

Alzheimer's Disease and Possible Gene Interaction

We recently described (1) an extended pedigree in which a Val→Ile missense mutation at codon 717 of the amyloid β protein precursor gene (APP) on chromosome 21q apparently co-segregated with early onset familial Alzheimer's disease (AD). In affected members of this family, AD follows a relatively stereotyped progression with onset at 47.6 ± 3.0 years and death at 58.8 ± 4.0 years. During prospective follow-up studies of this kindred, we identified a person who carries the APP717 mutation yet who, at the age of 1 standard deviation (SD) above the mean age of onset in this pedigree, showed no sign of clinical disease on neurologic or neuropsychologic tests or on computerized axial tomography or magnetic resonance imaging scans. Furthermore, this person has continued to remain asymptomatic at 2 SDs beyond the mean age of onset in this pedigree. Other, younger relatives of this person who also carry the APP717 mutation, however, are clinically affected.

E. H. Corder *et al.* (2) recently observed that inheritance of the $\epsilon 4$ allele of the apolipoprotein E (APOE) gene appeared to influence the risk (or the age of onset, or both) of late onset AD in a "dose dependent" fashion. This finding prompted us to investigate the APOE genotypes of the person under study and of other clinically affected relatives. All ($n = 3$) living clinically affected family members with the APP717 mutation had $\epsilon 3/\epsilon 4$ genotypes at the APOE gene, while the older, asymptomatic carrier of the APP717 mutation lacked the $\epsilon 4$ allele at APOE (genotype $\epsilon 2/\epsilon 3$). Schmechel *et al.* (3) found a relationship between the presence of the $\epsilon 4$ allele and the density of plaques containing APP in tissue from people affected by AD who also carry wild-type APP genes.

These observations suggest that genotypes at the APOE and APP genes may interact (possibly with still other genetic and nongenetic factors) to determine the final pathologic phenotype of AD. The

respective gene products may act functionally within the same pathogenetic pathway leading to AD. A close functional interaction would be in keeping with the appearance of APOE in extracellular amyloid deposits in AD (5). In contrast, we have observed no relationship between the APOE genotype and age of onset or other clinical features in affected members of a large familial AD (FAD) pedigree (FAD3) linked to chromosome 14 (6). This implies a more remote relationship between the effects of APOE and the as yet unidentified chromosome 14 FAD susceptibility gene in the pathogenesis of AD.

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5. P. St George-Hyslop *et al.*, *Nature Genetics* **2**, 330 (1992); G. D. Schellenberg *et al.*, *Science* **258**, 668 (1992); D. Pollen, *Hannah's Heirs: The Quest*

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Response: This is an interesting hypothesis about the only known person with the APP717 Val→Ile mutation who is alive at more than 2 SDs above the mean age of onset. Of course, more data are needed, but the comment is consistent with our observations (1) about the role of APOE- $\epsilon 4$ in familial and sporadic late onset Alzheimer's disease.

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