

Protection against Alzheimer's Disease with APOE Christchurch Variant — How?

John Hardy, M.D., Ph.D.

Protective variants of genetic loci are of particular interest for two reasons: first, because they are important from a clinical genetic perspective; and second, because they may give mechanistic clues about potential therapeutic strategies. In Alzheimer's disease, the most prevalent protective allele is *APOE2* (encoding apolipoprotein E2), which has a population allele frequency of approximately 10%.¹ With regard to the age at onset, sporadic Alzheimer's disease is delayed by approximately 10 years in persons with *APOE2* homozygosity as compared with the general population.²⁻⁴ *APOE2* heterozygosity delays the onset of sporadic Alzheimer's disease by approximately 5 years (relative to *APOE3* homozygosity) and has similar effects in delaying the onset of Alzheimer's disease in persons with Down's syndrome and in those with mutations in the genes encoding amyloid precursor protein (*APP*) and presenilin 1 (*PSEN1*) that cause familial Alzheimer's disease.^{2,3}

The Colombian family that is the subject of the article by Quiroz et al.⁵ in this issue of the *Journal* is a remarkable kindred whose data have been collected by the group from the University of Antioquia; the family now has more than 1000 members carrying the E280A mutation in *PSEN1*. In this family, the mean age at the onset of Alzheimer's disease is approximately 45 years,⁶ and the age at onset is influenced by the *APOE* genotype, with *APOE4* carriers having an age at onset that is approximately 5 years earlier and *APOE2* carriers seeming to have an onset that is later by approximately 5 years.³ Exome sequencing in an unaffected person older than 70 years of age in this kindred who had the *PSEN1* mutation and was homozygous for *APOE3* enabled the identification of a rare, but previously described variant, *APOE* Christchurch (R136S; *APOE3*^{Ch}). On the basis of this information, the *APOE3*^{Ch} variant was postulated to be protective against the pathogenesis of Alzheimer's disease in the presence of disease-causing presenilin variants.⁷ In the current study by Quiroz et al., this suggestion is confirmed and extended, with the identification of 27 persons with the presenilin muta-

tion who were heterozygous for the *APOE3*^{Ch} variant, in whom the age at onset was approximately 5 years later than in their relatives who were homozygous for the *APOE3* wild-type sequence. Neuropathological examination of 4 of these persons has suggested, surprisingly, that they had more amyloid deposition but less tangle deposition than corresponding persons in the kindred without *APOE3* mutations.⁸

Understanding the mechanism of the protection of *APOE3*^{Ch} could point to therapeutic targets. It is intriguing that both *APOE3*^{Ch} homozygosity and *APOE2* homozygosity are also associated with type III hyperlipoproteinemia (Online Mendelian Inheritance in Man database number, 617347). This observation suggests that both protective *APOE* variants have disrupted interactions with *APOE* receptors in a similar manner, which, in itself, may offer a mechanistic clue for both conditions.

Genetic variation at the *APOE* locus is, by far, the most important determinant of risk of Alzheimer's disease discovered so far. Despite this, we have relatively little understanding of its pathogenic role beyond the fact that genetic variation is closely associated with amyloid deposition.² The effects of the protective *APOE3*^{Ch} variant and the many other rare variants that are associated with increased and decreased risks of both Alzheimer's disease and blood lipid disorders^{9,10} perhaps offer starting points for cell biologic and transgenic work designed to dissect these mechanisms. Both the current work and previous work⁷ certainly suggest that understanding the precise dynamics of the interactions among *APOE* variants and their many receptors, in both the central and peripheral nervous systems, may yield important clues. In this regard, the recent report that genetic variation in the low-density lipoprotein receptor-related protein 1B (*LRP1B*) locus may also influence the age at onset of Alzheimer's disease in the Colombian kindred may be relevant.¹¹ Clearly, the time is ripe for a focused and detailed study of the pathogenic involvement of *APOE* in Alzheimer's disease. The

dissection of the biochemical characteristics of the various APOE alleles will undoubtedly play a crucial part in such an investigation.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the U.K. Dementia Research Institute and the Department of Neurodegenerative Diseases, Institute of Neurology, University College London, London.

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