Consistency in gene-Alzheimer’s disease association studies

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RESULTS

Figure 1 displays the evolution of the cumulative odds ratio for each gene. Only myeloperoxidase polymorphism had an initial odds ratio close to 1, and suffered small changes when adding later studies. The LRP-exon 3 gene had the highest initial odds ratio (2.41); when adding further studies the cumulative odds ratio progressively decreased down to 1.35. Similar changes may be seen for cathepsine D gene (its odds ratio changes from 2.40 to 1.26) and NOS-3 (its odds ratio falls from 1.72 to 1.07).

DISCUSSION

Our results, similar to those reported by Ioannidis et al., suggest that the first study dealing with a gene-AD relation tends to overestimate this association. A possible explanation would be publication bias, leading to a delay in publication of studies with ORs closer to the null.

One of the main causes for publication bias is that papers with negative results (that is, no association) would have a higher probability of being rejected regardless of their scientific quality, while papers with novel positive results would be seen as more attractive and would be more likely to be published. While genetic epidemiology develops, a progressively higher number of genetic markers would be tested for gene-disease association, and more papers on this subject would compete for the limited space in scientific journals; the editors would, therefore, have to make a choice and, probably, papers with positive results hold the advantage. However, the probability of type I error rises as the proportion of studies with positive results increases.

Once a strong association has been described, studies with negative results would be published because they contradict the first report. Then, if the first paper was attributable to a type I error, the next results would tend towards the null hypothesis (that is, OR = 1).

Our gene selection is partial; therefore, we do not intend to establish our results as a kind of gold standard in the gene-disease association, but as a called for scepticism facing the very first results on any genetic marker.

This layout is a challenge for researchers, referees, editors and, we believe, especially for readers. When a genetic marker is suggested as a putative cause for a disease, readers should have in mind the need for consistency in causation epidemiology. Consistency refers to the reliability of the results in different populations and under different circumstances, and is one of the causality criteria proposed by Hill and generally admitted. Before a gene-disease association is to be recognised as true, it is necessary to independently replicate investigations and, if needed, to combine their results in meta-analyses.

ADDENDUM

After sending the last version of our paper, a meta-analysis on association between cathepsin D and AD has appeared. It substantially coincides with our results and also remarks the dissipation of the postulated effect.

Abbreviations: AD, Alzheimer’s disease; LDP, lipid related protein.
Figure 1  Odds ratios and 95% confidence intervals for the individual studies (left column) and the cumulative meta-analyses (right column).

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