Gene Mapping Studies with the Syndrome of Autism

M. Anne Spence, Edward R. Ritvo, Mary L. Marazita, Steve J. Funderburk, Robert S. Sparkes, and B. J. Freeman

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The UCLA Registry for Genetic Studies of Autism had collected data on 308 families by February 1, 1983. A subsample of 46 families with at least two affected children was analyzed for evidence of a Mendelian mode of inheritance. The data were consistent with an autosomal recessive mode of inheritance (Ritvo, E. R., Spence, M. A., Freeman, B. J., Mason-Brothers, A., Mo. A., and Marazita, M. L., 1985, American Journal of Psychiatry, in press). Thirty-four of these families were subjected to gene linkage analyses with 30 standard phenotypic gene markers. There is no evidence of linkage between the purported autism locus and HLA, either from analysis of HLA haplotype sharing or from lod scores. In addition, close linkage with autism, i.e., ≤5% recombination, could be excluded for 19 of the other autosomal genetic markers. The largest positive lod score, 1.04, was with haptoglobin (HP), at recombination frequencies of 10% in males and 50% in females. Normal C- and Q-banded chromosome polymorphisms were evaluated for association with autism and as additional linkage markers.

KEY WORDS: autism syndrome; family studies; gene linkage

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1 Departments of Psychiatry and Biomathematics, Mental Retardation Research Center, UCLA School of Medicine, University of California, Los Angeles, California, 90024.
2 Department of Psychiatry, Division of Mental Retardation and Child Psychiatry. UCLA School of Medicine, University of California, Los Angeles, California 90024.
3 Departments of Medicine, Pediatrics, and Psychiatry. Division of Medical Genetics, UCLA School of Medicine, University of California, Los Angeles, California 90024.
4 To whom correspondence should be addressed.
INTRODUCTION
Numerous authors have suggested a genetic etiology for autism, given that the recurrence risk for sibs is many times that of the population at large (Spence, 1976; Hanson and Gottesman, 1976). Twin studies have been undertaken in an attempt to find evidence of a genetic contribution. Folstein and Rutter (1977) reported 11 pairs of monozygotic (MZ) twins with a concordance rate of 36% and 10 dizygotic (DZ) twins with a concordance rate of 0%. However, their diagnostic criteria differed from those applied in our study. Also, the twin pairs reported in the literature do not conform to the expected proportions (based on normal twin pairs) of MZ to DZ twin pairs or same-sex to unlike-sex DZ pairs (Hanson and Gottesman, 1976). The reported data are consistent with a genetic contribution to the etiology of autism but certainly not with the predictions of a simple autosomal or X-linked recessive model. Genetic analyses more rigorous than twin studies have not been reported for childhood autism.

Our study design was based on the assumption that autism is an etiologically heterogeneous syndrome, thus implying that (1) no single genetic hypothesis would be expected to explain all cases of autism and (2) the chances of finding a genetic subgroup would be enhanced by analyzing families with at least two affected siblings. Segregation analysis of a sample of 46 families selected for having at least two children affected with autism could not reject an autosomal recessive hypothesis. Details of the segregation analyses are described in full by Ritvo et al. (1985).

Given this suggestive evidence for a genetic form of the disorder, a genetic linkage study was undertaken in an attempt to map and thereby confirm a gene responsible for familial autism. We expect less linkage information from families when the phenotype of interest is inherited in a recessive fashion. However, in this sample the majority of families had at least two children affected, somewhat reducing the ambiguity of assigning genotypes and increasing the available linkage information.

MATERIALS AND METHODS
The UCLA Registry for Genetic Studies of Autism has been collecting data on families with autistic children since 1980. The data include pedigree information, a 500-item developmental questionnaire, and prenatal, delivery, pediatric, diagnostic, treatment, and education records for each autistic child and any other family member reported to have a developmental, neurological, or psychiatric illness. Details of the Registry's enrollment and data items have been described (Ritvo et al., 1982, 1985).

From a total of 308 families, 46 families were completely evaluated, were confirmed to have two or more affected children (i.e., multiplex).