Correspondence

Susceptibility to Herpes Simplex Labialis Conferred by the Gene Encoding Apolipoprotein E

To the Editor—In a recent issue of the *Journal*, Hobbs et al. [1] describe their identification of a region on the long arm of human chromosome 21 that is associated with susceptibility to herpes simplex labialis (HSL). This location is of special interest to those who, like us, work on Alzheimer disease, because it includes the gene encoding the amyloid precursor protein and several other genes that might play a role in the etiology of Alzheimer disease. Hobbs et al. [1] mention a few earlier studies that sought human HLA types associated with HSL susceptibility but point out that such studies suffered from use of serological assays that could not distinguish between infection with herpes simplex virus type 1 (HSV-1) and infection with HSV-2. They refer also to recent work suggesting that apolipoprotein E alleles might affect expression of HSV-1 disease but state that this association has not yet been confirmed in human populations.

In fact, in 1997 and 1998, we published data on HSL that showed that APOE-ε4 is a strong risk factor for this disorder [2, 3]. This followed our discovery that HSV-1 DNA is present in the brain of a large proportion of elderly humans and that the virus in the brain of carriers of APOE-ε4 confers a strong risk of Alzheimer disease [2, 3]. Our finding that APOE-ε4 confers a risk for HSL, known to be caused by HSV-1, strongly if indirectly supported our conjecture that the combination of HSV-1 and APOE-ε4 is harmful in both the central and peripheral nervous system. In fact, our subsequent studies on certain diseases of known infectious cause showed that APOE influences the susceptibility to infection or the severity of infection outcome in several diverse cases [4–7]. In addition, peptides derived from the apoE protein have anti-infective properties, including anti–HSV-1 activity [8]. The probable mechanisms involved support our suggestion [2, 3] that apoE, which has binding sites in common with those of each microbe in the above studies [4–7], might compete with and thus prevent attachment of HSV-1; this would affect the entry of HSV-1 into cells and, hence, the extent of damage it causes, the competition effect being isoform dependent.

We initially investigated 40 persons with HSL and 33 persons without HSL [2], but the study group was later augmented to 69 persons with HSV-1, 60 of whom had had clinical diagnoses of HSL and/or had responded to acyclovir, and 77 persons without HSV who reported that they had never had a cold sore [3] (85 persons without HSV were enrolled in the study by Hobbs et al. [1]). The prevalences of APOE-ε4 among persons with and persons without HSV were 29.7% and 8.4%, respectively, a difference that was significant (odds ratio, 4.58; 95% confidence interval, 2.3–9.0; *P* < .001). All participants were volunteers who responded to advertisements posted on The University of Manchester campus (Manchester, United Kingdom). All participants were white (an important point, because the prevalence of APOE can vary greatly among different ethnic groups), and the mean age was 40 years for the HSL group and 38 years for the non-HSL group. Of persons with HSL, 41 (59%) had a first-degree relative with HSL, consistent with the hypothesis that a genetic factor affects the outcome of HSV-1 infection. Serological investigation for detection of HSV was performed for 27 persons with HSL and 27 persons without HSL, and all but 2 (both of whom did not have HSL) were seropositive. As for the type of HSV, because several studies showed that, at least until very recently, HSV has very rarely been caused by HSV-2 [9, 10], it is very unlikely that any of our cases were due to HSV-2. The percentage of individuals with ≥2 recurrences per year—the same criterion as that used by Hobbs et al. [1]—was 56% in the HSL group (28% had ≥1 recurrence per year, and the remaining persons did not provide sufficient information about this characteristic), and the frequency of APOE-ε4 was 34%. No significant difference was found between males and females with respect to allele frequency.

In a preliminary study of a cohort of several hundred children (The Avon Longitudinal Study of Parents and Children; R. Wynn-Jones and R. F. Itzhaki, unpublished data), we also found that the first episode of HSL occurs at a younger age in children with APOE-ε4 than in those with the other alleles (and also that APOE-ε2 may be protective), suggesting that susceptibility to as well as outcome of HSV-1 infection might be determined by APOE.

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References


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Reply to Itzhaki and Wozniak

To the Editor—Itzhaki and Wozniak [1] raise several important issues regarding our recent report of a herpes simplex labialis (HSL) susceptibility region on the long arm of human chromosome 21 [2]. The first issue is the suggestion that the HSL candidate region overlaps or contains several known genes with a possible etiologic role in Alzheimer disease. Multiple studies in many populations have identified genes on chromosome 21 that are associated with the Alzheimer disease, as summarized in figure 1. The HSL candidate region on 21q21.1 appears to exclude the nearest Alzheimer disease candidate gene (PRSS7) by virtue of the recombination event at marker D21S364 [2]. However, it is possible that sequences in the HSL candidate region may influence the expression of genes associated with a risk of Alzheimer disease. Alternatively, genes associated with a susceptibility to HSL may increase the risk of HSV-1 reactivation and the inflammatory responses in the brain that may ultimately lead to Alzheimer disease in some people [4].

We appreciate Itzhaki and Wozniak re-minding us of their data that showed an association between the apolipoprotein E-e4 allele and Alzheimer disease risk and

Figure 1. Map of human chromosome 21, showing the herpes simplex labialis (HSL) susceptibility region and genes associated with development of Alzheimer disease (AD). Candidate genes on chromosome 21 with a possible role in AD were taken from the AlzGene database of the Alzheimer Research Forum (available at: http://www.alzforum.org/res/com/gen/alzgene/) [3]. The solid bar to the left of the chromosome indicates the implied AD linkage region, whereas genes that have been associated with AD are listed on the right. The box over the diagram of 21q21.1 indicates the HSL susceptibility region, as defined by recombination events at markers D21S1234 and D21S364.