Case-control study of presenelin-1 intronic polymorphism

There is no doubt that candidate gene association studies can play a useful part in detecting genetic variations contributing to complex diseases such as Alzheimer’s disease.\(^1\) Yasuda et al present a paper in this issue (pp 772-6) in which they use this approach to test for an association between the 1-1 genotype of an intronic polymorphism in the presenilin 1 (PS-1) gene and Alzheimer’s disease, originally reported by Wragg et al.\(^2\) Although Yasuda et al did not replicate this effect in their sample of 217 patients and matched controls, they did find a significant excess of the 1-1 genotype in a meta-analysis of published studies.

Several reasons could account for the lack of consistency in these findings. Firstly, as highlighted by Yasuda et al, ethnic variation between studies may have influenced the results. There seemed to be differences between Japanese and white controls and also between Japanese and African-American controls. As the intronic polymorphism is unlikely itself to be of functional relevance, it is probable the putative association with Alzheimer’s disease reflects linkage disequilibrium with a disease susceptibility locus. This may result in different associations in different populations dependent on the extent to which they have maintained linkage disequilibrium.

Secondly, the samples of cases and controls could have been the subject of stratification effects,\(^3\) such that cases may have differed from controls in characteristics other than affection status (for example, ethnic origin). This could have resulted in the possibility of false positives or false negatives, although, the similarity in allele frequency within specific population samples argues against this explanation.

Finally, the issue of statistical power could have played a part in the ability of studies to detect association. The effect size of the first association between the intronic polymorphism of the PS-1 gene and Alzheimer’s disease seems extremely small (odds ratio =1.16). If this is a true reflection of the effect size then it is likely that most of the individual studies included in the meta-analysis would have been too small to have replicated the association. This is an obvious problem with studying genes of small effect, but one that can be overcome by collecting very large, well characterised samples from defined populations. It is also noteworthy that genes of small genetic effect can provide valuable knowledge concerning the disease process. It may consequently be important to explore fully the contribution of all genes, by performing both individual and meta-analytical studies such as those undertaken by Yasuda et al.

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