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The UCLA–University of Utah Epidemiologic Survey of Autism: Genealogical Analysis of Familial Aggregation

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To assess familial aggregation of autism, 86 autistic subjects were linked to the Utah Genealogical Database. Kinship coefficients were estimated for all possible pairs of autistic subjects and then averaged. Fifty replicate sets of matched control subjects (86 members in each set) were drawn randomly from the database, and the average kinship coefficient was computed for all possible pairs of individuals in each set. The average kinship coefficient for the autistic subjects was approximately 1/1,000, while the average kinship coefficients for the 50 control groups ranged from 4/100,000 to 1.6./10,000. These results indicate a strong tendency for autism to cluster in families. When kinship was analyzed by specific degrees of relationship, it was shown that the familial aggregation of autism is confined exclusively to sib pairs and does not extend to more remote degrees of relationship. This finding indicates that a single-gene model is unlikely to account for most cases of autism.

KEY WORDS: kinship coefficient, sib recurrence

INTRODUCTION

Autism is a relatively rare childhood neurological disorder, with a prevalence of roughly 2–5 in 10,000 [Zahner and Pauls, 1987; Ritvo et al., 1989a]. A large number of possible causal factors, both environmental and genetic, have been suggested [Ritvo and Freeman, 1984]. In spite of a considerable amount of research, the etiology of this disorder remains largely unknown.

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Autism tends to cluster in families; published sib recurrence risks range from 2 to 6% [Smalley et al., 1988]. Twin studies have shown that monozygotic twins have substantially higher concordance rates than do dizygotic twins [Folstein and Rutter, 1977; Ritvo et al., 1985a; Wahlström et al., 1989]. Although the sib recurrence risks for autism would suggest a "multifactorial" inheritance pattern, autosomal recessive inheritance has been suggested [Coleman and Rimland, 1976], and segregation analysis has provided limited evidence for autosomal recessive inheritance of a subtype of autism [Ritvo et al., 1985b]. Spence et al. [1985] found no evidence of linkage between autism and a small series of genetic markers. Most previously published studies of the genetics of autism have been criticized because of small sample sizes and ascertainment biases [Folstein and Rutter, 1988; Pauls, 1987; Smalley et al., 1988].

In order to help overcome these criticisms, a collaborative study of autism was initiated at UCLA and the University of Utah. The goal of this study was complete ascertainment of all autistic individuals born in Utah from 1965 to 1984. Utah's population is ideally suited to this type of investigation, since it is relatively small (1.6 million individuals), geographically stable, and highly cooperative with medical researchers. In addition, a large portion of the population has kept extensive genealogical records for religious purposes. Utah's population is genetically homogeneous and has experienced relatively little genetic drift since its founding in the mid-nineteenth century [Jorde, 1982; McLellan et al., 1984]. The average inbreeding coefficient is about 10^{-4}, which is similar to that of other populations in the United States [Jorde, 1989].

Intensive review of medical records and referrals, followed by a personal evaluation of each subject using DSM-III criteria, produced 241 individuals diagnosed as autistic [Ritvo et al., 1989a]. This yielded a prevalence figure of 4 in 10,000, with a 4 : 1 male-female sex ratio. These figures are in close agreement with other published data [Zahner and Pauls, 1987]. The sib recurrence risk, measured as the incidence of autism among all sibs of the first-born autistic subject in each sibship, was

4.5% (95% confidence limits = 2.8%, 6.2%) [Ritvo et al., 1989b]. Among sibs born *after* the first-born autistic subject, 8.6% were affected (95% confidence limits = 5.8%, 12.2%).

To study familial aggregation of autism at all levels of kinship, the ascertained cases of autism have been linked to the Utah Genealogical Database. The results of this analysis are reported here.

MATERIALS AND METHODS

Autistic subjects were identified and diagnosed using previously described protocols [Ritvo et al., 1989a]. The Utah Genealogical Database consists of 1.2 million individuals linked into large pedigrees [Skolnick, 1980]. The autistic subjects were linked with the genealogical database by matching on first and last name and birth date. Of 241 subjects, 86 were found in the database. The lack of completeness in matching reflects two factors: First, nearly all individuals in the genealogical database are members of the Church of Jesus Christ of Latter-day Saints (LDS, or Mormon), while only 68% of the autistic subjects were members of the LDS Church. Second, the database is not complete in more recent years, so many of the subjects born in the late 1970s and early 1980s were not found in the database. In the case-control approach described below, it is unlikely that incomplete matching will induce significant biases.

To assess familial aggregation, kinship coefficients were estimated between all possible pairs of the 86 linked autistic subjects ("cases"). The kinship coefficient is defined as the probability that two individuals "have the same allele at a randomly chosen" locus due to descent from a common ancestor [Malécot, 1969]. The kinship coefficients among all possible pairs of cases were averaged in order to yield an index of familial aggregation of autism. This index was then compared with a similarly estimated index for a series of matched replicate control subjects drawn from the genealogical database. Control cohorts were defined by matching controls with autistics on the basis of gender and birth year. Fifty replicate sets (86 controls each) were drawn randomly from these cohorts. Use of replicate control sets provided a collection of 50 average kinship coefficients for unaffected controls. These coefficients thus constitute a distribution of kinship coefficients that can be used for an empirical test of the "significance" of the difference in kinship coefficients between cases and the control sets (conventional statistical tests, such as t tests, are inappropriate because of the lack of independence among pairs). This approach has been used previously in studies of the familial aggregation of cancer [Cannon et al., 1982; Hill 1980], coronary disease [Williams et al., 1979], and neural tube defects [Jorde et al., 1983].

RESULTS

The average kinship coefficient among all pairs of autistic cases was 0.000967, or about 1/1,000. The average kinship coefficients of the 50 control sets ranged from 0.000004 to 0.000157, with an overall average of 0.000046 (approximately 1/22,000). Thus the autism cases are substantially more closely related than are the unaffected controls. Figure 1 displays the distribution of average kinship coefficients for the 50 control sets and the autism cases. This figure shows that the average kinship coefficient for the autism cases lies well outside the distribution of the control sets. If the distribution of control sets is treated as an empirical distribution, the kinship coefficient for the cases could be considered statistically significant at the 0.02 level.

Figure 2 provides a breakdown of the number of related pairs at each level of kinship. The coefficient of kinship is given in the X axis. A coefficient of 0.5^2 represents sib pairs, 0.5^3 represents pairs at the uncle-niece or double first-cousin level, and so on. The figure shows the actual number of related pairs among the autism cases versus the number of related pairs *averaged* over the 50 control sets. There were 14 sib pairs among the cases, while the controls averaged only about 0.5 sib pairs per set. At most of the more remote levels of kinship, there were slightly more related pairs among the controls than among the cases. Thus the observed familial aggregation of autism is due entirely to clustering among sib pairs.

DISCUSSION

This analysis shows that, while there is a substantial degree of familial aggregation of autism, it is confined to sib pairs. Aggregation at this level of kinship can reflect shared genes as well as shared environment, and this statistical approach cannot distinguish between the two. The rapid decline in the incidence of autism among more distant relatives implies that relatives other than sibs do not have a substantial risk of developing the disorder. This pattern is consistent with "multifactorial" causation, as is the sib risk of 4.5%. In addition, the recurrence risk for sibs of affected females is twice as high as that of sibs of affected males [Ritvo et al., 1989b]. A higher recurrence risk for the less commonly affected sex is consistent with a multifactorial model in which there are sex-specific thresholds [Carter, 1976].

As noted above, some previous studies have suggested an autosomal recessive mode of inheritance for at least some cases of autism [Coleman and Rimland, 1976; Ritvo et al., 1985b]. The lack of first-cousin pairs of autistics observed in this study provides a convenient test of the autosomal recessive model. If, for the sake of illustration, we suppose that an autosomal recessive gene were responsible for *all* cases of autism in this population, the gene frequency would be approximately 1/50 (using the observed incidence of 1/2,500). Then, it is straightforward to show that the expected frequency of affected first cousins is p/4, where p is the gene frequency for the recessive disorder [Crow, 1965]. Thus 1/200 first cousins should be affected. The average completed family size in Utah has recently ranged between three and four births [Heaton, 1986], so each autistic subject in this study would have about 15–20 first cousins. The 86 subjects that linked into the genealogical database would then have between 1,000 and 1,500 first cousins. Even allowing for incompleteness of data, the autosomal recessive hypothesis would predict at least several first-cousin pairs based on these figures. Therefore, unless gene penetrance is very low, it seems

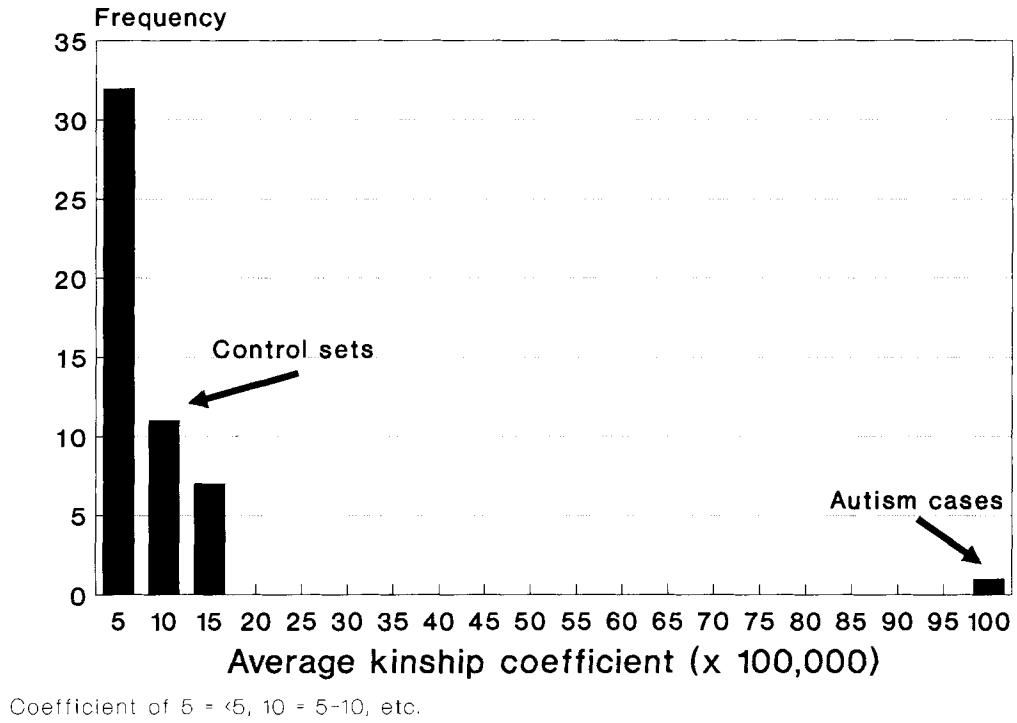

Fig. 1. Average kinship coefficient (×100,000) among the 86 autistic subjects, compared with the distribution of average kinship coefficients in 50 replicate sets of matched controls (86 individuals each).

unlikely that autosomal recessive inheritance could account for a large proportion of cases of autism.

Autism is clearly a heterogeneous disorder [Ornitz, 1978]. Some autistic subjects (mostly males) have the fragile X syndrome [Payton et al., 1989; Brown et al., 1986]. A few cases respond favorably to fenfluramine treatment [Ritvo et al., 1986], and others have abnormal electroretinograms [Ritvo et al., 1988]. Autism is also sometimes associated with rubella infection, untreated PKU, Rett syndrome, and a variety of other conditions

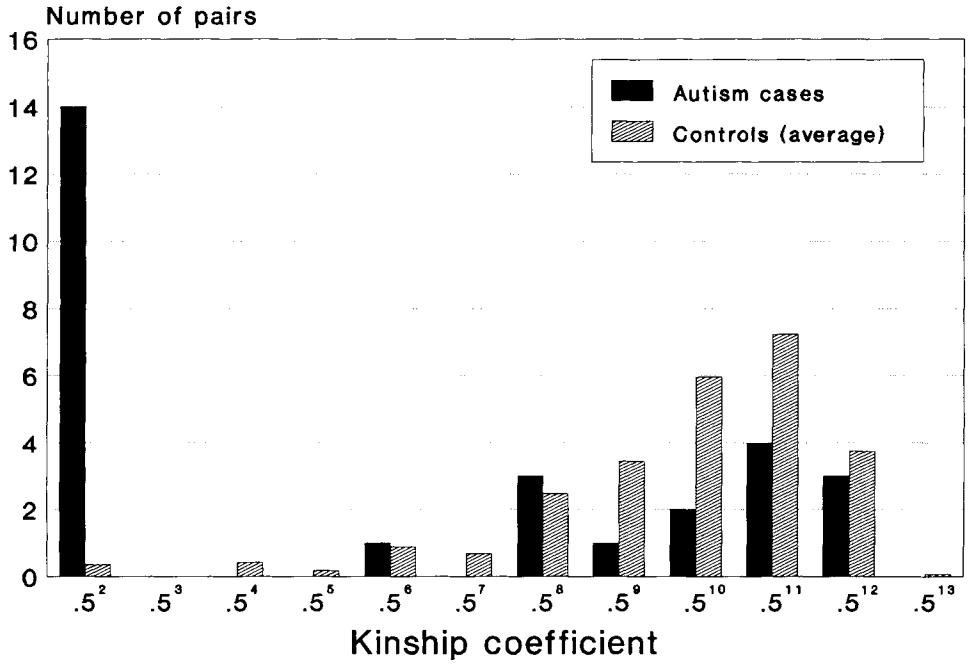

Fig. 2. Number of related pairs among autistic and control subjects, grouped by kinship coefficients. The number of related pairs for controls represents an *average* taken over the 50 replicate sets.

[Coleman and Gillberg, 1985]. Considering this diversity of associations, it is not surprising that an analysis of an unsorted set of subjects would produce results most compatible with a multifactorial etiology. Recently, there has been some success in uncovering major genes for subtypes of multifactorial disorders. Examples include coronary disease [Brown and Goldstein, 1986], bipolar affective disorder [Egeland et al., 1987], schizophrenia [Sherrington et al., 1988], and cleft lip/palate [Moore et al., 1987]. With further research, a major-gene subtype of autism may yet be discovered.

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