting are again the hypotheses of recessive inheritance with no phenocopies giving $t = 0.059$ and a likelihood-ratio $\chi^2_{(105)}$ of 11.50, followed by the additive mode of inheritance with no phenocopies giving $t = 0.070$ and a $\chi^2_{(105)}$ of 12.43. No clear discrimination seems possible between these two alternative hypotheses.

TABLE 4

TESTS OF MODEL OF MULTIFACTORIAL INHERITANCE FOR CL(P) AND CP

Condition	Likelihood-Ratio χ^2	df	Heritability
CL(P)	38.20	83	.99
CP	11.32	105	.72

Table 4 shows the result of segregation analysis based on the hypothesis of multifactorial inheritance with threshold effect. The likelihood-ratio χ^2 for CL(P) was 38.20 for 83 df, whereas that for CP was 11.32 for 105 df. These are comparable to the χ^2 values of the best fitting rank-1 hypotheses of the two-allele, single-locus model of each condition. The heritabilities estimated from the data were .99 and .72 for CL(P) and CP, respectively. It should be noted that the value of .99 for CL(P) is limited by the boundary condition on heritability of 1.

Recurrence Risks

In light of the demonstration from the complex segregation analysis that no single genetic hypothesis fits the data unequivocally better than alternative hypotheses, it may be too arbitrary to select only one model with the least χ^2 value in calculating recurrence risks. For this reason, we selected two alternative models with least χ^2 values and good contrast of mode of inheritance for predicting recurrence risks of sibs. These are the models of recessive inheritance with no sporadic cases and multifactorial inheritance for both CL(P) and CP. Thus the single-locus models were based on $d = 0$, $x = 0$, and $t = 0.175$ for CL(P) and $d = 0$, $x = 0$, and $t = 0.059$ for CP.

Table 5 shows CL(P) recurrence risks for sibs for various combinations of sibship size (s) and number of affected sibs (r) on the single-locus model for the cases of both parents normal and only one parent affected. The number represents the probability of the next sib being affected with CL(P) after having r affected sibs in a sibship of size s based on the formula proposed by Morton et al. [2]. The risk for the case of $s = 0$ and $r = 0$ with no parent affected corresponds

TABLE 5

CL(P) RECURRENCE RISKS OF SIBS FOR VARYING SIBSHIP SIZE AND NUMBER OF AFFECTED SIBS BASED ON SINGLE-LOCUS MODEL WITH $d = 0$, $x = 0$, AND $t = 0.195$ FOR CASES OF BOTH PARENTS NORMAL AND ONLY ONE PARENT AFFECTED

No. Affected Sibs (r)	Sibship Size (s)								
	0	1	2	3	4	5	6	7	8
0	.001 (.016)	.001 (.014)	.001 (.013)	.001 (.012)	.001 (.011)	.001 (.010)	.001 (.009)	.001 (.008)	.001 (.007)
1	...	.055 (.104)	.055 (.103)	.055 (.103)	.054 (.102)	.054 (.102)	.054 (.101)	.053 (.101)	.053 (.100)
2	...	...	.061 (.109)	.061 (.108)	.060 (.107)	.060 (.106)	.059 (.105)	.058 (.105)	.058 (.104)
3	...	...	...	.073 (.119)	.071 (.117)	.070 (.115)	.069 (.114)	.068 (.112)	.067 (.111)
4	...	...	...	...	.090 (.133)	.088 (.130)	.086 (.128)	.084 (.125)	.082 (.123)
5	...	...	...	...	...	.114 (.149)	.111 (.146)	.108 (.144)	.105 (.141)

NOTE.—Figures in parentheses for one parent affected.

approximately to the general population incidence. Not surprisingly, the risk is seen to change very little with s within a given r. The recurrence risks for the families with $r = 1$ are at maximum when $s = 1$: .055 and .104 for $h = 0$ (no parent affected) and $h = 1$ (one parent affected), respectively. It is of interest to note that within a given sibship size the risk gradually increases with increasing r over $r = 0$. For example, with $s = 3$ the risks are .055, .061, and .073 for the cases of $r = 1$, 2, and 3, respectively, when $h = 0$. The increases of the risk under $h = 1$ over the case of $h = 0$ are much greater when r is small. Thus for $s = 3$, the risk is about 12-fold for $h = 1$ when $r = 0$, while the risk for $h = 1$ approximately doubles that for $h = 0$ when $s = 2$.

Table 6 gives the CL(P) recurrence risks under the model of multifactorial inheritance. In contrast to the single-locus model, the risks decrease significantly with increasing s within a given r. The increases of recurrence risks with r within a fixed s are much more drastic than in the single-locus model. For example, with $s = 3$ the risk has tripled (.038 to .113) from $r = 1$ to $r = 2$ when $h = 0$. The increase of risks from the case of $h = 0$ to that of $h = 1$ is much more pronounced than in the single-locus model.

It is important to note that in general the recurrence risks are greater for the multifactorial model compared to the alternative models for every combination of s and r whether $h = 0$ or $h = 1$. However, the differences are rather small to be of major consequence when $r = 1$ and $h = 0$, which is a usual situation in human families. The differences become very pronounced as r increases over 1 or when $h = 1$. The significance of this finding will be discussed presently.

TABLE 6

CL(P) RECURRENCE RISKS OF SIBS FOR VARYING SIBSHIP SIZE AND NUMBER OF AFFECTED SIBS BASED ON MULTIFACTORIAL MODEL FOR CASES OF BOTH PARENTS NORMAL AND ONLY ONE PARENT AFFECTED

No. Affected Sibs (r)	Sibship Size (s)								
	0	1	2	3	4	5	6	7	8
0	.001 (.061)	.001 (.053)	.001 (.047)	.001 (.043)	.001 (.039)	.001 (.036)	.001 (.034)	.001 (.032)	.001 (.030)
1	...	.044 (.179)	.041 (.155)	.038 (.137)	.035 (.123)	.033 (.111)	.031 (.102)	.029 (.094)	.028 (.088)
2	...	...	.123 (.288)	.113 (.254)	.104 (.226)	.097 (.204)	.090 (.186)	.084 (.171)	.079 (.158)
3	...	...	...	.194 (.372)	.181 (.334)	.169 (.302)	.158 (.275)	.148 (.253)	.139 (.233)
4	...	...	...	...	.249 (.436)	.235 (.397)	.222 (.364)	.210 (.335)	.198 (.310)
5	...	...	...	...	...	.291 (.485)	.278 (.448)	.265 (.415)	.253 (.385)

NOTE.—Figures in parentheses for one parent affected.

Table 7 gives CP recurrence risks of sibs based on the single-locus model with $d = 0$, $x = 0$, and $t = 0.059$. Table 8 shows recurrence risks based on multifactorial inheritance with heritability of .72. As expected, the levels of sib risks

TABLE 7

CP RECURRENCE RISKS OF SIBS FOR VARYING SIBSHIP SIZE AND NUMBER OF AFFECTED SIBS BASED ON SINGLE-LOCUS MODEL WITH $d = 0$, $x = 0$, AND $t = 0.059$ FOR CASES OF BOTH PARENTS NORMAL AND ONLY ONE PARENT AFFECTED

No. Affected Sibs (r)	Sibship Size (s)								
	0	1	2	3	4	5	6	7	8
0	.0008 (.007)	.0008 (.007)	.0007 (.006)	.0007 (.006)	.0007 (.006)	.0007 (.006)	.0007 (.006)	.0007 (.006)	.0007 (.005)
1	...	.018 (.033)	.018 (.033)	.018 (.032)	.018 (.032)	.018 (.032)	.018 (.032)	.018 (.032)	.018 (.032)
2	...	...	.021 (.035)	.021 (.035)	.021 (.035)	.021 (.035)	.021 (.035)	.021 (.034)	.020 (.034)
3	...	...	...	.026 (.039)	.026 (.039)	.026 (.039)	.025 (.039)	.025 (.038)	.025 (.038)
4	...	...	...	...	.033 (.044)	.033 (.044)	.032 (.043)	.032 (.043)	.032 (.043)
5	...	...	...	...	...	.041 (.049)	.040 (.049)	.040 (.048)	.040 (.048)

NOTE.—Figures in parentheses for one parent affected.

TABLE 8

CP RECURRENCE RISKS OF SIBS FOR VARYING SIBSHIP SIZE AND NUMBER OF AFFECTED SIBS BASED ON MULTIFACTORIAL MODEL FOR CASES OF BOTH PARENTS NORMAL AND ONLY ONE PARENT AFFECTED

No. Affected Sibs (r)	Sibship Size (s)								
	0	1	2	3	4	5	6	7	8
0	.0008 (.020)	.0007 (.019)	.0007 (.018)	.0007 (.017)	.0007 (.016)	.0007 (.016)	.0007 (.015)	.0007 (.015)	.0007 (.014)
1	...	018 (.073)	.017 (.067)	.016 (.063)	.016 (.059)	.015 (.056)	.015 (.053)	.014 (.050)	.014 (.048)
2	...	...	.063 (.141)	.059 (.130)	.056 (.120)	.053 (.112)	.050 (.105)	.048 (.099)	.046 (.094)
3	...	...	...	.121 (.208)	.113 (.192)	.106 (.178)	.100 (.167)	.094 (.157)	.090 (.148)
4	...	...	...	...	.181 (.268)	.169 (.249)	.158 (.232)	.149 (.218)	.141 (.205)
5	...	...	...	...	...	.238 (.320)	.222 (.299)	.208 (.280)	.196 (.264)

NOTE.—Figures in parentheses for one parent affected.

of CP are considerably lower than those of CL(P) for the corresponding s and r combinations for both models. However, the observation made on (CL(P) appear equally applicable to the case of CP.

DISCUSSION

Unfortunately, the complex segregation analysis has offered no clear-cut discrimination between the single-locus and multifactorial models in both CL(P) and CP. For either condition, the best fitting rank-1, single-locus hypothesis appeared to be recessive inheritance with reduced penetrance and no phenocopies. The estimated penetrance was much higher for CL(P) than for CP (.195 compared to .059). The difference in penetrance (.136 $\pm$ .050) was highly significant. Under this hypothesis, the respective estimated gene frequencies were .0811 and .1152. The estimated heritabilities under multifactorial inheritance were .99 and .72 for CL(P) and CP, respectively. These values are in contrast to .86 and .69 which were obtained by the method of Falconer [4] without adjusting for ascertainment probability and affected parents.

Our findings appear to confirm generally the observations of others that under certain conditions the discrimination between the single-locus and multifactorial genetic models is difficult. Based on results on simulated data, Smith [8] concluded that the single-locus model is very flexible and can fit multifactorial data well unless the frequency is low and the heritability is high. Conversely, the model of multifactorial inheritance can fit fairly well the single-locus data as the parameters of the single-locus model become less Mendelian. Cavalli-Sforza

and Kidd [9] were not able to discriminate the alternate models on schizophrenia. Reich et al. [10] investigated conditions under which the discrimination is possible.

The conclusion of lack of discriminating power in the present study and others is based on the usual human family data with relatively rare traits in which no parents are affected, family size is small, and affected individuals per sibship are predominantly isolated. Though the calculation of recurrence risks was largely based on the data with $h = 0$, certain useful conclusions can be drawn from the expected recurrence risks under the alternative models. As demonstrated earlier, the recurrence risks computed indicate an increasing degree of divergence between the two alternative models as r and h become large which increases the power of discrimination. Therefore, we expect that disproportionately more critical information can be obtained from families with one or both parents affected and/or families with two or more affected sibs. For example, the predicted CL(P) recurrence risks for families with $r = 2$ and $s = 3$ for $h = 1$ are .108 and .254 for the single-locus and multifactorial models, respectively. Based on a small amount of data for $h = 0$ and without adjustment for s, Curtis et al. [11] estimated the recurrence risk of CL(P) after two affected sibs as .09, whereas Woolf [12] gave .146 for the similar situation. These figures appear to be more close to the predicted values on the multifactorial model. However, it should be kept in mind that our predicted CL(P) risks for multifactorial inheritance were based on an artificial boundary value of heritability of 1. Further informative family data are needed for CP as well as CL(P).

According to the criterion suggested by Morton [13], very high heritability can be considered as an indicator of the presence of major genes. This was further corroborated by Smith [8] on simulated data. If we apply this criterion, our CL(P) data are consistent with the hypothesis of the presence of major genes, which are most likely to be recessive with reduced penetrance. It would be of further interest to compare published monozygotic twin concordance data with the predicted recurrence risks from the two alternative models (table 9). On face value, the concordance rates are consistent with the single-locus model for CL(P) and the multifactorial hypothesis for CP.

Irrespective of the mode of inheritance, our data show that recurrence risks for CL(P) are generally higher than for CP. This is in agreement with earlier

TABLE 9

COMPARISON OF PUBLISHED MONOZYGOTIC TWIN CONCORDANCE DATA WITH PREDICTED RECURRENCE RISKS UNDER SINGLE-LOCUS AND MULTIFACTORIAL MODELS

Model	CL(P)	CP
Recessive	0.195	0.059
Multifactorial	1.000	0.169
Concordance rate [14]	0.377	0.235

studies [11, 15–17]. The differences in our data may be partially explained by a higher risk for Orientals [1] in CL(P), but Ching [18] has shown only slight differences among races in segregation frequency. It would be of interest to test possible differences between races in the genetic etiology when larger racial samples are available in the future.

SUMMARY

Family data on cleft lip with or without cleft palate and isolated cleft palate collected in Hawaii were analyzed to discriminate the two models of two-allele, single-locus and multifactorial inheritance using the method of complex segregation analysis. The three parameters in the single-locus model were degree of dominance, penetrance, and proportion of phenocopies.

For either condition, the best fitting single-locus model was found to be as good as the multifactorial model in explaining the data. However, the heritability of cleft lip with or without cleft palate was so high that involvement of major genes was suspected. Sib recurrence risks for various combinations of sibship size and number of affected sibs showed that disproportionately more critical information can be derived from families with familial cases and/or one or more affected parents.

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REFERENCES

1. Ching GHS, Chung CS: A genetic study of cleft lip and palate in Hawaii. I. Interracial crosses. *Am J Hum Genet* 26:162–176, 1974
2. Morton NE, Yee S, Lew R: Complex segregation analysis. *Am J Hum Genet* 23: 602–611, 1971
3. Morton NE: Genetic tests under incomplete ascertainment. *Am J Hum Genet* 11: 1–16, 1959
4. Falconer DS: The inheritance of liability to certain diseases, estimated from the incidence among relatives. *Ann Hum Genet* 29:51–76, 1965
5. Smith C: Recurrence risks for multifactorial inheritance. *Am J Hum Genet* 23: 578–588, 1971
6. Morton NE: Segregation analysis, in *Computer Applications in Genetics,* edited by Morton NE, Honolulu, Univ. Hawaii Press, 1969, pp 129–139
7. Haldane JBS: The mean and variance of χ^2, when used as a test of homogeneity, when expectations are small. *Biometrika* 31:346–355, 1939
8. Smith C: Discriminating between different modes of inheritance in genetic disease. *Clin Genet* 2:303–314, 1971
9. Cavalli-Sforza LL, Kidd KK: Prospects for research in schizophrenia. A report based on an NRP work session. *Neurosci Res Program Bull* 10:406–419, 1972

10. REICH T, JAMES JW, MORRIS CA: The use of multiple thresholds in determining the mode of transmission of semi-continuous traits. *Ann Hum Genet* 36:163–184, 1972
11. CURTIS E, FRASER FC, WARBURTON D: Congenital cleft lip and palate: risk figures for counseling. *Am J Dis Child* 102:853–857, 1971
12. WOOLF CM: Congenital cleft lip. A genetic study of 496 propositi. *J Med Genet* 8:65–83, 1971
13. MORTON NE: The detection of major genes under additive continuous variation. *Am J Hum Genet* 19:23–34, 1967
14. FRASER FC: The genetics of cleft lip and cleft palate. *Am J Hum Genet* 22:336–352, 1970
15. FOGH-ANDERSEN P: *Inheritance of Harelip and Cleft Palate.* Copenhagen, Busck, 1942
16. KOBAYASI Y: A genetic study on harelip and cleft palate. *Jap J Hum Genet* 3:73–107, 1958
17. SANUI Y: Clinical statistics and genetics on the cleft-lip and the cleft-palate. *Jap J Hum Genet* 7:194–233, 1962
18. CHING GHS: A genetic and epidemiological study of cleft lip and cleft palate in Hawaii. Ph.D. diss., Univ. Hawaii, 1970