No Association Between a Presenilin 1 Polymorphism and Alzheimer Disease

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Background: Homozygosity of allele 1 of a presenilin 1 intron 8 polymorphism (PS1-1) has been associated with doubling of the risk of sporadic late-onset Alzheimer disease (LOAD), in some, but not all studies.

Objective: To genotype the PS1 intron 8 polymorphism in predominantly Hispanic families with LOAD to test for association and for linkage between this polymorphism and LOAD.

Design: A family-based, case-control, genetic-linkage study.

Setting: Predominantly Hispanic families were selected from probands who were part of a random sample of 2128 Medicare beneficiaries aged 65 years or older who were residing in the community of Washington Heights, which is located in the northern part of Manhattan, NY.

Participants: Fifty-one families with 103 affected family members, 67 unaffected family members, and 7 family members with other diagnoses were genotyped for the PS1 polymorphism. All patients met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria for either probable or possible Alzheimer disease. Age was truncated at 55 years or older.

Main Outcome Measures: Association analyses, conditional logistic regression, and traditional linkage methods were applied to the families for the PS1 polymorphism and for the presence of the gene for apolipoprotein E (APOE). Results of the association and conditional logistic regression analyses of PS1 intron 8 polymorphism were subsequently adjusted for the effect of APOE-e4, sex, age, and education of each sibling.

Results: No association between the PS1 intron 8 polymorphism and LOAD was observed (relative risk, 0.99; 95% confidence interval, 0.3-3.4). An association between presence of the APOE-e4 allele and LOAD (relative risk, 4.05; 95% confidence interval, 1.3-12.5) was observed.

Conclusion: We could not confirm the relationship between the PS1 intron 8 polymorphism and LOAD in this collection of families.

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The only known susceptibility gene for late-onset Alzheimer disease (LOAD) is the gene for apolipoprotein E (APOE). The e4 allele is associated in a dose-dependent way with decreased age at disease onset. This finding has been well replicated worldwide, but still only explains 45% to 55% of Alzheimer disease (AD) risk.¹

More than 45 known mutations in the gene for presenilin 1 (PS1) have been observed.² These mutations account for a significant proportion of early-onset autosomal dominant AD. However, overall PS1-related early-onset AD accounts for fewer than 1% of all cases of AD.

Wragg et al³ suggested that PS1 may also be a susceptibility gene for LOAD. Among US whites (n = 493, P = .006), but not African Americans (n = 52, P > .05), examination of an A-to-C single nucleotide polymorphism located in intron 8 revealed evidence of disequilibrium between the more common allele (PS1-1, in which A is present at nucleotide 16 in the intron [A represents the nucleotide adenosine]) and LOAD. These results were confirmed in case-control studies carried out in Japan (n = 292, P < .05)⁴ and the United Kingdom (n = 201, P = .006 [for 1/1 genotype only]).⁵ Several other studies in similar ethnic and racial populations, including a recent autopsy series from the United States (n = 103, P > .05)⁶ and a family study from the United States (n = 574, P > .05), did not confirm the association.⁷

The affiliations of the authors appear in the acknowledgment section at the end of the article.
PARTICIPANTS AND METHODS

SAMPLE

A sample of predominantly Hispanic families was derived from probands identified in a random sample of 2128 Medicare beneficiaries aged 65 years or older who were residing in the community of Washington Heights, which is located in the northern part of Manhattan, NY. Family members were evaluated, and all affected individuals met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association for probable or possible AD.7 The age cutoff for LOAD was set at age 55 years. The ethnic group of the participants was classified by self-report as previously described.8

The sample consisted of 51 families: 44 were Hispanic and 7 were white. The majority of the study participants were sib pairs (82.3%). Fifty-eight percent of the family members were affected; 38% were unaffected, and 4% were considered either too young to be given a diagnosis (age <40 years) or were given other diagnoses, such as stroke or Parkinson disease. Among the Hispanic families, 3 pedigrees had complex structures other than sib pairs (eg, parent-child pairs, cousins, and half siblings); 26 families had at least 2 affected siblings; 9 families had 1 affected sibling (these provided information for ALL-SIBPAIR analysis); and 6 families had 1 parent-child pair and at least 2 affected siblings. The white families consisted of 7 sibships, 4 with at least 2 affected siblings and 3 with 1 affected sibling.

Genotypes were obtained on 170 family members for PS1 and on 193 family members for APOE. The difference in numbers was because the DNA of 9 sib pairs (6 with 1 affected sibling and 3 with 2 affected siblings) was insufficient for inclusion of both the PS1 intron 8 polymorphism and APOE. The association analyses were performed using 138 family members with at least 1 sibling for PS1 intron 8 polymorphism and 156 family members with at least 1 sibling for APOE.

AMPLIFICATION AND GENOTYPING OF PS1 AND APOE

Genotyping of APOE was performed as previously described.10 The PS1 intron 8 polymorphism was genotyped as described,3 except the reverse primer was fluorescently labeled and the polymerase chain reaction product was detected with a DNA sequencer (model 377; PE Biosystems, Foster City, Calif). Allele 1 was composed of 199 base pairs, and allele 2 was cleaved by BamHI into fragments of 181 and 18 base pairs. Genotypes were quantitated using commercially available software packages (GENESCAN and GENOTYPER; PE Biosystems).

STATISTICAL ANALYSIS

Allele and genotype frequencies were generated for family cases and controls, and differences were examined using a χ² test of association. This method, however, does not control for family-specific effects and must be supplemented by additional methods when family-based data are being used. We therefore used conditional logistic regression to estimate the Mantel-Haenzel odds ratio for the effect of APOE and the PS1 intron 8 polymorphism on AD risk. The outcome was disease status of sibling, conditioning on family using an n-to-m matching paradigm, or treating family as random. Like the Mantel-Haenzel odds ratio, this model is a standard method for analysis of data from matched sets and can control for clustering of genotypes within families of arbitrary size. These analyses were performed using commercially available software (PHREG and GLMMIX procedures; SAS Institute Inc, Cary, NC).11

Genotype data on all LOAD families was also analyzed using a commercially available program package (Analyze).3 Linkage analysis was performed assuming an autosomal dominant model, a gene frequency of 0.00001, and phenocopy rate of 0.05. The same package included nonparametric analyses (SIBPAIR, ALL-SIBPAIR, and Transmission Disequilibrium Test), which were used with a P value of less than .05 considered as significant. Linkage analysis was performed for 60 families for APOE and for 51 families for PS1-1. There were 48 and 51 affected sib pairs for PS1-1 and APOE, respectively, available for affected sib pair analysis with the SIBPAIR program.

RESULTS OF ASSOCIATION ANALYSES

Allele and genotype frequencies for the PS1 intron 8 polymorphism were generated for the total group and separated by cases and family controls (Table 2). No significant differences in allele or genotype frequencies were seen between cases and family controls (Table 2). Allele frequencies were also analyzed for each proband, each affected sibling, and each oldest unaffected sibling (Table 3). A higher frequency of both the allele 1 for PS1 and the e4 allele for APOE were seen in both the probands and the affected siblings compared with the unaffected oldest siblings (Table 3). No increased risk was associated with the 1/1 genotype as compared with the 1/2 and 2/2 genotypes (relative risk [RR] 0.99; 95% confidence interval [CI], 0.3-3.4), even after age, education, sex, family size, and presence of the APOE-e4 allele (RR, 1.14;
A relationship between LOAD and the PS1 intron 8 polymorphism was hypothesized based on the several known mutations in PS1 seen in early-onset AD, and on the observation of a genetic association between the polymorphism and LOAD.4 Conflicting evidence for the association between PS1-1 and LOAD has been produced in several case-control studies and in one family-based study.4,6 We examined the relationship between this polymorphism and LOAD in our Hispanic family-based sample. We did not find evidence for linkage, and we did not detect an association between the PS1 intron 8 polymorphism and LOAD. In contrast, we did confirm the association between LOAD and possession of the APOE-e4 allele. Results were similar whether the small number of white families were present or absent from the analysis.

Because of the possibility of population stratification confounding case-control analysis in the initial studies, we decided to look at the relationship between this polymorphism and LOAD in our Hispanic family-based sample. Family studies may be useful in this regard when the results of several initial case-control studies are contradictory. However, it is possible that the power of our study was insufficient to detect a relationship between LOAD and PS1. It is also important to consider that Caribbean Hispanics come from a mix of white and African American racial backgrounds. As a result, because of population admixture in Caribbean Hispanics, our findings may even be consistent with those of the study by Wragg et al,3 who observed no association between LOAD and PS1-1 in their small group of African Americans. This polymorphism is intronic, and it has been suggested that its mode of action could be through modulation of alternate splicing.2 Because it is near exon 8, an area where most mutations leading to early-onset AD reside, it has been suggested that the polymorphism is in linkage disequilibrium with a more relevant polymorphism in the PS1 gene.3 Linkage disequilibrium would help explain the ethnic variability observed by other investigators. However, despite the initial positive results in the United Kingdom and Japan, the majority of the data point away from an association between this polymorphism and LOAD.

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