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A Unified Model for Complex Segregation Analysis

J. M. LALOUEL,[1,2] D. C. RAO,[2] N. E. MORTON,[3] AND R. C. ELSTON[4]

SUMMARY

Various methods have been proposed for statistical inference of major genes by segregation analysis of human familial data. An attempt is made to resolve some divergences that have occurred in this context by the consideration of a unified model, with some practical applications.

INTRODUCTION

The genetic analysis of common diseases and biological correlates of affection has stimulated various developments for the detection of major genes by statistical methods. Extending on classical methods for segregation analysis [1–5], the strategies proposed differ with respect to genetic models, sampling procedures, family structures, statistical methods of analysis, and algorithms for numerical calculations (see [6–9] for reviews and references). Although it is unlikely that one single strategy should prove optimal in all practical applications, it is reasonable to expect that, as more experience accumulates with actual and simulated data, some convergence should emerge in several respects.

This paper attempts to resolve divergences that have occurred with respect to models for complex segregation analysis of familial data by discussing a unified model in the light of some practical applications.

GENERAL TRANSMISSION SINGLE-LOCUS MODEL AND MIXED MODEL

In early attempts to interpret patterns of familial aggregation for common diseases, clinical geneticists have argued convincingly for the need of a model

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[1] Laboratoire d'Anthropologie Biologique, Université Paris 7, 2, Place Jussieu, 75251 Paris Cedex 05, France.

[2] Division of Biostatistics, Department of Preventive Medicine, Washington University Medical School, Box 8067, 4566 Scott Avenue, St. Louis, MO 63110.

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

[4] Department of Biometry, Louisiana State University Medical Center, 1901 Perdido Street, New Orleans, LA 70112.

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bridging the gap between the classical biometrical approach and single-gene Mendelian genetics, in effect supposing that familial patterns of transmission of a disease exhibiting incomplete penetrance would result from the effect of a major locus whose phenotypic expression could be modulated by both the rest of the individual's genetic composition as well as by his living environment [10–12]; that is, rather than attempting to compare the goodness of fit of familial data to polygenic and single-gene models in different parameter spaces, a general model of inheritance should allow for a given phenotype to result from the joint effects of a major locus, a polygenic component, and random environment.

Such a model was explicity considered by Elston and Stewart [13]. However, for reasons of practical feasibility, they also proposed a more tractable general transmission single-locus model under which one could test the agreement of transmission probabilities to Mendelian expectations; ancillary tests were later proposed [14] to safeguard against falsely asserting the segregation of a major gene. Morton and MacLean [15] developed, and implemented for nuclear families, a mixed model of inheritance that subsumed a major locus with Mendelian transmission, a polygenic component, and random environmental effects; in addition, they made allowance for common sibling environment in order to prevent such an effect from simulating dominance variance at the major locus. With increased attention being paid to cultural inheritance as well as to trends in variance components with age that have recently come to light in genetics [16–19], this mixed model of inheritance has been reformulated in terms of intergenerational differences of multifactorial transmissible factors, reflecting both polygenic and cultural inheritance [20].

Operational characteristics of both the mixed model and the general transmission single-locus model have been investigated by simulation studies [14, 21]. Under the mixed model, it appeared that skewness in the distribution of a quantitative phenotype would in some instances lead to the false inference of a major gene [21]; this prompted the need for investigations of distributions to resolve skewness and commingling [22] and to perform segregation analysis after transformation to eliminate skewness in an attempt to prevent such false inferences [23, 24]. Under the general transmission single-locus model, it was found that with some combinations of skewness, polygenic inheritance, and common sibling environment there was similarly a serious possibility of falsely detecting a major gene effect [14]; these observations led to the elaboration of a number of criteria that should be met before inferring segregation of major gene [14]. As a consequence, the process of making inferences has become more elaborate and cumbersome in practical applications. In one instance where both models have been used to analyze the same set of data [25], mixed conclusions have been reached, which emphasizes the need for a unified approach reconciling both models.

FORMULATION OF A UNIFIED MODEL

Under the mixed model, inference of a major gene proceeds by rejecting the hypothesis of no major gene; for such a hypothesis, family resemblance is imputed to the multifactorial transmissible component, but this component cannot account for commingling (i.e., mixture of normal distributions). Under the general

transmission single-locus model, the hypothesis of no major gene coincides with that of no parent-offspring resemblance. Hence, inference of a major gene proceeds by: (1) rejecting the hypothesis of no transmission of the major effect, under which no family transmission is possible; and (2) accepting the hypothesis of Mendelian transmission when tested against a more general transmission model of major effect. Clearly, in these two approaches, type I and type II errors play different roles.

These two approaches can be reconciled into a unified model, for which we shall make the following assumptions. A trait x results from the joint, additive, unobservable contributions of a major transmissible effect, g, a multifactorial transmissible component, c, and random, nontransmitted environment, e, with $x = g + c + e$. These three factors are independently distributed. Factors c and e are normally distributed, N(0, C) and N(0, E), respectively. The major effect results under a genetic hypothesis from segregation at a single locus of two alleles A, a, leading to three genotypic classes with prior probabilities expressed in terms of binomial parameter q, the prior probability of allele a in the reference population. Genotypic effects can either be expressed as three means, μ_{AA}, μ_{Aa}, and μ_{aa}, or, alternately, in terms of their mean effect, $E(g) = u$; the distance between opposite homozygous mean effects on the scale of x, called displacement, t, where $t = \mu_{AA} - \mu_{aa}$, and the position of the heterozygous mean effect relative to both homozygous classes expressed by the dominance parameter $d = (\mu_{Aa} - \mu_{aa})/(\mu_{AA} - \mu_{aa})$. It follows that $E(x) = E(g) = u$, and, denoting G the variance due to the major effect, the variance of x, denoted V, is such that $V = G + C + E$.

Specification of the general model requires the definition of mating and transmission rules from parent to offspring. We shall assume random mating; an additional parameter could be introduced to test deviations from such assumptions, although power seems low. If τ_1, τ_2, and τ_3 denote the probabilities of transmitting allele A for genotypes AA, Aa, and aa, respectively, Mendelian transmission obtains for $\tau_1 = 1$, $\tau_2 = ½$, $\tau = 0$, as assumed in [15, 20]. In a general model, we shall keep these parameters unrestricted, following [7, 13]. Multifactorial transmission can be specified through the parent-offspring correlation conditional on major genotypes and random residuals; denoted r, it may be constrained to $r = ½$ as expected in a classical polygenic model, or remain unrestricted [18, 19, 26].

Dominance at the major locus leads to greater correlation between sibs than between parent and offspring. The latter observation may, however, result from a variety of other factors such as common sibling environment [15], trends of variance components with age [19], or deviations from assumptions about linearity and additivity of effects. More generally, multifactorial transmission may concern cultural as well as genetic effects, and one could account explicitly for cultural and genetic transmission in terms of two latent variables, as in path analysis of family resemblance [16, 18, 19]. However, identification of such variables requires particular family structures [27, 28], and the power to resolve such effects, when identified, may be small. As resolution of such effects is not essential when the purpose of the investigator is to detect a major gene, one may, in such instances,

resort to a simpler, parsimonious model. One approach consists in allowing for intergenerational differences in the multifactorial variance components, as well as general transmission through the parameter r. The data can be adjusted so that V is the same in each generation; if C_A and C_K denote variance components due to multifactorial transmission in adults and young, respectively, and r, the parent-offspring correlation conditional on major genotypes and residuals, we may define childhood "heritability" as $H = C_K/V$, adult "heritability" as $HZ = C_A/V$, where $Z = C_A/C_K$, and parent-offspring and sib correlations as $rHZ^{1/2}$ and $2r^2H$, respectively.

Identification of r, H, and Z requires availability of both adult and young children in nuclear families, while pointers [20] or other more distant relatives can contribute additional information on such parameters for more extended family structures. Power to resolve r and Z may be low [18]; in the following applications, multifactorial transmission is fixed to the value $r = ½$.

Affection status may be defined by a threshold either directly on the scale x, or on a scale y related to x via an added random component, w, distributed N(0,W), with $y = x + w$. The latter formulation allows handling both a disease classification and a biological correlate; the correlation between disease liability, y, and the biological marker is $\rho = [V/(V + W)]^{1/2}$ [15]. Such formulation adds flexibility to the model by allowing the phenotype to be defined by affection status and/or a quantitative trait, which, for example, allows for the treatment of partial quantitation or for a disregard of the biological correlate among affected in order to test whether elevation of the correlate is primary or secondary to affection.

STATISTICAL INFERENCE UNDER THIS MODEL

In contrast to both the general transmission and the mixed models, this unified model allows a more thorough investigation about the existence and the nature of familial transmission.

Setting all parameters but mean and total variance to zero provides a test of no transmission and no commingling of normal distributions. A test of no transmission of both major effect and multifactorial component can be obtained by imposing the restrictions $\tau_1 = \tau_2 = \tau_3 = \tau$ and $H = 0$. Subhypotheses of no transmission of major effect or no multifactorial transmission can be tested by setting $\tau_1 = \tau_2 = \tau_3 = \tau$ or $H = 0$, respectively. When there is no evidence of transmission of major effect, one may test a hypothesis of homogeneity of commingling in parents and offspring with the restriction $\tau_1 = \tau_2 = \tau_3 = 1 - q$, the prior probability of allele A among parents. A test of no major effect is provided by the restriction $q = 0$. Test of the Mendelian transmission hypothesis is achieved by the restriction $\tau_1 = 1$, $\tau_2 = ½$, $\tau_3 = 0$. One may suspect, however, that the test of $\tau_2 = ½$ is probably more relevant to segregation analysis. When a Mendelian hypothesis is acceptable and the hypothesis of no transmission of major effect is rejected, further tests concerning dominance ($d = 0$ or $d = 1$) can be carried out against the mixed model with Mendelian transmission; in order to reduce the number of alternatives to be tested.

TABLE 1

ANALYSIS OF IgE DATA UNDER THE UNIFIED MODEL

Major effect			Multifactorial effect	Conditional likelihood		Joint likelihood		No. parameters estimated
Present?	Transmission	Dominance		One component	Two components	One component	Two components	
No			No	82.61	105.70	73.72	110.65	2
No			Yes	13.34	34.70	4.63	39.76	3
	Mendelian	$d = 1$		16.42	20.91	14.58	17.63	4
	"	$d = 0$		10.29	16.91	13.55	15.69	4
Yes	"	$\hat{d}$	No	9.05	12.79	7.04	10.53	5
	General	$\hat{d}$		7.62	11.21	73.72	10.47	8
	None	$\hat{d} = 0$		77.88	77.83	73.72	75.41	5
	$\tau_1 = \tau_2 = \tau_3 = 1 - q$							
	Mendelian	$d = 1$		8.07	16.18	3.30	12.45	5
	"	$d = 0$		1.21	3.45	0.08	1.69	5
Yes	"	$\hat{d}$	Yes	1.21	3.45	0.08	1.69	6
	General	$\hat{d}$		0.00	0.00	0.00	0.00	9
	None	$\hat{d} = 0$		13.23	20.82	4.60	15.94	6
	$\tau_1 = \tau_2 = \tau_3 = 1 - q$							

NOTE: Likelihood statistics are: $-2 \ln (L)$ + a proportionality constant. Parameters of best fitting genetic model for joint likelihood and two components are: V = 0.947, $u = -0.0612$, $d = 0$, $t = 1.595$, $q = 0.458$, H = 0.233. Intergenerational difference of heritabilities was not significant, hence Z = 1 throughout.

ILLUSTRATIVE EXAMPLES

Salient features of the analyses of three data sets with the computer program POINTER [20, 29] appropriately extended for the present model are reported in tables 1, 2, and 3. The first data set concerns immunoglobulin E (IgE) levels previously analyzed by Gerrard et al. [23] and Rao et al. [24]. The second set consists of a random sample of 68 nuclear families where the phenotype studied was red blood cell magnesium concentrations (RBC Mg). The third data set is Glueck's sample of 33 kindreds ascertained through probands with elevation of both cholesterol and triglyceride levels; results presented here concern total cholesterol levels. The last two analyses will be reported more extensively elsewhere. Only those features of such analyses bearing on the prime topic of the present paper will be discussed here. It should be clear that, although numerous hypotheses are tested here primarily to evaluate the consequences of various assumptions, such elaborate analyses may not be necessary in practical applications.

The analysis of IgE data [23, 24] epitomized some difficulties inherent to segregation analysis of a quantitative trait. The distribution of the trait, ln IgE, departed from normality, exhibiting significant skewness. Such skewness may be real, in the sense that it results from nonadditivity of numerous effects on the measurement scale defined, or it may reflect a mixture of two or more underlying distributions. Resolution of skewness from commingling may be attempted by analysis of a control sample of unrelated individuals [22]; when such data are lacking, as was the case for the present IgE data, one may use the familial data themselves as a crude control sample provided that families were selected at random, although there may be a slight loss of power in such a commingling analysis. For the IgE data, there was evidence of commingling [23]. The analysis was repeated four ways for two types of data transformation with the two types of likelihood: data transformed under the assumption of one or two distributional components, and conditional or joint likelihood. All analyses under the mixed model, except one, led to rejection of the hypothesis of no major gene ($q = 0$): analysis under the assumption of one component using the joint likelihood. This last result was interpreted by these authors [24] as the consequence of an inconsistency induced between parents and sibs by the transformation to a symmetric distribution.

Table 1 gives a summary of re-analyses of these data, four ways, under the unified model. Apart from the analysis by joint likelihood under the assumption of one underlying component, for which the major effect does not reach significance, we can make the following inferences (the quoted χ^2 is that for the analysis with joint likelihood under the assumption of two components): (1) support is greater for a generalized single-locus model than for a multifactorial model; (2) a mixed model is yet better supported, with both major gene ($\chi^2_3 = 39.76 - 1.69 = 38.07$) and multifactorial effect ($\chi^2_1 = 10.53 - 1.69 = 8.81$) significant; (3) the dominance parameter estimated equal to zero under the mixed model takes values around 0.2–0.3 when multifactorial transmission is neglected [24], probably indicating contamination of major gene parameters by neglected additive factors; and (4) transmission of major effect is compatible with Mendelian expectations

TABLE 2

ANALYSIS OF RBC Mg DATA UNDER THE UNIFIED MODEL

MAJOR EFFECT			MULTIFACTORIAL EFFECT	CONDITIONAL LIKELIHOOD		JOINT LIKELIHOOD		No. PARAMETERS ESTIMATED
Present?	Transmission	Dominance		One component	Two components	One component	Two components	
No			No	153.51	165.86	150.64	170.09	2
No			Yes	16.33	27.87	13.18	31.04	4
	Mendelian	$d = 1$		76.35	85.58	74.92	92.73	4
	"	$d = 0$		78.97	93.54	85.67	103.14	4
Yes	"	$\hat{d}$	No	35.31	32.18	44.31	42.58	5
	General	$\hat{d}$		26.91	24.56	43.17	40.64	8
	None	$\hat{d}$		144.80	146.11	140.62	144.59	5
	$\tau_1 = \tau_2 = \tau_3 = 1 - q$							
Yes	Mendelian	$\hat{d}$		2.35	0.28	0.00	0.67	7
	General	$\hat{d}$	Yes	0.00	0.00	0.00	0.00	10
	None	$\hat{d}$		16.54	24.84	12.07	18.24	7
	$\tau_1 = \tau_2 = \tau_3 = 1 - q$							

NOTE: Likelihood statistics are $-2 \ln (L)$ + a proportionality constant. Both H and Z are estimated wherever a multifactorial effect is allowed for. Parameters of best-fitting genetic model for joint likelihood and two components are: V = 1.004, u = 0.033, d = 0.31, t = 2.62, q = 0.23, H = 0.56, Z = 0.75.

TABLE 3

ANALYSIS OF CHOLESTEROL DATA UNDER THE UNIFIED MODEL

Multifactorial effect	Dominance	One component	Two components
No	$d = 1$	5.78	4.86
	$d = 0.5$	5.94	2.97
	$d = 0$	2.85	2.68
	$\hat{d}$	6.23	2.80
Yes	$d = 1$	5.35	0.95
	$d = 0.5$	5.40	0.19
	$d = 0$	2.07	1.79
	$\hat{d}$	5.65	0.10

NOTE: Test statistics (χ^2 with 1 df) of the hypothesis: $\tau_2 = 0.5$.

($\chi^2_3 = 1.69 - 0.00 = 1.69$); the hypothesis of no transmission of major effect is rejected whether multifactorial transmission is considered ($\chi^2_3 = 15.94 - 0.00 = 15.94$) or not ($\chi^2_3 = 75.41 - 10.47 = 64.94$), but it is clearly quite inflated in the latter case. The previous analyses and the present ones, in testing transmission of major effects and their agreement with Mendelian expectations, add support in favor of the hypothesis that a significant proportion of the familial resemblance for the IgE levels results from segregation of a recessive major gene, in addition to other sources of transmission.

A similar analysis was carried out on a random sample of nuclear family data on erythrocyte magnesium concentrations (RBC Mg), which is reported in more detail in [30, 31]; only the main results are discussed here. There was significant evidence for commingling, and again segregation analysis was repeated four ways. Here, however, a major gene effect reached similar significance levels, under the assumption of one underlying component, whether the conditional or the joint likelihood was used (table 2). A multifactorial model is better supported than a generalized single-locus model, leading to a heritability estimate H = 1. Here again, both major gene and multifactorial transmission are significant under a mixed model. The dominance parameter is estimated as $d = 0.3$ when a multifactorial effect is considered; it is estimated as $d = 0.4$ when such effect is absent. The hypothesis of no transmission of major effect is rejected, and transmission agrees with Mendelian expectations. Note that the latter hypothesis would have been rejected by a model neglecting multifactorial transmission when conditional likelihood is used.

Some aspects of a re-analysis of cholesterol levels in 33 kindreds [32, 33] are relevant to the present discussion. Only the conditional likelihood was used to take sampling into account. Commingling being significant, segregation analysis was repeated under assumptions of one and two underlying distributions. Tests of the hypothesis $\tau_2 = .5$ in both cases, for various values of the dominance parameter, with or without multifactorial transmission, seem to indicate that here this parameter is sensitive to distributional assumptions (table 3). This was not

observed in the two other data sets, which may be due to the fact that the estimated gene frequency was smaller by an order of magnitude for cholesterol levels.

CONCLUSION

We have shown how the general transmission single-locus model and the mixed model can be reconciled into a single, unified approach. While straightforward, this had not been done until now, although it was proposed by Boyle and Elston [26]. This should help resolve some disagreement expressed with regard to methodology in segregation analysis. The need for such a unified approach was implicit in [25], and we feel the data analyses discussed here clearly emphasize this point.

Indeed, we have seen that no conclusion could be reached by comparing likelihoods of models in disjoint parameter spaces. This is illustrated by the fact that while a generalized single-locus model is better supported than a multifactorial model for IgE, the converse is observed for RBC Mg. Testing that the transmission probabilities are equal to Mendelian expectations should help prevent falsely inferring the segregation of a major gene under the mixed model. Testing that they are equal is a test of no transmission of a major effect alone only under the unified model, as this test, in the framework of the general transmission single-locus model, is an overall test of no parent-offspring resemblance, whether due to the transmission of a major effect or residual family resemblance.

While we feel this model will, in most instances, have sufficient generality, segregation analysis has become more and more cumbersome. Perhaps some simplification is in order. In particular, the task of analyzing data and presenting and discussing them could be simplified if one could do away with the need for repeated analyses with joint and conditional likelihood, or under various transformations of the data.

The operational value of such alternative strategies should be tested with both real and simulated data. While for nuclear family data a joint likelihood approach is in theory more informative about population parameters such as a gene frequency, a conditional likelihood approach is likely to be less sensitive to selection, temporal trends, or other deviations from assumptions of the model that tend to induce systematic differences between parents and offspring that may be relevant to the parameters of the model that characterize the model of transmission.

The results presented in table 3 indicate that, at least for not too common traits, using a scale of measurement that eliminates skewness in a trait may lead to deviations from true Mendelian expectations. As it may be inconvenient in practice to repeat the analysis under various transformations of the data, the relative merits of at least two possible strategies need to be evaluated. One consists of analyzing the data after a transformation to remove overall skewness. Although this should reduce the risk of falsely inferring segregation of a major effect, it also implies a systematic loss of power; moreover, such transformation may affect transmission probabilities, as emphasized above. Another strategy would consist of analyzing the data using a transformation that removes residual skewness under the assumption of commingling, when the latter is significant. If commingling results from a Mendelian factor, then transmission should be compatible with Mendelian expectations; if not, one would hope that the hypothesis of Mendelian

transmission will be rejected. This latter approach should in theory be more powerful, but its robustness has yet to be examined. Indeed, there is little support at the moment to favor this strategy. In any case, whenever the analysis results in significant departure from Mendelian expectations, tests of heterogeneity among partitions of the data, whenever feasible, allow further investigation of this matter. No doubt more experience with real data as well as simulation studies will help to clarify this issue. Whatever decision an investigator may make, he should consider a test of $\tau_2 = \frac{1}{2}$ before accepting the mixed model.

REFERENCES

1. FISHER RA: The effects of methods of ascertainment upon the estimation of frequencies. *Ann Eugen (Lond)* 6:13–25, 1934
2. HALDANE JBS: The estimation of the frequencies of recessive conditions in man. *Ann Eugen (Lond)* 8:255–262, 1938
3. HALDANE JBS: A test for homogeneity of records of familial abnormalities. *Ann Eugen (Lond)* 14:339–341, 1949
4. MORTON NE: Segregation analysis in human genetics. *Science* 127:79–80, 1958
5. MORTON NE: Genetic tests under incomplete ascertainment. *Am J Hum Genet* 11:1–16, 1959
6. MORTON NE, CHUNG CS, EDS: *Genetic Epidemiology*. New York, Academic Press, 1978
7. ELSTON RC, RAO DC: Statistical modeling and analysis in human genetics. *Ann Rev Biophys Bioeng* 7:253–286, 1978
8. SING CF, SKOLNICK M: *Genetic Analysis of Common Diseases: Applications to Predictive Factors in Coronary Disease*. New York, Alan R. Liss, 1979
9. LALOUEL JM: Analyse génétique des caractères quantitatifs, in *Génétique Médicale, Acquisitions et Perspectives*, edited by FEINGOLD J, Paris, Flammarion, 1981, pp 161–178
10. LAMY M, FREZAL J, REY J: Hérédité du diabète sucré, in *Journées Annuelles de Diabétologie de l'Hôtel Dieu*, Paris, Flammarion, 1961, pp 5–15
11. CARTER CO: The inheritance of congenital pyloric stenosis. *Br Med Bull* 17:251–254, 1961
12. EDWARDS JH: Familial predisposition in man. *Br Med Bull* 25:58–63, 1969
13. ELSTON RC, STEWART J: A general model for the genetic analysis of pedigree data. *Hum Hered* 21:523–542, 1971
14. GO RC, ELSTON RC, KAPLAN EB: Efficiency and robustness of pedigree segregation analysis. *Am J Hum Genet* 30:28–37, 1978
15. MORTON NE, MACLEAN CJ: Analysis of family resemblance. III. Complex segregation analysis of quantitative traits. *Am J Hum Genet* 26:489–503, 1974
16. RAO DC, MORTON NE, YEE S: Analysis of family resemblance. II. A linear model for familial correlation. *Am J Hum Genet* 26:331–359, 1974
17. RICE J, CLONINGER CR, REICH T: Multifactorial inheritance with cultural transmission and assortative mating. I. Description and basic properties of the unitary models. *Am J Hum Genet* 30:618–648, 1978
18. CLONINGER CR, RICE J, REICH T: Multifactorial inheritance with cultural transmission and assortative mating. II. A general model of combined polygenic and cultural inheritance. *Am J Hum Genet* 31:176–198, 1979
19. RAO DC, MACLEAN CJ, MORTON NE, YEE S, LEW, R: Analysis of family resemblance. V. Height and weight in Northeastern Brazil. *Am J Hum Genet* 27:509–520, 1975
20. LALOUEL JM, MORTON, NE: Complex segregation analysis with pointers. *Hum Hered* 31:312–321, 1981
21. MACLEAN CJ, MORTON NC, LEW R: Analysis of family resemblance. IV. Operational characteristics of segregation analysis. *Am J Hum Genet* 27:365–384, 1975

22. MACLEAN CJ, MORTON NE, ELSTON RC, YEE S: Skewness in commingled distributions. *Biometrics* 32:695–699, 1976
23. GERRARD JW, RAO DC, MORTON NE: A genetic study of immunoglobulin E. *Am J Hum Genet* 30:46–58, 1978
24. RAO DC, LALOUEL JM, MORTON NE, GERRARD JW: Immunoglobulin E revisited. *Am J Hum Genet* 32:620–625, 1980
25. DEMENAIS F, ELSTON RC, BONAITI C, BRIARD ML, KAPLAN EB, NAMBOODIRI KK: Segregation analysis of congenital glaucoma: approach by two different models. *Am J Hum Genet* 33:300–306, 1981
26. BOYLE CR, ELSTON RC: Multifactorial genetic models for quantitative traits in man. *Biometrics* 35:55–68, 1979
27. RAO DC, MORTON NE: I.Q. as a paradigm in genetic epidemiology, in *Genetic Epidemiology*, edited by MORTON NE, CHUNG CS, New York, Academic Press, 1978, pp. 145–176
28. CLONINGER CR, RICE J, REICH T: Multifactorial inheritance with cultural transmission and assortative mating. III. Family structure and the analysis of separation experiments. *Am J Hum Genet* 31:366–388, 1979
29. MORTON NE, RAO DC, LALOUEL JM: *Methods in Genetic Epidemiology*. Basel, Switzerland, S. Karger. In press, 1983
30. DARLU P, RAO DC, HENROTTE JG, LALOUEL JM: Genetic regulation of plasma and red blood cell magnesium concentrations in man. I. Univariate and bivariate path analysis. *Am J Hum Genet* 34:874–887, 1982
31. LALOUEL JM, DARLU P, HENROTTE JG, RAO DC: Genetic regulation of plasma and red blood cell magnesium concentrations in man. II. Segregation analysis. *Am J Hum Genet* 35:938–950, 1983
32. GLUECK CJ, FALLAT R, BUNCHER CR, TSANG R, STEINER P: Familial combined hyperlipoproteinemia: studies in 91 adults and 95 children from 33 kindreds. *Metabolism* 22:1403–1428, 1973
33. LALOUEL JM, WILLIAMS WR, MORTON NE, RAO DC, GLUECK CJ: Combined hyperlipidemia: bivariate segregation analysis of cholesterol and triglyceride levels. In preparation