Alzheimer's disease and the family effect

Sir—Van Duijn *et al.*[1] reported in the May 1994 issue of *Nature Genetics* that both the number of ε4 alleles in the apolipoprotein E (apoE) genotype and a family history of a first-degree relative with memory problems influence risk of early-onset Alzheimer disease (EOAD), in a population-based sample. However, their data do not demonstrate that family history modifies the apoE genotype effect. Such modification, statistical interaction, would mean that the effect of family history is not the same for all genotypes. When logistic regression is used to formally test for a statistically significant interaction in their data, interaction can be rejected ($p = 0.65$, or $p = 0.38$ if the small number of ε4ε4 individuals are excluded). There are highly significant additive effects of both family history ($p = 0.0001$) and number of apoE ε4 alleles ($p = 0.0001$). Given recent evidence that the ε2 allele modifies AD risk, pooling the genotypes by number of ε4 alleles is contraindicated and could mask some types of interaction[2]. Whether these two factors act additively or interact in the prediction of AD, has important implications on the patho-physiologic mechanisms at work. We have presented evidence that family history and apoE genotype interact in the prediction of AD in a primarily late-onset (LOAD), population-based sample[3]. The contradictory results in EOAD and LOAD are consistent with an aetiologic difference between these two groups.

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IN REPLY—Jarvik and Wijsman argue that our data do not show evidence for modification, by family history, (FH) of the effect of the Apolipoprotein ε4 (APOE*4) genotype on the risk of EOAD[1]. Absence of such an effect contrast with their observation in late-onset Alzheimer's disease (LOAD) and may underlie aetiological differences between EOAD and LOAD.

Their argument is based on the results of the statistical tests for interaction which are indeed non-significant. However, lack of statistical significance should be interpreted with caution because of the limited statistical power[4–6]. Given our finding of a 1.6 fold increase in risk of EOAD associated with the APOE*4 genotype in those with a positive FH as compared to those with a negative FH, a population of more than 1,000 patients and controls is needed to reject the hypothesis of no interaction with a probability of 95%.

To increase the statistical power, we have reanalysed our data adding 373 age-matched control subjects derived from another Rotterdam population-based study[7]. This analysis did not change any of our initial conclusions[1]. For the APOE*4 heterozygotes with a positive FH, a significant increase in EOAD risk was found, but not in those with a negative FH (OR 1.3; 95% confidence interval 0.7–2.3). The risk of EOAD for the APOE*4 homozygotes was always significantly increased. The effect of the APOE*4 allele and FH was non-additive ($p=0.03$), confirming effect modification. Also, in both homozygotes and heterozygotes the risk for those with a positive FH was 1.6 times increased compared to those with a negative FH.

Our new data indicate that there is no evidence for differences between EOAD and LOAD with respect to FH modifying the APOE genotype effect.

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