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Segregation Analysis of Schizophrenia and Related Disorders

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SUMMARY

Segregation analysis was applied to 79 nuclear families ascertained through chronic schizophrenic probands. Analysis was performed on the diagnosis of schizophrenia alone and on schizophrenia and schizotypal personality disorder (milder phenotype) combined. The models used were the transmission probability model and the mixed model. Because the disease is associated with reduced fertility, all likelihoods were calculated conditional on parental phenotypes. However, compatibility of the mating-type distribution predicted by each model with the observed was also examined. In all analyses, results suggested consistency with genetic transmission. In the analysis of schizophrenia alone, discrimination among models was difficult. In the analysis including the milder phenotypes, all single-locus models without polygenic background were excluded, while pure polygenic inheritance could not be eliminated. The polygenic model also gave good agreement with supplementary observations (lifetime disease incidences, mating-type distribution, and monozygotic twin concordance). The estimated components of variance for the polygenic model were: polygenes (H) 81.9%; common sib environment (B) 6.9%; random environment (R) 11.2%.

Although the polygenic model was parsimonious, segregation analysis and the supplementary observations were also consistent with a mixed model, with a single major locus making a large contribution to genetic liability. Such a locus is more likely to be recessive than dominant, with a high gene frequency and low penetrance. The most likely recessive

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mixed model gave the following partition of liability variance: major locus, 62.9%; polygenes, 19.5%; common sib environment, 6.6%; and random environment, 11.0%.

INTRODUCTION

The characterization of diabetes as a geneticist's nightmare [1] can be applied equally to schizophrenia. In fact, in many respects, the genetic-epidemiologic study of schizophrenia has been more difficult and more controversial. While many accept that schizophrenia may be familial, there are those who believe the aggregation to be due to nongenetic factors [2, 3]. Then there are some who contend that schizophrenia is not, in fact, familial [4]. Finally, others argue that schizophrenia is not even a disease entity [5]. Whether considered as a disease or not, schizophrenia poses a major public-health concern, with many of its victims incapable of functioning in a self-sufficient manner. This fact alone makes it a phenotype worthy of study.

One of the major problems characterizing schizophrenia research is diagnostic—that is, how does one decide whether an individual is schizophrenic or not? Accurate phenotype definition is a critical aspect of any genetic-epidemiologic study. Diagnostic criteria have varied both in time and place, often making it difficult, or impossible, to compare studies.

Nearly every study design available to the genetic epidemiologist has been applied to schizophrenia: familial-aggregation studies, twin studies, and adoption studies (for a review, see [6]); segregation analysis [7–10], linkage analysis [11–13], and biochemical-marker association [14]. The recent path-analysis applications [15–16] seem to suggest that a large proportion of the familial aggregation is due to genetic inheritance. This result is consistent with the evidence from the adoption studies (still considered by some to be controversial; e.g., see [2]). As to what a likely genetic mechanism may be, everything from a single major locus [17] to multiple loci [18] to a polygenic system [19] has been proposed. A recent report [20] suggested that single-locus inheritance underlying all of schizophrenia could be ruled out. However, this study, as well as the path-analysis reports, was based on historical data (mostly of northern European origin), which were prone to varying diagnostic criteria, as well as to crude methods of risk estimation, which may lead to bias [21]. In addition, the report of O'Rourke et al. [20] focused on risk to parents and sibs of probands, both of which (and especially the former) are sensitive to the strong reproductive disadvantage of schizophrenics [22]. In fact, the crude risk to parents may be too low by a factor of three [23].

Results of segregation analysis applied to family data have been largely equivocal. Elston et al. [7], using Kallman's twin family data [24], found evidence for vertical transmission, but Mendelian transmission probabilities were strongly rejected. Similarly, Tsuang et al. [10], analyzing schizophrenia families from the Iowa 500 [25], found evidence for vertical transmission, but Mendelian transmission was again strongly rejected. Carter and Chung [9], analyzing hospital

records in Hawaii, found high heritability estimates for hospitalized schizophrenia (H = .62), but were unable to distinguish between single locus and polygenic alternatives. Finally, Debray et al. [8], using a simple likelihood analysis, found that their French families were most consistent with single-locus, two-locus, and four-locus models.

Both linkage analysis and biological-marker association studies have been unsuccessful in identifying major contributing loci [13, 14]. However, much work remains to be done in this area.

In the following passages, we review in greater detail the principles underlying segregation analysis and the various reports on segregation analysis of schizophrenia.

SEGREGATION ANALYSIS

Segregation analysis has evolved considerably since its initial applications in human genetics. Original formulations were designed to test a recessive hypothesis by estimating the segregation ratio in sibships, and testing its equality to 1/4. It was primarily applied to rare diseases, where nuclear families were ascertained through affected siblings and parents were normal. Because the method of sampling families influences the observed segregation ratio, statistical procedures were devised to account for ascertainment [26–28].

Within the past decade, the goal of segregation analysis has expanded to include the identification of major-locus effects underlying variation in both qualitative and quantitative traits, rare or common [29]. Many more parameters are now estimated than simply the segregation ratio and/or ascertainment probability: gene frequencies, transmission probabilities, penetrances (or means), polygenic heritability, common sib environmental effects (or intergenerational differences in heritability), and age-of-onset parameters. Nuclear families have given way to extended pedigrees, although ascertainment correction for pedigrees remains an unresolved problem except for simple, limiting cases [30, 31].

It has been suggested that evidence for a major locus can be accrued in two ways: (1) by inability to reject Mendelian transmission in a model that allows for arbitrary transmission probabilities, coupled with the ability to reject equal transmission probabilities (an environmental hypothesis) [32], and (2) by rejection of pure polygenic inheritance in a mixed model that incorporates the combined effects of a major locus, polygenic background, and common sib environment (or intergenerational differences in heritability) [33]. Recently, the two approaches have been combined into a single "unified" model [34].

An additional consideration has been whether likelihoods calculated in nuclear families should include parental phenotypes, or should be conditioned on parental phenotypes. Conditions that argue in favor of a conditional approach are fertility differences related to the trait, and assortative mating [35]. In these cases, the observed parental-mating-type distribution is influenced by factors other than the genotype distribution in the population, and a joint likelihood may induce misleading results. On the other hand, not including the parental-mating-type distribution may lead to a loss of power in testing hypotheses about inheritance and in estimating gene frequencies [36].

There is an additional question in segregation analysis as to whether one should constrain the model parameters to conform to a previously determined disease incidence value. This approach has been advocated when using a conditional likelihood [33]. However, such constraint can significantly influence the results of segregation analysis. Hence, one should be cautious about imposing incidence constraints, particularly when such values are not known to a high degree of certainty.

SEGREGATION ANALYSIS OF SCHIZOPHRENIA

Two of the reports on segregation analysis of schizophrenia employed a single-locus model with arbitrary transmission probabilities. The first of these, the study of Elston et al. [7], used nuclear families of schizophrenic twins collected by Kallmann [24]. The families were divided into two groups based on diagnosis in the proband: catatonic or hebephrenic (nuclear) and paranoid or simple (peripheral). Individuals characterized by Kallmann as "probable schizophrenic" were included as schizophrenic. An additional diagnostic category of "schizoid state" was defined, giving three phenotypes: schizophrenia, schizoid state, and normal. Age of onset was assumed to be log-normally distributed. Two models were described: (1) susceptibility to schizophrenia and schizoid state are fixed, while mean age of onset is genotype dependent, and (2) susceptibility is genotype dependent, while age of onset is not; mean age of onset for schizoid state is less than for schizophrenia, and all susceptible individuals eventually pass through the schizoid state and become schizophrenic. Probability of ascertainment was allowed to be a function of age at onset. These two models have differing implications. Model 1 predicts that sporadic (nongenetic) cases have a later mean age of onset, and/or that age of onset is correlated in families. Equivalently, individuals with early onset should show a higher risk to relatives. Model 2 predicts that age of onset is uncorrelated in families. Both models imply that schizophrenic and schizoid individuals have identical genotype distributions, and therefore equal risk to relatives (i.e., schizoid state is not genetically "less severe" than schizophrenia). Joint likelihoods were calculated, and disease incidence was left unconstrained.

Results of parameter estimation and hypothesis testing using the two models and two sets of families were similar. In all cases, Mendelian transmission probabilities were strongly rejected. Equal transmission probabilities were also rejected. In general, the unrestricted model gave estimates of τ_{AaA} and τ_{aaA} significantly greater than their Mendelian values of .5 and 0, respectively.

Tsuang et al. [10] analyzed 134 families of schizophrenia probands from the Iowa 500 series [25]. The segregation analysis model used was the same as model 1 described above in the study of Elston et al. [7]. Disease incidence was constrained to .006. In this study, once again, Mendelian transmission probabilities were rejected at enormous levels of significance. Equal transmission probabilities (environmental hypothesis) were similarly rejected.

The rejection of Mendelian inheritance in both these studies should be interpreted with caution. First of all, both studies employed joint likelihoods of parents and offspring. The reproductive disadvantage of schizophrenics is well-documented: the number of offspring produced by schizophrenics may be one-third that of

normals [23]. In terms of segregation analysis, we would expect a significantly reduced number of affected parents, causing distortion in parameter estimation. The general effect of such bias has been unexplored, but we can guess that the transmission probabilities will be estimated so as to predict a higher incidence of disease in the offspring generation than in the parental generation (note that Mendelian transmission probabilities imply equal incidences in the parental and offspring generations). The reason the transmission probabilities will be affected is because they are the only component of the model that can absorb such a difference between generations.

Another possible bias relates to ascertainment. In the study of Elston et al. [7], all probands were twins. However, ascertainment correction in their model was apparently applied to all individuals in the family. Clearly, nontwin relatives could not have been probands. Hence, the effect of their ascertainment correction on parameter estimates is unknown. Also, ascertainment was assumed to be a function of age of onset, the probability of ascertainment decreasing with increasing age of onset. However, the reduced fertility effect also causes affected parents to have a later age of onset than affected offspring—that is, individuals with later onset are more likely to have children. If affected parents were included when comparing ages of onset for probands vs. nonprobands, this may account, at least in part, for the ascertainment-age-of-onset relationship. In addition, the age-of-onset distribution function is estimated from all individuals in the sample, including parents. Hence, it will be biased toward later ages.

We have examined the parameter estimates in the unrestricted models from both Elston et al. [7] and Tsuang et al. [10]. From the Elston et al. [7] analysis of model 1 for the group 1 families, the predicted incidence of schizophrenia in the parental generation is .016, while in the offspring generation, it is .127. Similarly, from the model 1 analysis of the group 2 families, the incidence in the parental generation is .008, while in the offspring generation, it is .078. How much of this discrepancy may be accounted for by fertility and ascertainment effects is unknown. From Tsuang et al. [10], the dominant unrestricted model predicts a frequency of disease of .006 in the parental generation (fixed), while the frequency in the offspring generation is .348. In the recessive unrestricted model, the incidence in the offspring generation is .354. These offspring values seem enormously inflated and may raise questions concerning the ascertainment correction procedure. No description of ascertainment correction was given by Tsuang et al. [10] (although ascertainment correction was applied; M. T. Tsuang, personal communication). Also, predicted risk to offspring by parental-mating type in the unrestricted models are counter to genetic expectations. In the dominant unrestricted model, the risk to offspring of a normal $\times$ normal mating is .349, while the risk from a normal $\times$ affected mating is .193. Similarly, in the recessive unrestricted model, the risk from a normal $\times$ normal mating is .356, while for a normal $\times$ affected mating it is .111. Furthermore, the chi-square values testing the Mendelian and environmental models in the Tsuang et al. [10] analysis were 3157.02 and 2442.62 on 3 and 2 degrees of freedom, respectively. These values seem to be unrealistically high, particularly considering the moderate sample size involved (total of 480 individuals).

Carter and Chung [9] examined admission records from the State Mental Hospital of Hawaii (which is the sole mental hospital in Hawaii). Probands were identified as those cases of schizophrenia existing in the State Mental Hospital in 1942 according to the 1942 Hawaii census. Records contained information on names and birthdates of first-degree relatives. The hospital admission files up to the year 1977 were then examined to determine which of the relatives had been admitted after 1942 with a diagnosis of schizophrenia. One advantage of this approach is that the family members have been followed up over an extended period of time and, therefore, are substantially through the risk period. Any individual who was followed up must have been born prior to 1942, and, hence, was at least 35 years old by 1977. However, loss of individuals through death or migration cannot be accounted for. It should also be remembered that the phenotype examined here is "hospitalized" schizophrenia.

The observed distribution of probands among affecteds within sibships was used to calculate the ascertainment probability π. "Prevalence of hospitalized schizophrenia" was then estimated as $a/\pi N$, where a is the number of probands, and N, the size of the baseline population in 1942 (all individuals older than 15 years). However, this number is not, in fact, the prevalence of hospitalized schizophrenia in 1942, because nonproband sibs were those hospitalized after 1942. In fact, the prevalence of hospitalized cases in 1942 is just a/N. The number $a/\pi N$ represents something closer to the cumulative lifetime incidence of hospitalized schizophrenia (i.e., the probability that an individual will be hospitalized for schizophrenia at any time during his or her life). In fact, this is the appropriate population parameter for use in segregation analysis. However, the baseline population (N) included only individuals over age 15; certainly, some of the siblings who were hospitalized after 1942 were under 15 years in 1942. Hence, the values given by Carter and Chung [9] are probably overestimates of the true values.

Segregation analysis was performed using the mixed model [33]. According to the simple polygenic model, heritability (H) was estimated at .62. The likelihood surface was apparently somewhat flat, as there was little power to distinguish between single locus and polygenic alternatives.

Debray et al. [8] studied the families of 25 chronic schizophrenics in France. The total sample comprised 1,333 individuals. Information on relatives was apparently obtained both through family history and family-study methods, although the proportion in each category was not given. Individuals were weighted according to the quality of information obtained. Three diagnostic categories were defined: (1) schizophrenia; (2) schizophrenia spectrum—acute schizophrenia, chronic delusion, psychopathy, paranoid personality, non-unipolar depression, neurotic depression, and anorexia nervosa; and (3) normal. Clearly, category 2 is quite broad and probably contains conditions unrelated to schizophrenia.

The statistical method used to analyze these families differed from conventional approaches. The likelihood of the data for each of 12 different genetic models was calculated. Parameters within each model were fixed—that is, no parameters, such as gene frequency or penetrances, were estimated. Also, ascertainment

correction was unconventional. Hence, it is difficult to interpret the results of their analysis. Some of the models gave higher likelihoods than others. However, no statistical tests could be performed.

Finally, with the exception of the study of Tsuang et al. [10], none of the previous studies fully satisfied modern criteria for collection of family data on schizophrenia: (1) prospective proband identification (to minimize selection bias); (2) use of structured interview schedules and explicit diagnostic criteria (to enhance diagnostic reliability); (3) use of personal interviews as opposed to the family history method (to avoid underreporting of psychopathology); and (4) blind assessment of family members with respect to clinical and kinship status (to minimize bias in determining the presence or absence of psychiatric illness according to a preconceived notion). In addition, none of the previous studies assessed the "spectrum" of schizophrenia (i.e., milder phenotypes thought to be genetically related to schizophrenia) using structured diagnostic instruments and explicit criteria of demonstrated reliability. The importance of these issues for schizophrenia research has been discussed [37].

The objective of this investigation was to perform segregation analysis using appropriate statistical-genetic methodology on a body of family data collected according to the guidelines discussed above.

MATERIALS AND METHODS

Our probands were patients consecutively admitted with a diagnosis of chronic schizophrenia to clinical research wards at two New York City psychiatric hospitals. All probands were white and between the ages of 17 and 45. There were 52 males and 27 females. All probands were directly interviewed, at which time names of all first-degree relatives (parents, sibs, spouses, and offspring) were obtained. As many of the first-degree relatives as possible were directly interviewed (85%), using both the Schedule for Affective Disorders and Schizophrenia (SADS) [38] and the Schedule for Interviewing Borderlines (SIB) [39]. Most of the interviewers were blind to the proband's diagnosis, although in a small percentage of cases (25%), complete blindness could not be achieved. Family-history information on the unavailable relatives was obtained through as many interviewed first-degree relatives as possible. A detailed description of the sampling procedure has been given [40, 41].

For each individual, assignment of diagnosis was based on a combination of the direct interview, medical records, and family-history data. Diagnosis of chronic schizophrenia was according to the Research Diagnostic Criteria (RDC) [42], which are more restrictive than DSM-III criteria [43] (all schizophrenic probands were also diagnosed as such by DSM-III criteria); schizotypal personality disorder (SPD) was diagnosed according to DSM-III criteria. Two subclassifications of SPD were made according to number of schizotypal features: definite (SPD-D) with four or more features (DSM-III criteria), and probable (SPD-P) with two or three features. The rationale for inclusion of the milder phenotypes in the analysis was their higher frequency among relatives of schizophrenics than among relatives of controls [41, 44]. Both age at interview and age at onset (defined as earliest age at which subject met criteria for the diagnosis) were obtained for all individuals.

Because few of the probands were married and/or had children, the analysis presented here focuses on the nuclear families consisting of the probands and their sibs and parents. In all, there are 79 probands, 158 parents (of whom five are unknown), and 185 sibs (of whom 13 are unknown). Each family was ascertained through a single proband (i.e., no multiple ascertainments occurred).

Statistical Methods

The data were analyzed twice: (1) first using only the phenotypic dichotomy affected (schizophrenic) and normal (all others); and (2) allowing for four distinct phenotypes—schizophrenic (S), schizotypal personality disorder-definite (SPD-D), schizotypal personality disorder-probable (SPD-P), and normal (N). Individuals with unknown phenotype were classified as unknown (U).

Two different statistical models were used to analyze the data: the transmission probability model (TPM) and the mixed model (MM). In the analysis of the dichotomized phenotype (S vs. N), the two models can be combined into a single, unified model (UM) [34]. In the UM, affection is defined in terms of a continuous liability scale, with a threshold above which individuals are deemed affected. Contributions to liability occur through a single, diallelic major locus, polygenic background, environment common to sibs, and random environment. The overall population mean for liability is assumed to be 0, and total variance within each major-locus genotype is 1. Parameters of the unified model are as follows: ψ_1, ψ_2, and ψ_3, the frequencies for genotypes *AA*, *Aa*, and *aa*, respectively (the frequency p of allele $A = \psi_1 + \psi_2/2$); τ_1, τ_2, and τ_3, the probabilities that individuals of genotypes *AA*, *Aa*, and *aa*, respectively, transmit allele *A*; g_1, g_2, and g_3, the mean liability of individuals of genotype *AA*, *Aa*, and *aa*, respectively; T, the threshold for affection; H, the proportion of within-genotype variance due to polygenic background; B, the proportion of within-genotype variance due to common sib environment; R, the proportion of within-genotype variance due to random environment; and μ and σ, the respective mean and standard deviation of the age-of-onset distribution. The penetrance for each major-locus genotype can be calculated directly from g_1, g_2, g_3, and T.

Calculation of the likelihood of the nuclear family was obtained as in equation (17) of Morton and MacLean [33]. However, their numerical integration scheme was replaced by Gauss-Hermite quadrature equations, similar to the program POINTER [45].

Preliminary evidence suggested that the age-of-onset distribution could be well characterized by a square-root normal distribution after subtracting 8 years. Also, examination of the age of onset in our sibships indicated no relationship between age of onset and risk to relatives (e.g., onset was the same in multiplex and simplex families). Therefore, age of onset was modeled as follows: only individuals with liability greater than the threshold T are "susceptible," and their age of onset is determined by the square-root normal distribution. All individuals with liability greater than T are "equally" susceptible—that is, they have the same age-of-onset distribution irrespective of their liability value. Clearly, this model predicts that age of onset in probands is uncorrelated with morbid risk in relatives.

When polychotomous phenotypes are considered, the TPM and MM (or UM) no longer precisely overlap. This is because the MM (or UM) is defined in terms of a liability scale, with different thresholds for the different severities of disorder (e.g., S, SPD-D, SPD-P). This parameterization necessarily constrains the relationship among the various genotypes and phenotypes. More specifically, penetrances of the three genotypes for the four phenotypes are determined by the three g's and three thresholds (T's), a total of six parameters. In a general model with four phenotypes, we could allow for a maximum of nine independent penetrances (three genotypes for three phenotypes; the total penetrance for each genotype must be 1).

Therefore, in the analysis of the polychotomous phenotypes (S, SPD-D, SPD-P, N), we have employed two different models. The first is a transmission probability model with the following parameters: ψ_1, ψ_2, ψ_3, p, τ_1, τ_2, τ_3, μ, and σ, defined as above; γ_{ij}, $i = 1, 2, 3, j = 1, 2, 3$, where γ_{ij} is the penetrance of genotype i to phenotype j. The genotypes *AA*, *Aa*, and *aa* are ordered 1, 2, and 3, respectively; the phenotypes S, SPD-D, SPD-P, and N are ordered 3, 2, 1, and 0, respectively.

We assumed the same age-of-onset distribution for the three disease phenotypes. In fact, preliminary examination suggested some slight differences among them; however,

genetic analyses were virtually identical when three distinct age-of-onset functions were allowed vs. one.

Parameterization for the unified model (UM) applied to the polychotomous data is similar to the previous description. In this case, however, we define three thresholds instead of one: T_1, T_2, and T_3. Only individuals with liability greater than T_3 are susceptible to schizophrenia; individuals with liability between T_2 and T_3 are susceptible to SPD-D; individuals between T_1 and T_2 are susceptible to SPD-P; and individuals below T_1 are normal. As before, age of onset is assumed independent of liability; that is, an individual's susceptibility to each disease form is determined by his or her liability, and then age of onset is derived from the single, square-root normal distribution.

Likelihoods were calculated conditional on parents' phenotypes and ages of onset (if affected). A conditional approach is necessary, in this case, because of the severe reduction in fertility of schizophrenics. As described above, conditioning on parents' ages of onset is also required because affected parents tend to have later onset, biasing the distribution to older ages. All families were ascertained through a single proband. Hence, equations for ascertainment correction assuming single ascertainment were applied (the likelihood for each family was multiplied by the number of schizophrenic sibs and divided by the sum of the probabilities for each sib to be affected by his age at examination, given the parental phenotypes).

In general, we did not impose an incidence condition for any of the disease phenotypes. The cumulative lifetime incidence of schizophrenia is probably in the range of .005 to .015. In our control sample [41], the rate was .006. Less information exists about the incidence of SPD. In our control sample [41], the frequency of SPD-D was .021, and for SPD-P, .065. If our maximized likelihoods gave predicted incidence values for schizophrenia clearly out of range, we then imposed an incidence condition (.01), which also acted as a test of the adequacy of that particular model.

Likelihoods for the UM were calculated using the FORTRAN program MIXQUAL [46], and for the TPM, with the program TPMQUAL [47]. Likelihood maximizations were obtained using MAXLIK [48]. Tests of hypotheses were derived using the likelihood-ratio criterion, comparing twice the log-likelihood difference between a restricted and unrestricted model with a chi-square distribution, the degrees of freedom determined by the number of independent constraints applied in the restricted model.

Although likelihoods were calculated conditional on parents' phenotypes, we did compare the observed phenotypic-mating-type distribution with that predicted by each of the models to further assess the plausibility of each model. To do this, for each model, we calculated the joint probability of each mating type and a schizophrenic child. From these we determined the posterior probability of each mating type given an affected child. Because of the effects of reduced fertility and possible assortative mating, no formal goodness-of-fit tests were performed.

RESULTS

Considering schizophrenia alone, among the 79 families, 67 were simplex with both parents normal or unknown, eight families were multiplex with both parents normal or unknown, three were simplex with one parent affected, and one was multiplex with one parent affected. Considering the schizophrenia spectrum, 23 families were simplex with both parents normal or unknown, eight were multiplex with both parents normal or unknown, 13 were simplex with one parent affected, 13 were multiplex with one parent affected, five were simplex with both parents affected, and 13 were multiplex with two parents affected.

Results of segregation analysis of schizophrenia alone using the mixed model (MM) are presented in table 1. In all cases, the MM converged to a single-locus

TABLE 1

RESULTS OF SEGREGATION ANALYSIS FOR SCHIZOPHRENIA ALONE

	MODEL						
			MENDELIAN				
PARAMETER	Unrestricted	Environmental	Codominant HWE*	Dominant HWE*	Recessive HWE	Polygenic	Polygenic†
τ_1	(1.000)	.237	(1.000)	(1.000)	(1.000)	...	...
τ_2	.468	.237	(.500)	(.500)	(.500)	...	...
τ_3	0	.237	(0)	(0)	(0)	...	...
ψ_1	0	...	0	0	.0010	...	...
ψ_2	.0128	...	.0063	.0063	.0610	...	...
ψ_3	.9872	...	.9937	.9937	.9381	...	...
ρ	.0064	...	.0032	.0032	.0315	...	...
γ_1	1.0000	0	1.0000	.9826	1.0000	...	...
γ_2	.9790	.3040	.9805	.9826	.0015	...	...
γ_3	.0014	0	.00069	.00064	.0015	...	...
H	0	0	0	0	0	1.000	.954
B	0	0	0	0	0	0	.046
R	1.0000	1.0000	1.0000	1.0000	1.0000	0	0
T	...	...	...	...	...	2.050	(2.330)
$\mu^2 + 8$	22.010	22.661	22.012	22.003	22.478	22.508	22.508
σ	.929	.969	.928	.928	.960	.962	.962
$-2\ln L$	695.88	708.60	695.90	695.94	703.02	703.24	703.58

NOTE: Values in parentheses are fixed.
* Models without Hardy-Weinberg equilibrium converged here also.
† Cumulative lifetime incidence of schizophrenia constrained to .01.

TABLE 2

TESTS OF HYPOTHESES IN THE ANALYSIS OF SCHIZOPHRENIA ALONE

Hypothesis	Unrestricted model	Parameter restriction	χ^2	df	P
Environmentalism	Unrestricted	$\tau_1 = \tau_2 = \tau_3$	12.72	2	$< .01$
Mendelism	Unrestricted	$\tau_1 = 1.0, \tau_2 = 0.5, \tau_3 = 0$	0.02	2	.90
Dominance	Codominant	$\gamma_1 = \gamma_2$	0.04	1	$> .80$
Recessivity	Codominant	$\gamma_2 = \gamma_3$	7.12	1	$< .01$
No major locus	Dominant*	$p = 0$	7.30	1–2	$< .05$
Incidence = .01	Polygenic	$T = 2.330$	0.34	1	$> .50$

* The dominant mixed model converged to the dominant single-locus model.

model (i.e., $H = B = 0$). Therefore, in the table, penetrances for each major-locus genotype (γ_i, $i = 1, 2, 3$) are given instead of means on the liability scale. In the unrestricted model, τ_1 was fixed at 1.0 because ψ_1 converged toward 0.

Table 2 gives tests of hypotheses using the log likelihoods from table 1. The environmental model is clearly rejected. Mendelian transmission probabilities are not rejected (in fact, the unrestricted τ values are quite close to their Mendelian values). Dominant inheritance is not rejected compared with codominant. Since the genotype frequency ψ_1 in both the dominant and codominant models converged toward 0, and ψ_2 was also near 0, these models with and without the Hardy-Weinberg assumption are identical. Comparing the recessive model with the codominant model assuming Hardy-Weinberg equilibrium in both gives a significant rejection of the recessive model. The major-locus effect is significant when comparing the dominant mixed model (MM) (which converged to the single-locus dominant model) with the polygenic model ($P < .05$). An incidence of .01 for schizophrenia was not rejected in the polygenic model.

In table 3 we calculated the predicted mating-type distribution, incidence and monozygotic (MZ) twin concordance for the various models and compared them with the observed (ranges for cumulative lifetime incidence [CLI] and MZ concordance are taken from Gottesman and Shields [6]). Only mating types where both parents are known are included (hence, four are excluded). The mating-type distribution predicted by the dominant model is clearly discordant from the

TABLE 3

SUPPLEMENTARY PREDICTIONS OF MODELS FOR SCHIZOPHRENIA ALONE

		Model			
Mating type	Observed	Dominant	Recessive	Polygenic	Polygenic*
N × N	71	8.1	72.8	50.2	57.8
N × S	4	66.5	2.1	24.0	16.8
S × S	0	0.4	0.1	0.8	0.5
Incidence	.005–.015	.0068	.0025	.0202	.010
MZ concordance	.35–.58	.89	.40	1.00	1.00

* Cumulative lifetime incidence of schizophrenia constrained to .01.

TABLE 4

RESULTS OF SEGREGATION ANALYSIS FOR SCHIZOPHRENIA SPECTRUM WITH THE TRANSMISSION PROBABILITY MODEL

1192.36

	MODEL						
			MENDELIAN				
PARAMETER	Unrestricted	Environmental	Codominant	Codominant HWE	Recessive HWE	Dominant HWE	Dominant HWE*
τ_1	.844	.827	(1.000)	(1.000)	(1.000)	(1.000)	(1.000)
τ_2	.489	.827	(.500)	(.500)	(.500)	(.500)	(.500)
τ_3	0	.827	(0)	(0)	(0)	(0)	(0)
ψ_1	.030	...	.015	.010	.504	.007	.001
ψ_2	.530	...	.358	.181	.412	.157	.043
ψ_3	.440	...	.627	.809	.084	.835	.956
ρ	.295	...	.194	.101	.710	.086	.022
γ_{13}	.072	.067	.051	.056	.132	.230	.230
γ_{23}	.213	.153	.212	.209	.037	.230	.230
γ_{33}	0	.029	0	0	.037	0	0
γ_{12}	.569	.211	.584	.566	.346	.357	.406
γ_{22}	.305	.177	.305	.308	0	.357	.406
γ_{32}	0	.072	0	0	0	0	0
γ_{11}	.349	.200	.354	.363	.329	.406	.350
γ_{21}	.482	.177	.482	.480	.004	.406	.350
γ_{31}	0	.037	0	0	.004	0	0
$\mu^2 + 8$	20.917	20.674	21.054	21.061	20.831	20.824	20.681
σ	.942	.925	.955	.956	.938	.936	.927
$-2\ln L$	1189.80	1221.22	1192.22	1192.36	1198.52	1193.82	1194.12

NOTE: Values in parentheses are fixed.

* Cumulative lifetime incidence of schizophrenia constrained to .01.

observed, even allowing for reduced fertility. Also, the MZ concordance is overestimated. The recessive model gives reasonable agreement with the observed mating-type distribution, but slightly underpredicts the number of N × S matings, especially considering the reduced fertility effect. Also, incidence is slightly underestimated. The polygenic models overpredict the number of N × S matings, but might be acceptable in the presence of a strong fertility effect. The MZ concordance, however, is overestimated. Implications of these rsults are elaborated in the DISCUSSION section.

Tables 4 and 5 give the results of segregation analysis for the schizophrenia spectrum using the transmission probability model (TPM) and the mixed model (MM), respectively. Tests of hypotheses are given in table 6. The environmental hypothesis is strongly rejected ($P < .001$), while Mendelian transmission probabilities are not rejected ($P > .40$). Both dominant and recessive models are acceptable when compared with the codominant model. The CLI of schizophrenia predicted by the dominant model is somewhat high (.038); however, a CLI of .01 is not rejected ($P > .50$). Tests of no polygenic component are not quite rejected in the mixed-dominant and mixed-recessive models ($.10 < P < .20$ in both cases). Similarly, tests of no major locus are not rejected in the dominant and recessive mixed models ($P > .40$ and $P > .30$, respectively). The polygenic model gives an estimate of CLI (.0006) well below the observed. However, a CLI of .01 was not rejected in the polygenic model ($P > .50$).

Table 7 gives observed and predicted mating-type distributions, CLIs, and MZ concordance for various models. The CLIs for SPD-D and SPD-P were obtained from a control series [41]. Considering the observed mating-type distribution (for which we have combined SPD-D and SPD-P into a single category: SPD), we expect the frequency of N × S, SPD × S, and S × S matings to be reduced because of the fertility effect, while SPD × SPD matings may be increased if there is positive assortative mating. Comparing predictions of the various models with the observed, we see that once again the dominant model predicts distributions highly discrepant from the observed. Allowing for possible fertility and assortative mating effects, none of the other models can be strictly ruled out, although clearly the recessive mixed model gives the closest correspondence to the observed. Examining the incidence estimates, the dominant and recessive models overpredict the observed, and the polygenic model underpredicts them. However, the polygenic model with a CLI of .01 for schizophrenia imposed gives reasonable agreement with the observed CLIs for SPT-D and SPT-P, as do the dominant and recessive mixed models. Considering the estimated MZ concordance, the dominant mixed model and the dominant model without polygenic background overpredict while the single-locus recessive model underpredicts the observed. Other models give reasonable agreement.

DISCUSSION

In the analysis allowing for a dichotomous phenotype (schizophrenic vs. normal), segregation analysis using a conditional likelihood yielded significant evidence for a major-locus effect. Mendelian transmission probabilities were not rejected, while the polygenic model was rejected. The most likely model was dominant

TABLE 5

RESULTS OF SEGREGATION ANALYSIS OF SCHIZOPHRENIA SPECTRUM WITH THE MIXED MODEL

	MODEL							
PARAMETER	Mixed codominant	Mixed dominant	Mixed recessive	Codominant H = B = 0	Dominant H = B = 0	Recessive H = B = 0	Polygenic	Polygenic*
p	0.579	0.615	0.611	0.660	0.003	0.665	...	...
g_1	1.694	0.685	1.684	1.855	3.024	1.803	...	...
g_2	−0.920	0.685	−1.005	−1.310	3.024	−1.426	...	...
g_3	−0.6824	−3.9320	−1.005	−1.912	−0.019	−1.426	...	...
H	0.484	0.981	0.524	(0)	(0)	(0)	0.789	0.819
B	0.218	0.018	0.179	(0)	(0)	(0)	0.155	0.069
R	0.298	0.001	0.297	(1.000)	(1.000)	(1.000)	0.058	0.112
T_3	3.918	2.964	3.800	2.876	3.723	2.829	3.235	(2.330)
T_2	3.068	2.249	2.937	1.885	2.348	1.846	2.553	1.638
T_1	2.392	1.749	2.249	0.999	0.935	0.976	2.092	1.167
$\mu^2 + 8$	20.838	20.709	20.845	20.913	20.505	20.902	20.674	20.709
σ	0.939	0.931	0.939	0.943	0.911	0.942	0.927	0.929
−2lnL	1195.58	1196.42	1195.68	1200.24	1200.34	1200.26	1198.02	1198.44

NOTE: Values in parentheses are fixed.
* Cumulative lifetime incidence of schizophrenia constrained to .01.

TABLE 6

TESTS OF HYPOTHESES IN THE ANALYSIS OF SCHIZOPHRENIA SPECTRUM

Hypothesis	Unrestricted Model	Parameter restriction	χ^2	df	*P*
Environmentalism	Unrestricted SML*	$\tau_1 = \tau_2 = \tau_3$	31.42	2	< .001
Mendelism	Unrestricted SML	$\tau_1 = 1.0, \tau_2 = .5, \tau_3 = 0$	2.42	3	> .40
Hardy-Weinberg equilibrium	Codominant	$\psi_2^2 = 4\psi_1\psi_3$	0.14	1	> .70
Dominance	Codominant	$\gamma_{11} = \gamma_{21}, \gamma_{12} = \gamma_{22}, \gamma_{13} = \gamma_{23}$	0.80	3	> .80
Recessivity	Codominant	$\gamma_{21} = \gamma_{31}, \gamma_{22} = \gamma_{32}, \gamma_{23} = \gamma_{33}$	2.28	3	> .50
Incidence = .01	Dominant HWE	$\psi_1\gamma_{13} + \psi_2\gamma_{23} + \psi_3\gamma_{33} = .01$	0.30	1	> .50
Single-locus only	Mixed dominant	H = 0, B = 0	3.92	2	> .10
Single-locus only	Mixed recessive	H = 0, B = 0	4.58	2	> .10
No major locus	Mixed dominant	p = 0	1.60	1–2	> .40
No major locus	Mixed recessive	p = 0	2.34	1–2	> .30

* SML stands for single major-locus model.

TABLE 7

SUPPLEMENTARY PREDICTIONS OF MODELS FOR SCHIZOPHRENIA SPECTRUM

MATING TYPE	OBSERVED	MODEL					
		Dominant	Recessive	Mixed dominant	Mixed recessive	Polygenic	Polygenic*
N × N	31	1.1	18.0	12.1	32.3	42.1	17.6
N × SPD	24	49.8	29.8	28.6	28.3	23.7	30.2
N × S	2	15.1	6.8	9.9	4.0	2.8	8.2
SPD × SPD	16	5.4	13.5	16.6	8.0	2.7	13.4
SPD × S	2	3.2	6.1	7.3	2.3	3.7	5.4
S × S	0	0.5	0.7	0.4	0.1	0	0.3
Incidence:							
S	.005–.015	.0380	.0850	.0097	.0064	.0006	(.0100)
SPD-D	.021	.0550	.1744	.0405	.0329	.0047	.0407
SPD-P	.065	.0625	.1678	.0722	.0680	.0129	.0709
MZ concordance	.35–.58	.89	.11	.95	.31	.55	.50

* Cumulative lifetime incidence of schizophrenia constrained to .01.

inheritance. However, examination of the observed mating-type distribution and that predicted by the dominant model revealed an enormous discrepancy.

For comparison, we also performed segregation analysis using a joint likelihood (ignoring the effect of reduced fertility). The results were entirely different. Twice the negative log likelihoods for the various models were as follows: dominant, 748.46; recessive, 740.16; and polygenic, 741.48. Evidence for a major locus disappears (the polygenic model is not rejected), and the recessive model is much more likely than the dominant model. We also calculated the joint likelihoods for the single-locus models, specifying the penetrance for schizophrenia in the parents to be one-third the value in the offspring [23]. In this case, the dominant and recessive models had nearly identical likelihoods.

These results indicate that great caution must be taken when interpreting results of segregation analysis using a conditional likelihood, even though, in this case, it is required because of significant fertility effects related to the disease. In a preliminary presentation of the segregation analysis results [49], we had not considered the observed and predicted mating-type distributions and were unable to reject the single-locus dominant model. In any event, the results do suggest consistency with Mendelian transmission, but little power to distinguish among hypotheses.

An increase in power is derived by incorporating SPD into the analysis as part of the schizophrenia spectrum. In the transmission probability model (TPM), Mendelian transmission probabilities are not rejected, and the dominant model gives the highest likelihood. However, the dominant model is once again highly discordant with the observed mating-type distribution as well as the MZ concordance. Examination of results from the mixed-model (MM) analysis suggests that familiality is not due exclusively to the effect of a single locus as these models were nearly rejected in segregaton analysis and were discordant with supplementary observations. The polygenic model could not be rejected in segregation analysis, and its predictions were in reasonable agreement with the observed mating-type distribution, SPD incidences, and MZ concordance. However, the results here suggest that a single locus *may* contribute significantly to the liability of schizophrenia and SPD; it is more likely to be recessive than dominant, with high gene frequency (.611) and low penetrance for schizophrenia (.017). The recessive mixed model gives the highest likelihood in segregation analysis, good correspondence to the observed mating-type distribution and incidences for S, SPD-D, and SPD-P, and reasonable agreement with the MZ concordance. Furthermore, considering the strong selection against schizophrenia, it is difficult to reconcile a dominant major gene with the high incidence of disease. A recessive allele may be maintained at high frequency in the population through balanced selection [50]. The components of liability variance for the recessive mixed model are: major locus, 62.9%; polygenes, 19.5%; common sib environment, 6.6%; and random environment, 11.0%.

Many qualitative and quantitative traits that seemed to conform to polygenic inheritance have subsequently been shown to have a small number of major loci making the major contribution to their genetic variance. Such loci can be found either through genetic linkage studies or through associated biochemical traits.

Because of the high predicted gene frequency, the results presented here suggest that for schizophrenia such a trait might be very frequent among schizophrenics, but also not infrequent among normals (i.e., there is low specificity).

Segregation analysis was also performed assuming two thresholds, one for schizophrenia and one for SPD-D, with SPD-P classified as normal. The results were not significantly different from the analysis with three thresholds. Also, results of parameter estimation with the polygenic model assuming one, two, or three thresholds (for S alone; S and SPD-D; and S, SPD-D, and SPD-P) gave consistent estimates for thresholds and components of liability variance (results not shown). This provides further evidence that SPD-D and SPD-P are in the genetic spectrum of schizophrenia.

In evaluating the observed and predicted parental-mating-type distribution, we have allowed for reduced fertility among schizophrenics. It is possible that fertility is reduced in SPD as well. From our sample, we can obtain the distribution of number of offspring produced by the various mating types. The number of matings and mean number of children per mating is given in table 8 for the various mating types. These values do not represent true relative fertilities, since each mating has produced at least one schizophrenic child. However, if we assume that within each mating type the risk for a child having schizophrenia is independent of the number of children in the family, then the parameter represented by the values in table 8 is $\mu + \sigma^2/\mu$, where μ and σ^2 are the mean and variance of the progeny distribution, respectively (see APPENDIX). The mean number of progeny in table 8 for SPD × SPD, SPD × N, and N × N matings are 3.57, 3.29, and 3.23, respectively. These results suggest that either SPD individuals have at least the same number of children as normals or, if not, then they are more variable with respect to their mean than normals. In fact, if fertility within marriage for SPD is the same as for normals, but the frequency of marriage reduced, the parameter $\mu + \sigma^2/\mu$ is expected to stay the same (see APPENDIX). Hence, the question of fertility differential related to SPD is difficult to assess from our data.

The question of assortative mating is also difficult to answer. If we combine all three diagnoses (S, SPD-D, SPD-P) into a single category called schizophrenia spectrum (SS), the observed mating-type distribution from table 7 becomes 31 N × N, 26 N × SS, and 18 SS × SS. The frequency in category SS × SS seems to be somewhat high. However, the expected values depend strongly on mode of inheritance. For example, if we let a = freq(N × N), b = freq(N × SS), and c = freq(SS × SS), the ratio $b^2/4ac$ can take on values greater than 1 (e.g., dominant inheritance), equal to 1 (e.g., recessive inheritance), or less than 1 (e.g., recessive with sporadic cases). Hence, the issue of assortative mating with regard to the schizophrenia spectrum requires more direct study.

TABLE 8

NO. OFFSPRING PRODUCED BY THE VARIOUS MATING TYPES

Mating type	N × N	N × SPD	SPD × SPD	N × S	SPD × S	S × S
No.	31	24	16	2	2	0
Mean no. children	3.23	3.29	3.57	1.50	1.50	...

Inferences with regard to mode of inheritance in this study were based on a sample of 79 nuclear families. We would therefore expect greater power to obtain either in a larger sample of nuclear families or in extended pedigrees.

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APPENDIX
FERTILITY IN MATINGS PRODUCING AN AFFECTED CHILD

Let N be a random variable representing the number of children produced (progeny distribution). Let $q_i = \text{Prob}(N = i)$, and let μ and σ^2 be the mean and variance of N, respectively. The probability that a child comes from a sibship of size s is $sq_s/\Sigma iq_i = sq_s/\mu$. The number of children in such a family is s. Therefore, the expected number of children in the family with at least one affected is $\Sigma s(sq_s/\mu) = (\Sigma s^2 q_s)/\mu = (\sigma^2 + \mu^2)/\mu = \mu + \sigma^2/\mu$.

Suppose fertility of affecteds is normal within marriage but marriage rate is reduced. Then the progeny distribution for affecteds (A) may be given by $r_0 = \text{Prob}(A = 0)$, $r_i = (1 - r_0)p_i/(1 - p_0)$, $i > 0$.

$$\mu_A = \Sigma i r_i = \Sigma\, i(1 - r_0)p_i/(1 - p_0) = (1 - r_0)\mu/(1 - p_0) .$$

$$\begin{aligned}\sigma_A^2 &= \Sigma i^2 r_i - \mu_A^2 = \Sigma i^2(1 - r_0)p_i/(1 - p_0) - \mu_A^2 \\ &= (1 - r_0)(\sigma^2 + \mu^2)/(1 - p_0) - (1 - r_0)^2\mu^2/(1 - p_0)^2 \\ &= (1 - r_0)\sigma^2/(1 - p_0) + (1 - r_0)(r_0 - p_0)\mu^2/(1 - p_0)^2 .\end{aligned}$$

Thus, $\mu_A + \sigma_A^2/\mu_A = (1 - r_0)\mu/(1 - p_0) + \sigma^2/\mu + (r_0 - p_0)\mu/(1 - p_0) = \mu + \sigma^2/\mu$.

REFERENCES

1. NEEL JV, FAJANS SS, CONN JW, DAVIDSON RT: Diabetes mellitus, in *Genetics and the Epidemiology of Chronic Diseases,* edited by NEEL JV, SHAW MW, SHULL WJ, Washington, D.C., Government Printing Office, 1965, pp 105–132
2. LIDZ T, BLATT S: Critique of the Danish-American studies of the biological and adoptive relatives of adoptees who became schizophrenic. *Am J Psychiatry* 140:426–435, 1983
3. LIDZ T, BLATT S, COOK B: Critique of the Danish-American studies of the adopted away offspring of schizophrenic parents. *Am J Psychiatry* 138:1063–1068, 1981
4. ABRAMS R, TAYLOR MA: The genetics of schizophrenia: a reassessment using modern criteria. *Am J Psychiatry* 140:171–175, 1983
5. SZASZ T: The myth of mental illness. *Am Psychol* 15:113–118, 1960
6. GOTTESMAN II, SHIELDS J: *Schizophrenia: The Epigenetic Puzzle.* Cambridge, Cambridge Univ. Press, 1982
7. ELSTON RC, NAMBOODIRI KK, SPENCE MA, RAINER JD: A genetic study of schizophrenia pedigrees. II. One-locus hypotheses. *Neuropsychobiology* 4:193–206, 1978
8. DEBRAY Q, CAILLARD V, STEWART J: Schizophrenia: a study of genetic models and some of their implications. *Neuropsychobiology* 4:257–269, 1978
9. CARTER CL, CHUNG CS: Segregation analysis of schizophrenia under a mixed genetic model. *Hum Hered* 30:350–356, 1980

10. TSUANG MT, BUCHER KD, FLEMING JA: Testing the monogenic theory of schizophrenia: an application of segregation analysis to blind family study data. *Br J Psychiatry* 140:595–599, 1982
11. ELSTON RC, KRINGLEN E, NAMBOODIRI KK: Possible linkage relationships between certain blood groups and schizophrenia or other psychoses. *Behav Genet* 3:101–106, 1973
12. TURNER WJ: Genetic markers for schizotaxia. *Biol Psychiatry* 14:177–206, 1979
13. MCGUFFIN P, FESTENSTEIN H, MURRAY R: A family study of HLA antigens and other genetic markers in schizophrenia. *Psychol Med* 13:31–43, 1983
14. BARON M, RISCH N, LEVITT M, GRUEN R: Genetic analysis of platelet monoamine oxidase activity in families of schizophrenic patients. *J Psychiat Res.* In press, 1984
15. RAO DC, MORTON NE, GOTTESMAN II, LEW R: Path analysis of qualitative data on pairs of relatives: application to schizophrenia. *Hum Hered* 31:325–333, 1981
16. MCGUE M, GOTTESMAN II, RAO DC: The transmission of schizophrenia under a multifactorial threshold model. *Am J Hum Genet* 35:1161–1178, 1983
17. ELSTON RC, CAMPBELL MA: Schizophrenia. Evidence for the major gene hypothesis. *Behav Genet* 1:3–10, 1970
18. KARLSSON JL: A two-locus hypothesis for inheritance of schizophrenia, in *Genetic Factors in Schizophrenia,* edited by KAPLAN AR, Springfield, Ill., Charles C. Thomas, 1976, pp 246–255
19. GOTTESMAN II, SHIELDS J: A polygenic theory of schizophrenia. *Proc Natl Acad Sci USA* 58:199–205, 1967
20. O'ROURKE DH, GOTTESMAN II, SUAREZ BK, RICE J, REICH T: Refutation of the general single-locus model for the etiology of schizophrenia. *Am J Hum Genet* 34:630–649, 1982
21. RISCH N: Estimating morbidity risks with variable age of onset: a comparison of methods and a maximum likelihood approach. *Biometrics* 39:929–939, 1983
22. RISCH N: Estimating morbidity risks in relatives: the effect of reduced fertility. *Behav Genet* 13:441–451, 1983
23. ESSEN-MÖLLER E: The calculation of morbid risk in parents of index cases, as applied to a family sample of schizophrenics. *Acta Genet Stat Med (Basel)* 5:334–342, 1955
24. KALLMANN FJ: The genetic theory of schizophrenia: an analysis of 691 schizophrenic twin index families. *Am J Psychiatry* 103:309–322, 1946
25. TSUANG MT, WINOKUR G, CROWE RR: Morbidity risks of schizophrenia and affective disorders among first degree realtives of patients with schizophrenia, mania, depression and surgical conditions. *Br J Psychiatry* 137:497–504, 1980
26. MORTON NE: Genetic tests under incomplete ascertainment. *Am J Hum Genet* 11:1–16, 1959
27. LI CC, MANTEL N: A simple method of estimating the segregation ratio under complete ascertainment. *Am J Hum Genet* 20:61–81, 1968
28. DAVIE AM: The 'singles' method for segregation analysis under incomplete ascertainment. *Ann Hum Genet* 42:507–512, 1979
29. MORTON NE: The detection of major genes under additive continuous variation. *Am J Hum Genet* 19:23–34, 1967
30. ELSTON RC, SOBEL E: Sampling considerations in the gathering and analysis of pedigree data. *Am J Hum Genet* 31:62–69, 1979
31. CANNINGS C, THOMPSON EA: Ascertainment in the sequential sampling of pedigrees. *Clin Genet* 12:208–212, 1977
32. ELSTON RC, STEWART J: A general model for the genetic analysis of pedigree data. *Hum Hered* 21:523–542, 1971
33. MORTON NE, MACLEAN CJ: Analysis of family resemblance. III. Complex segregation analysis of quantitative traits. *Am J Hum Genet* 26:489–503, 1974
34. LALOUEL JM, RAO DC, MORTON NE, ELSTON RC: A unified model for complex segregation analysis. *Am J Hum Genet* 35:816–826, 1983

35. MORTON NE, YEE S, LEW R: Complex segregation analysis. *Am J Hum Genet* 23:602–611, 1971
36. GO RCP, ELSTON RC, KAPLAN EB: Efficiency and robustness of pedigree segregation analysis. *Am J Hum Genet* 30:28–37, 1978
37. BARON M, ASNIS L, GRUEN R: The schedule for schizotypal personalities: a diagnostic interview for schizotypal features. *Psychiatry Res* 4:213–228, 1981
38. ENDICOTT J, SPITZER RL: A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry* 35:837–862, 1978
39. BARON M, GRUEN R: *The Schedule for Interviewing Borderlines (SIB)*. New York, New York State Psychiatric Institute, 1980
40. BARON M, GRUEN R, ASNIS L, KANE J: Familial relatedness of schizophrenia and schizotypal states. *Am J Psychiatry* 140:1437–1442, 1983
41. BARON M, GRUEN R, RAINER JD, KANE J, ASNIS L, LORD S: A family study of schizophrenic and normal control probands: implications for the spectrum concept of schizophrenia. Submitted for publication
42. SPITZER RL, ENDICOTT J, ROBINS E: Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry* 35:773–779, 1978
43. AMERICAN PSYCHIATRIC ASSOCIATION: *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. Washington, D.C., American Psychiatric Assoc., 1980
44. KENDLER KS, GRUENBERG AM, STRAUSS JS: An independent analysis of the Copenhagen sample of the Danish adoption study of schizophrenia. II: The relationship between schizotypal personality disorder and schizophrenia. *Arch Gen Psychiatry* 38:982–984, 1981
45. LALOUEL J-M, MORTON NE: Complex segregation analysis with pointers. *Hum Hered* 31:312–321, 1981
46. RISCH N: MIXQUAL: *A* FORTRAN *Program for Mixed Model Segregation Analysis of Qualitative Traits with Multiple Thresholds*. Unpublished program documentation, 1983
47. RISCH N: TPMQUAL: *A* FORTRAN *Program for Segregation Analysis of Polychotomous Phenotypes*. Unpublished program documentation, 1983
48. KAPLAN EB, ELSTON RC: *A Subroutine Package for Maximum Likelihood Estimation* (MAXLIK). Institute of Statistics Mimeo Series, No. 823, Univ. of North Carolina, Chapel Hill, 1972
49. BARON M, RISCH N: Segregation analysis of schizophrenia spectrum disorders. *Am J Hum Genet* 35:35A, 1983
50. HUXLEY J, MAYR E, OSMOND H, HOFFER A: Schizophrenia as a genetic morphism. *Nature* 204:220–221, 1964