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Invited Editorial: The Genetics of Alzheimer Disease—A Teasing Problem

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Controversy has been the hallmark of studies of virtually all diseases having a complex genetic etiology. This has been particularly true for neuropsychiatric disorders such as bipolar affective disorder (Reich et al. 1969; Gershon et al. 1979; Mendlewicz et al. 1979; Detera-Wadleigh et al. 1987; Egland et al. 1987; Hodgkinson et al. 1987), schizophrenia (Kennedy et al. 1988; Sherrington et al. 1988), and Alzheimer disease (AD). For AD, arguments over interpretation of linkage analysis results and even over the extent of genetic involvement have been both heated and protracted. However, two papers published in this issue of the *Journal* (Farrer et al. 1991; Pericak-Vance et al. 1991), along with recent data published elsewhere (Goate et al. 1991; Schellenberg et al. 1991), help to resolve these controversies and may serve as a paradigm for studies in other diseases of complex etiology.

AD is a neurodegenerative disorder manifesting late in life, with loss of memory, declining cognitive function, and, ultimately, decreasing physical function as well. It affects >4 million individuals in the United States and, given its long and arduous clinical course, is a major public health problem. Studies of AD have been complicated by a number of factors, including clinical, diagnostic, and genetic variability (Heyman et al. 1983; Chui et al. 1985; Mayeux et al. 1985; Schoenberg et al. 1987; Friedland et al. 1988; St George-Hyslop et al. 1989). The evidence for clinical heterogeneity is not surprising when one considers that a definitive diagnosis of AD requires pathological confirmation on autopsy (McKhann et al. 1984; Joachim et al. 1988). Thus clinical diagnosis is more difficult and is usually one of exclusion, whereby other causes of the observed dementia are eliminated. Although standard clinical criteria have been outlined (McKhann et al. 1984), they still lead to an inaccurate diagnosis in ~10% of cases (Joachim et al. 1988).

Evidence for genetic factors in AD has arisen from a number of different studies. Examinations of first-degree relatives (Appel 1981; Breitner and Folstein 1984; Mohs et al. 1987; Breitner et al. 1988; Huff et al. 1988; Farrer et al. 1989; St George-Hyslop et al. 1989) have generally agreed that such individuals have an increased risk of AD. However, there is wide disagreement on the extent of that risk, ranging from 5% (Appel 1981) to nearly 100% (given that the relative lives long enough) (Breitner et al. 1988). These studies have been complicated by the difficulties of measuring the variable and generally late age at onset in AD. Recent studies have attempted to resolve this particular problem by using life-table analyses on large data sets (Mohs et al. 1987; Huff et al. 1988; Farrer et al. 1989, 1990), including extensions to allow information from individuals without defined ascertainment ages (Farrer et al. 1990). The evidence from twin studies has been inconsistent in showing increased (but not 100%) concordance in MZ compared with DZ twins (Jarvik et al. 1980; Cook et al. 1981; Embry and Lippman 1985; Nee et al. 1987; St George-Hyslop et al. 1989). However, again the observed variability in age at onset makes interpretation difficult. Only now are larger long-term and/or follow-up studies designed to compensate for these problems being undertaken. The discrepancies in these risk and concordance studies have usually been explained as being due to difficulties and differences in methodology. An alternative suggestion proposes that underlying clinical and genetic heterogeneity may, in fact, be teasing us by causing a portion of the observed variability.

The extensive variability in AD is both an interesting and frustrating problem for the human geneticist but presents an excellent proving ground for an expanding set of statistical and molecular tools aimed at

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delineating genetic effects. Two papers in this issue of the *Journal* (Farrer et al. 1991; Pericak-Vance et al. 1991) use differing approaches to study AD. Farrer et al. (1991) employed complex segregation analysis to clearly define the mode(s) of inheritance of AD, while Pericak-Vance et al. (1991) have used molecular probes to test for genetic linkage of specific markers to AD genes. As described below, the results in both cases provide evidence for multiple genetic etiologies in AD and should help to resolve the ongoing arguments.

It is, perhaps, surprising that formal segregation analysis has not previously been attempted in AD. However, only recently have standard and rigorous clinical criteria been defined (McKhann et al. 1984). These criteria have allowed Farrer et al. (1991) to examine a set of 232 ascertainment-defined nuclear kindreds to more accurately delineate an overall genetic model for AD. Two aspects of their results are particularly interesting. The first provides good evidence for a major gene effect. Although Farrer et al. (1991) were able to reject autosomal recessive inheritance, they were not able to distinguish between a codominant and dominant model for the major gene (the latter provided a slightly better fit to the data). This is concordant with the suggested autosomal dominant pattern of inheritance found for several large families previously reported in the literature (Nee et al. 1983; Amaducci et al. 1986; Bird et al. 1988). It is interesting that the heterozygote transmission probability of the major gene effect was >.50, raising the possibility that two or more major genes (possibly with differing modes of inheritance) may exist. The second interesting aspect of their study provides evidence for a probable polygenic background. This suggests that other genes, possibly through pleiotropic effects, also affect the expression of AD.

If at least one major gene underlies AD, then it (they) should be detectable by using linkage analysis, given appropriate family material. In 1987, St George-Hyslop et al. (1987) tested markers on chromosome 21, because of the association between Down syndrome and the classical neuropathology of AD (Heston and Mastri 1977). They reported significant positive linkage results with markers on the proximal long arm of this acrocentric chromosome. At nearly the same time, the gene for the precursor protein of the amyloid (i.e., APP) deposited in the brains of AD patients was cloned and localized to the same region of chromosome 21 (Tanzi et al. 1987*a*). These results produced an initial flame of excitement that was later doused when several recombinants between APP and AD were observed (Tanzi et al. 1987*b*; Van Broeckhoven et al. 1987). Confirmation of the linkage results has been difficult, with both positive (Goate et al. 1989) and negative reports (Schellenberg et al. 1988) having been published, the latter including one from Pericak-Vance et al. (1988). The inability to provide unquestionable support for linkage engendered protracted debates on whether the positive results were spurious or whether the negative results were an indication of genetic heterogeneity. Recently, Goate et al. (1991) reexamined the possibility that APP is a causative gene, in light of the possibility of genetic heterogeneity. They found in the APP gene a mutation that cosegregated with AD in two early-onset families, one of which (family 372) is also reported in the Pericak-Vance et al. (1991) paper in this issue of the *Journal*. Many other early- and late-onset families did not exhibit this mutation. Thus, although the generality of the chromosome 21 finding has not yet been established, there is a high probability that one or more mutations in the APP gene explain a subset of inherited AD.

Pericak-Vance et al. have now extended their study by examining 32 AD families and including genetic markers on other chromosomes. Their results provide evidence of linkage between markers on the proximal long arm of chromosome 19 and AD while, in general, excluding chromosome 21 as a possible AD gene site. Given both the known difficulties in measuring age at onset and the uncertainty surrounding the possible mode(s) of inheritance in AD, Pericak-Vance et al. chose to examine their data by using a new strategy. They used the affected-pedigree-member (APM) method of analysis (Weeks and Lange 1988), which uses information only on affected individuals and makes no assumption about the modes of inheritance. By allowing the use of affected relatives regardless of their relationship, it is not restricted to particular pedigree structures, as is the affected-sib-pair methodology. For comparison purposes, they performed two alternative analyses: a standard full maximum likelihood analysis, including age-at-onset information, and a maximum likelihood analysis including disease status for only the affected individuals. The APM analysis found significant linkage to loci residing in the same region of chromosome 19, while the full maximum likelihood analysis failed to provide significant evidence of linkage to any chromosomal region. Maximum likelihood analysis only of affected individuals demonstrated significant linkage only to the chromosome 19 loci. These disparate results may be explained if the age-at-onset curve used in the full maximum likelihood analysis

was inaccurate. Alternatively, the effect may arise if a susceptibility rather than a primary causative gene resides on chromosome 19.

It is possible to reconcile the chromosome 19 linkage results with the previously reported chromosome 21 linkage when one realizes that those families showing linkage to markers on chromosome 21 have been, by and large, ones with an earlier age at onset (roughly defined as ≤65 years). Those families showing linkage to chromosome 19 markers in the Pericak-Vance et al. data, on the other hand, had generally late age at onset (≥65 years). When Pericak-Vance et al. used the APM methodology and explicitly divided their families into early- and late-onset subgroups, the early-onset subgroup gave evidence of linkage only to chromosome 21 loci. The late-onset subgroup gave evidence of linkage to both chromosomes. This is concordant with two recent collaborative studies (St George-Hyslop et al. 1990; Schellenberg et al. 1991) which found that only families with a mean age at onset ≤65 years showed any evidence of linkage to chromosome 21 loci. These studies further suggested that only a subset of familial AD may be linked to chromosome 21 markers.

Additional evidence for a division of early- versus late-onset families was found by Farrer et al. (1990), who examined age-at-onset data in families and found statistical evidence for an early- and a late-onset subgroup. The early-onset group exhibited the expected cumulative risk curve of an age-dependent, autosomal dominant disorder (i.e., total cumulative risk ~50%). The late-onset group had a cumulative risk curve that continued to increase past the 50% risk level, suggesting non-Mendelian inheritance and/or the inclusion of sporadic (nongenetic) cases. Pericak-Vance et al.'s (1991) finding of positive APM results for both chromosomes 21 and 19 in the late-onset families may be a further indication that more than one locus jointly influences the development of AD.

How can we best define the current state of our understanding of the genetics of AD? It is clear that age at onset, segregation, and linkage data now suggest a dichotomy between an early- and a late-onset form of AD. Early-onset AD may be explained as an autosomal dominant trait with at least one age-dependent but highly penetrant locus. This locus resides on chromosome 21 and is quite possibly explained by mutations in the APP gene. Another locus, if it exists, remains to be identified. The situation for late-onset AD is not as clear. Linkage results suggest that loci on both chromosomes 21 and 19 are involved. The modes of inheritance of these loci are unclear, and expression may involve some level of gene-gene interaction. Additional effects of polygenes and/or environmental factors cannot be ruled out and are, in fact, supported by the results of the complex segregation analysis.

What additional research would help to further our understanding of the genetics of AD? What is obviously needed is an independent confirmation of the results of Farrer et al. A larger sampling, including more distant relatives beyond the nuclear family, will provide more power for discrimination between the genetic models not yet excluded. In addition, ascertainment of such families will provide new material for genetic linkage studies. Results of the segregation studies will provide guidelines for how many genes one may expect to find via linkage analysis. The linkage results need to be confirmed as well. Given the increasing prospects for rapidly and efficiently screening the entire genome for linkage, it may be possible to identify other—although we dare not believe all—of the major and polygenic genes involved in AD. The prospects for teasing out and identifying these genetic components are many, and the approaches used should outline a strategy for the understanding of other complex etiologic traits.

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