ALZHEIMER'S DISEASE

Dominant susceptibility genes

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ALZHEIMER's disease is widely recognized as the most common form of dementia in older people, at least in most Western societies. Its prevalence (as determined by a set of clinical diagnostic guidelines, including important exclusionary criteria) increases exponentially as a function of age: a recent survey[1] in East Boston determined that nearly half of those over 85 years old showed signs of the disease. Neuropathologists (upon whom we must rely for a definitive diagnosis) have yet to document any qualitative differences between the several characteristic microscopic effects of the disease and the occasional lesions observed in association with normal ageing. The varying ages for the onset of Alzheimer's disease may simply reflect differing propensities for a common manifestation of ageing in the central nervous system (especially in the hippocampus) — analogous, for example, to the everyday observation that some people seem more susceptible to greying and thinning of the hair than others. If so, what are the precise nature–nurture interactions that underlie such differential susceptibilities?

Linkage assignment

Given the great importance of this question, there is much to admire in the huge collaborative research effort of Peter St George-Hyslop, John Hardy and colleagues, reported on page 194 of this issue[2], who provide evidence in support of a previously reported[3] linkage assignment to the long arm of chromosome 21 for early-onset pedigrees exhibiting autosomal dominant patterns of inheritance of probable Alzheimer's (mean age of onset ≤65 years). For the case of late-onset families, however, such a linkage is excluded, as in a previous report[4]. A statistical test comparing early with late-onset families supports the hypothesis of genetic heterogeneity. Other work indicates that there may be genetic heterogeneity even among early-onset Alzheimer's kindreds. Linkage analysis of a subset of families for which there is evidence of a genetic founder effect (Volga German familial Alzheimer's kindreds in which age of onset is approximately 57 years) gives consistently negative results using markers for the same region of chromosome 21 (ref. 5).

How certain can we be of the assignment in early-onset families to chromosome 21? The sceptical observer of the natural history of linkage research for neuropsychiatric disorders will note that there appear to be three contrasting ways that two-point lod scores evolve as additional data accumulate. ('Lod', the log of the odds, is the primary parametric statistical method for the determination of the strength of linkage, a score of 3.0 being the conventional threshold for the acceptance of linkage and a score of −2.0 being the conventional threshold for the rejection of linkage between a polymorphic test marker and the disease locus of interest.) On the one hand, we have the example of linkage of a marker on the short arm of chromosome 4 to Huntington's disease. The lod score for the original US pedigree[6] was 4.53 at a recombination frequency of 0.0. When these studies were extended to encompass 63 families (mostly Caucasians, but including a few black American and Japanese families), the combined maximum lod score[7] was 87.69 at a recombination frequency of 0.04. Another example is the linkage of a marker on the long arm of chromosome 19 to myotonic dystrophy, where lod scores have been rapidly increasing, with a recent report of 22.8 at a recombination frequency of 0.03 for the case of 65 families[8]. By contrast, there is the example of bipolar affective disorder in the Amish kindred, in which the original positive score of 4.08 disappeared after the pedigree was updated and extended, the last recorded score[9] for the 11p marker having become −9.31.

The new report on Alzheimer's disease[2] indicates something in between those above extremes — an original score of 2.37 for the first set of four families[3] now rising to 4.50 for the extended set of 30 early-onset families (linkage to the DNA haplotype D21S1/D21S11). A multipoint linkage analysis, however, in which the candidate Alzheimer's gene is 'passed' across an interval between two markers of known fixed positions, may lend further support to the hypothesis of a susceptibility gene on chromosome 21.

St George-Hyslop *et al.* also report on the use of a non-parametric method for evaluating the potential for linkage. As noted by the authors of this method[10], however, the method can confound linkage and association. The large number of missing data in the Alzheimer's pedigrees coupled with their ethnic heterogeneity increases the possibility of linkage disequilibrium between the Alzheimer's locus and some of the chromosome 21 markers in the sample. Therefore, the results need not indicate a *bona fide* genetic linkage. The method cannot be regarded as a confirmation of linkage, which would require the analysis of an independent, unselected set of early-onset pedigrees. But a perfectly reasonable proposition is that alleles at a locus on chromosome 21 may indeed contribute to susceptibility to Alzheimer's in at least some early-onset families.

What tentative conclusions can now be made regarding the genetic substrate for the clinically more significant and much more difficult[11] problem of late-onset Alzheimer's? The latest report[2] tells us only that there is no evidence for a comparable susceptibility gene in chromosome 21. It leaves open any number of possibilities, including the interaction of multiple minor genetic effects with multiple environmental factors. Recent research (ref. 12; M.A. Pericak-Vance *et al.*, submitted to *Am. J. hum. Genet.*) using the same set of parametric and non-parametric methods as St George-Hyslop *et al.* provide "highly suggestive" evidence for a linkage assignment to the proximal long arm of chromosome 19.

Linkage analysis

What of the future? Can the now tried-and-true approach of identifying additional more closely linked markers followed by chromosome walking and cloning be used to identify the first familial Alzheimer's gene? The spectacular successes with cystic fibrosis[13] and neurofibromatosis[14] were based on narrowing the possible loci to a genetic distance equivalent to 1–2 million base pairs using linkage analysis. If early-onset familial Alzheimer's is genetically heterogeneous, linkage analysis may give only a regional localization, perhaps as large as 20–30 million base pairs. If this is so, new approaches for identifying all the genes in a large region and screening those candidate genes for Alzheimer's mutations will have to be developed.

It will also be vital to pursue independent approaches, particularly efforts to document a phenotype in cultivated non-neuronal somatic cells. We should recall that this strategy led to the breakthrough (and a Nobel prize for Joe Goldstein and Michael Brown) on the pathogenesis of atherosclerosis, another common, late-onset disorder, the complex pathogenesis of which may serve as a model for Alzheimer's research[15]. There are some hints that this might be feasible[16]. □

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