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# Complex Segregation Analysis of Autism

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## Summary

**A complex segregation analysis of autism in 185 Utah families was carried out using the mixed model. The 209 affected individuals in these families represent nearly complete ascertainment of the autistic cases born in Utah between 1965 and 1984. The sibling recurrence risk for autism was 4.5% (95% confidence limits 2.8%–6.2%). Likelihoods were maximized for major-gene models, a polygenic model, a sibling-effect model, and a mixed model consisting of major-gene and shared-sibling effects. The analysis provided no evidence for major-locus inheritance of autism. Subdivision of the sample according to the probands' IQ levels showed that sibling recurrence risk did not vary consistently with IQ level. A segregation analysis of families in which the proband had an IQ <50 also failed to provide evidence for a major locus. However, because of the etiologic heterogeneity of this disorder, genetic analysis of other meaningful subsets of families could prove informative.**

## Introduction

Autism, a developmental disorder affecting approximately 1/2,500 individuals, is known to aggregate in families. Published estimates of sibling recurrence risks for autism vary between 2% and 6% (Smalley et al. 1988), and twin studies have consistently demonstrated higher concordance rates among MZ twins than among DZ twins (Folstein and Rutter 1977; Ritvo et al. 1985*a;* Wahlström et al. 1989). To test for the presence of a major gene for autism, Ritvo et al. (1985*b*) performed a segregation analysis of 43 nuclear families each containing two or more autistic children. Their statistical analysis could not reject an autosomal recessive model for the inheritance of autism. Their sample was ascertained in part by advertising for multiple-incidence families, leading Pauls (1987) to question the appropriateness of their ascertainment correction procedure and therefore to question the evidence for major-locus inheritance.

In the UCLA–University of Utah autism project, an attempt was made to ascertain all cases of autism born in the state of Utah between 1965 and 1984. This uniform collection of data helps to circumvent difficulties caused by selective ascertainment and thus produces a sample more appropriate for segregation analysis. Because Utah's population is relatively small (1.7 million individuals), well-defined, and genetically well characterized, it is highly appropriate for this type of survey. This population, 70% of whom are members of the Church of Jesus Christ of Latter-Day Saints (LDS or Mormon), is genetically representative of other American Caucasian populations (McLellan et al. 1984). Because of a large founding population and high immigration rates, Utah's average inbreeding coefficient is quite low ($10^{-4}$) and comparable in value to those of other North American populations (Jorde 1989, 1991).

Previous studies using the Utah autism data base have reported on data prevalence (Ritvo et al. 1989*a*), sibling recurrence risks (Ritvo et al. 1989*b*), familial aggregation at all levels of kinship (Jorde et al. 1990), associations between autism and perinatal factors (Mason-Brothers et al. 1990), and the etiologic role

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of rare diseases (Ritvo et al. 1990). In the present report, the results of a complex segregation analysis of autism in the Utah population are presented.

## Material and Methods

### *Data Collection*

Potential study subjects were ascertained through an exhaustive review of medical records and referrals at all clinics, agencies, and other facilities in which autistic individuals were treated (further details are given in Ritvo et al. 1989*a*). This initial screening identified 489 individuals who were thought to be possibly autistic. Each of these subjects was evaluated independently by at least two clinicians using DSM-III criteria (American Psychiatric Association 1980). A total of 241 subjects were ultimately diagnosed with autism. Extensive medical, psychological, and family history information was obtained for each of these individuals. IQ scores were obtained primarily from school or psychiatric records. Most subjects who were verbally competent were assessed using Stanford-Binet or appropriate Wechsler tests. The remainder were evaluated using a variety of nonverbal tests, including Leiter, Merrill-Palmer, Slosson, and Peabody Picture Vocabulary tests.

Subjects with known associated syndromes or nongenetic causes of autism (Ritvo et al. 1990) were excluded from the segregation analysis (table 1). In addition to these 27 exclusions, five cases were excluded because they had been adopted. When the excluded subject was the only affected individual in the family, the entire family was omitted from analysis. If there were additional affected individuals in the family who did not meet the exclusion criteria, only the excluded subject was omitted from analysis. A total of 209 affected subjects were thus available for segregation analysis.

### *Statistical Analysis*

The analysis sample consisted of 185 nuclear families. There were 166 sons and 43 daughters diagnosed as autistic, and there were 237 sons and 246 daughters who were unaffected. Initially, the analysis was done on a data set that included extended pedigrees for 97 families (information on second- and third-degree relatives). Since only one pair of second-degree relatives and one pair of third-degree relatives with autism were found, the analysis based on extended pedigrees gave results nearly identical to those of an analysis based only on nuclear families. Thus, the results presented here are confined to the analyses of nuclear families.

**Table 1**

**Cases Excluded from Segregation Analysis**

| Associated Disorder | No. of Cases |
|---|---|
| Chromosome 9 deletion | 1 |
| Congenital herpes | 3 |
| Congenital hypothyroidism | 2 |
| Congenital rubella | 3 |
| Cytomegalovirus infection | 1 |
| Down syndrome | 6 |
| Fragile-X syndrome | 2 |
| Hypopituitarism | 1 |
| Partial trisomy 8 | 1 |
| Rett syndrome | 4 |
| Sanfilippo syndrome | 2 |
| Tuberous sclerosis | 1 |
| Total | 27 |

Likelihood analysis was used to test for major-locus inheritance of autism. Likelihoods of the genetic models (Elston and Stewart 1971) were computed using PAP (Hasstedt 1989); maxima were obtained by using NPSOL (Gill et al. 1986). In an attempt to correct for ascertainment bias and also to account for the absence of adult autistics in the sample, the likelihood was divided by the probability of observing an affected offspring with unaffected parents. Since this correction assumes single ascertainment, its application to complete ascertainment represents an approximation. Significance was tested using $\chi^2$ statistics. Under certain conditions, the natural logarithm of the ratio of the likelihood of a submodel relative to the likelihood of a general model multiplied by $-2$ approximates a $\chi^2$ distribution. The number of df of the $\chi^2$ test is equal to the number of parameters restricted when the submodel is specified from the general model.

The genetic model, the mixed model (Elston and Stewart 1971; Morton and MacLean 1974), specifies a continuous liability to disease as the sum of independent effects attributed to segregation of alleles at a major locus, transmission by polygenic inheritance, sharing by siblings of environmental factors, and random factors specific to the individual. In this model, autism occurs when liability exceeds a threshold. It was assumed that two alleles are in Hardy-Weinberg equilibrium for the major locus and that the polygenic and sibling components follow a normal distribution. Likelihoods of the genetic model were computed by repeatedly specifying a genotype for all pedigree member, computing the likelihoods of the set of genotypes,

and then summing over the likelihoods of all possible sets of genotypes. For each set of genotypes, the multivariate normal integral was approximated (Mendell and Elston 1974; Rice et al. 1979).

The parameters specifying the major locus include the prevalence, $p$, the proportion of sporadic cases, $S$, and, among the remaining cases, the proportion of dominant cases, $D$. $D = 0$ specifies recessivity; $D = 1$ specifies dominance. Since one of the diagnostic criteria for autism is onset prior to 30 mo of age, it was not necessary to incorporate age-specific penetrance into the analysis. $p$ was fixed at values of .00064 in males and .00016 in females. In addition to sex-specific proportions of sporadic cases (i.e., $S_m$ and $S_f$) and dominant cases (i.e., $D_m$ and $D_f$), the parameters of the model included the frequency of the disease allele, $q$; the polygenic heritability, $h^2$; and the sibling effect, $e^2$. Parameters $h^2$ and $e^2$ represent proportions of the within-genotype variance that are attributable to polygenic inheritance and a sibling effect, respectively.

Polygenic heritability was also estimated using Falconer's (1965) method 3. This technique incorporates sex-specific sibling recurrence risks and population prevalence rates to produce four heritability estimates (male probands, female relatives; male probands, male relatives; female probands, male relatives; and female probands, female relatives). These are then weighted by the inverse of the sampling variance of each estimate to yield a single heritability value.

## Results

Among the 185 nuclear families analyzed, 166 contained a single affected individual. Of the 19 multiplex families, 16 contained two affected siblings, two contained three affected siblings, and one contained five affected siblings.

Results of the segregation analysis are summarized in table 2. The likelihood values show that all of the genetic models fit the data significantly better than does the sporadic model. The polygenic model with no sibling effect yields a heritability estimate of 1.00. This agrees quite closely with the heritability estimate obtained using the Falconer procedure ($h^2 = .94 \pm .05$). When the polygenic and sibling effect parameters were estimated simultaneously, values of .65 and 0 were obtained for $e^2$ and $h^2$, respectively. Accordingly, $h^2$ was fixed at 0 to evaluate the addition of a major-locus effect to the sibling-effect model (last three lines of table 2). For brevity, this model (sibling effect plus major locus) is referred to here as the "mixed model." The likelihood values of the mixed models are not significantly greater than that of the sibling-effect model.

The parameter estimates of the major locus and mixed models indicate a high proportion of sporadic cases and low penetrance, thereby explaining at most a few percent of the variance in liability. In addition, the sibling-effect model cannot be rejected ($\chi^2_{(5)} = 2.1$, $P > .05$; sibling-effect vs. codominant mixed model). Consequently, the analysis does not provide evidence of a major locus. When models without a major locus are considered, the sporadic ($\chi^2_{(2)} = 221.7$, $P < .001$) and the polygenic ($\chi^2_{(1)} = 12.8$, $P < .001$) models can both be rejected, while the sibling-effect model cannot ($\chi^2_{(1)} = 0$) (each of these models was compared with the polygenic-plus-sibling-effect model). Since the addition of major genes did not improve the fit vis-à-vis the multifactorial models, the parsimony criterion argues against a major-gene effect in the inheritance of autism.

Baird and August (1985) found that sibling recurrence risks were elevated when the autistic proband was severely retarded (IQ <50), suggesting that low IQ might delineate a subgroup of autistic subjects. In the present sample, the recurrence risk for siblings of probands with IQs <50 is 5.5%, while it is 3.9% for those with IQs ≥50. The 95% confidence limits for these two estimates overlap considerably (3.1%–9.4% and 2.2%–6.7%, respectively). In addition, table 3 shows that, when high-functioning autistic subjects (IQ >70) are separated from the remainder of the subjects, no clear association between IQ and recurrence risk is seen. In fact, the recurrence risk is *lowest* for siblings of subjects in the 50–70 IQ range.

A segregation analysis was performed on the subset of families in which the first-born autistic subject had an IQ <50. This sample consisted of 75 families with 87 autistics. As with the analysis of the complete sample, no evidence was found of segregation of an allele at a major locus in this subset. As expected, similar results were obtained when the analysis was performed on the subset defined by probands with IQs <70.

## Discussion

The prevalence of autism in Utah is approximately 1/2,500 births, and the male-female sex ratio is 4:1 (Ritvo et al. 1989*a*). These figures are very similar to those of other published studies (Zahner and Pauls

**Table 2**

**Results of Segregation Analysis**

| Model | $q$ | $S_f$ | $D_f$ | $S_m$ | $D_m$ | $h^2$ | $e^2$ | 2 ln Likelihood[a] |
|---|---|---|---|---|---|---|---|---|
| Sporadic | ... | (1) | ... | (1) | ... | (0) | (0) | .0 |
| Recessive | .01 | .63 | (0) | .74 | (0) | (0) | (0) | 196.0 |
| Dominant | .0001 | .57 | (1) | .69 | (1) | (0) | (0) | 197.4 |
| Codominant | .01 | .70 | .00 | .00 | .92 | (0) | (0) | 201.8 |
| Polygenic | ... | (1) | ... | (1) | ... | 1.00 | (0) | 208.9 |
| Sibling effect | ... | (1) | ... | (1) | ... | (0) | .65 | 221.7 |
| Polygenic + sibling effect | ... | (1) | ... | (1) | ... | .00 | .65 | 221.7 |
| Recessive mixed | .08 | .36 | (0) | 1.00 | (0) | (0) | .68 | 223.3 |
| Dominant mixed | .01 | 1.00 | (1) | 1.00 | (1) | (0) | .65 | 221.7 |
| Codominant mixed | .02 | .17 | 0.98 | 1.00 | ... | (0) | .68 | 223.8 |

[a] Obtained by subtracting the ln likelihood of the sporadic model from that of each model.

1987). The sibling recurrence risk of 4.5% (95% confidence limits 2.8%–6.2%) is also within the range of those in previously reported studies (Pauls 1987; Smalley et al. 1988; Ritvo et al. 1989*b*). A study of pre-, peri-, and postnatal factors associated with autism in the Utah sample showed that no factor is conspicuously associated with the disorder, although viral infections are seen more frequently among cases with no affected siblings (Mason-Brothers et al. 1990).

The results of the present study do not support major-locus inheritance of autism. This differs from the results of the one other segregation analysis that has been performed on families with autism (Ritvo et al. 1985*a*). The major difference between the two studies is that the present analysis included all cases of autism ascertained in a well-defined population. Also, the previous study employed only simple segregation analysis and, in a separate analysis, the polygenic-inheritance test formulated by Gladstien et al. (1978). In the present study, a mixed model was used.

The flatness of the likelihood surface complicated maximization of the likelihood of the mixed model. This difficulty is frequently experienced when the mixed model is applied to dichotomous traits (e.g., schizophrenia [Vogler et al. 1990] and leprosy [Wagener et al. 1988]). In spite of this problem, it is likely that, if a major gene were segregating in an appreciable proportion of the autistic families, its presence would have been detected in the present analysis.

**Table 3**

**Sibling Recurrence Risks Subdivided by Proband's IQ**

| IQ | No. of Affected Siblings | Total No. of Siblings | Recurrence Risk | 95% Confidence Limits |
|---|---|---|---|---|
| <50 | 13 | 238 | 5.5% | 3.1%–9.4% |
| 50–69 | 2 | 141 | 1.4% | .2%–5.6% |
| >70 | 11 | 196 | 5.6% | 3.0%–10.1% |

It was not possible to test systematically for the presence of fragile-X syndrome among these subjects. Since fragile-X syndrome is seen in a small percentage of autistic males (Brown et al. 1986; Payton et al. 1989; Cohen et al. 1991), it is probable that some subjects included in the segregation analysis had this disease. To the extent that it might have occurred among the multiplex families, it would have biased the results in favor of a major-gene model. Since no evidence for a major gene was uncovered, this effect must have been slight.

Although the sibling-effect model provided a better fit to the data than did the polygenic model, this result must be interpreted with caution. Since persons with autism seldom, if ever, reproduce, there is a strong bias against observing a parent-offspring correlation for the disorder. Even with the ascertainment correction scheme used here, this would tend to bias the data in favor of a sibling-effect model. Also, the sibling correlation of .65 would yield a heritability estimate of 1.3, which is incompatible with the polygenic model. In light of these considerations, it is likely that the familial clustering observed here and in other data sets is due to a combination of both polygenic and shared environmental effects.

In addition to the complex segregation analysis results, several other lines of evidence are consistent with the predictions of a multifactorial threshold model (Carter 1969, 1976):

1. This model predicts a rapid decline in recurrence risks among second- and third-degree relatives. A previous analysis assessed familial aggregation at all kinship levels by using autistic cases linked to the Utah Population Database (Jorde et al. 1990). The average kinship coefficient among all possible pairs of autistic subjects was 10 times higher than that of a sample of matched unaffected controls. However, excess familial clustering was seen only at the sibling level. This result is consistent with the present study's finding that, among 754 second-degree relatives of the autistic probands, only one was autistic (0.13%) and that of 2,105 third-degree relatives, only one (0.05%) was autistic.

2. Recurrence risks should increase in families with multiple affected offspring. Although based on a relatively small sample, there is evidence that sibling recurrence risks for autism increase after the birth of a second autistic child (Ritvo et al. 1989*b*).

3. The sex-specific sibling recurrence risks for autism are compatible with the prediction that relatives of the more frequently affected sex should have lower recurrence risks. The recurrence risk for siblings of male probands is 3.7% (95% confidence limits 2.3%–5.8%), while the recurrence risk for siblings of female probands is 7.0% (95% confidence limits 3.3%–12.9%). Although this difference in risks is not statistically significant, it is in the direction predicted by the multifactorial threshold model. It should be pointed out that these differences in sex-specific recurrence risks are also compatible with a single-gene model in which penetrance is higher among heterozygotes of the more commonly affected sex than it is in heterozygotes of the less commonly affected sex (Kidd and Spence 1976). The segregation analysis results derived from a codominant model argue against this interpretation, however.

A number of factors complicate genetic analyses of autism. As with many other behavioral disorders, the diagnosis is not straightforward (Coleman and Gillberg 1985). Since autistic adults seldom reproduce, the no-selection assumption implicit in segregation analysis is violated. Although the ascertainment correction used here was formulated in part to correct for this effect, it is unclear whether it does so fully. Perhaps most important, autism is undoubtedly a heterogeneous disorder (Ornitz 1978; Baird and August 1985; Smalley et al. 1988). If autism were due to several major genes, each with different penetrance values, a complex segregation analysis could easily produce results consistent with a multifactorial model. This situation is similar to a model proposed by Matthysse et al. (1979). Alternatively, a major gene could be segregating in such a small proportion of families that mixed-model segregation analysis, even with a relatively large data set, cannot detect it. Finally, a strong interaction between an environmental agent and a single susceptibility gene can produce the patterns of recurrence risks observed here (Khoury and Beaty 1987). Thus, while these results provide no evidence for a major gene for autism, they do not exclude the possibility that a major gene could be responsible for a minority of cases.

Clinical markers may hold the key to resolving the etiologic heterogeneity underlying autism. In addition to delineating subsets of this disorder, markers could potentially identify nonpenetrant gene carriers. For example, about one-third of autistic subjects have elevated whole-blood serotonin levels, and there is some evidence for elevated serotonin among first-degree relatives of autistics (Abramson et al. 1989). Serotonin abnormalities may account for the fact that a small subset of autistic individuals may respond to fenfluramine treatment, although the extent and reliability of this response remain controversial (Ritvo et al. 1986; Campbell 1988; Aman and Kern 1989). A subset of autistic subjects manifest abnormal electroretinograms (Ritvo et al. 1988; Creel et al. 1989), but the degree of familial aggregation of this trait is ambiguous (Realmuto et al. 1989). Also, a subset of autistic subjects exhibits significantly reduced members of certain classes of regulatory T lymphocytes (Warren et al. 1990).

Yet another possible subset consists of those autistic subjects with IQs <50. Although Baird and August (1985) provided some evidence in favor of this subgrouping, their sibling recurrence risk of 5.9% was based on three affected individuals among 51 siblings. The confidence limits about this estimate are large (1.5%–17.2%), making this result inconclusive. The figures reported in table 3 are based on a much larger sample and do not show a consistent relationship between IQ and recurrence risk. Furthermore, the segregation analysis failed to uncover evidence for a major-gene effect in the subset defined by probands with IQs <50.

One linkage analysis of autism, using a small series of genetic markers, has been carried out (Spence et al. 1985). It produced no evidence for linkage. This is not surprising, in light of the results of the present study and the strong evidence for causal heterogeneity in this

disorder. Until genetically meaningful subsets of the syndrome of autism are defined, linkage analyses would be unlikely to prove successful. Clearly, future efforts should be directed toward both better definition of the heterogeneity underlying autism and genetic analysis of the resulting subsets.

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