

# Do the Longevity Genes Prevent Dementia?

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**T**he identification of genetic risk factors for the familial dementias has been a productive area of scientific study, but the clinical impact for the far more common sporadic dementias has been modest at best. As a result, interest in the characterization of biomedical and psychosocial protective factors is intense as evidenced by the April 2010 National Institutes of Health (NIH) consensus conference on Preventing Alzheimer's Disease and Cognitive Decline. If genetic polymorphisms associated with exceptional longevity are associated with lessened incidence of dementia, their characterization may suggest novel pharmacologic interventions to prevent Alzheimer's disease.

## INTRODUCTION

The most common heritable dementias, familial Alzheimer's disease and Huntington's disease, exhibit an early age of onset and have a well described genetic profile. Genetic testing can inform family members of their risk status with near certainty. However, the search for genetic risk in the more common later-onset sporadic Alzheimer's disease has had little clinical impact. Moreover, pharmacologic strategies to counter cholinergic deficits, cerebral amyloidosis, and neurofibrillary tangles—the major neuropathologic manifestations of Alzheimer's dementia—have yet to show genuine disease-modifying effects. Failure to find a breakthrough in treatment has led to intense interest in prevention as evidenced by the April 26–28, 2010 NIH consensus conference on “Preventing Alzheimer's Disease and Cognitive Decline”.<sup>1</sup> Risk factors for vascular disease are often cited as risk factors for Alzheimer's disease such that a heart-healthy diet and life-

style are advocated by the Alzheimer's Association as reasonable steps to reduce one's chances of developing dementia.<sup>2</sup> In addition, studies of exceptional longevity suggest that polymorphisms involved in lipid transport may also provide protection against Alzheimer's disease.

## LONGEVITY GENES AND HEART DISEASE

Apolipoprotein (APOE) and cholesterol ester transfer protein (CETP) are both involved in central nervous system cholesterol homeostasis. The APOE ε4 allele is associated with late onset sporadic Alzheimer's disease while the APOE ε2 allele is associated with increased life span as well as reduced risk of heart disease. A functional single-nucleotide polymorphism (SNP) substitution of valine for isoleucine at codon 405 in the CETP gene has been associated with reduced CETP serum activity and an increase in high-density lipoprotein, both of which are thought to convey protection against heart disease.

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Additionally, like the APOE  $\epsilon$ 2 allele, the valine CETP SNP is associated with exceptional longevity. Thus, APOE  $\epsilon$ 2 and CETP V405 may be called “longevity genes”,<sup>3</sup> but the mechanism with which they provide benefits is unclear.

## LONGEVITY GENES AND DEMENTIA

In addition to conferring benefits for increased life span, evidence suggests that they also protect against cognitive decline and dementia. Most recently, investigators with the Einstein Aging Study<sup>4</sup> examined the genotypes of 523 community residents  $\geq$ 70 years of age who were dementia free at baseline. The mean age was 87 years, 69% were white, 25.6% were African American and 5.4% were of other ethnicity. Those who were either homozygous for the CETP valine SNP made up 66% of the group. Those homozygous or heterozygous for APOE  $\epsilon$ 4 numbered 23%. There were 40 people who developed dementia over the period of observation. Valine CETP homozygotes but not heterozygotes experienced a relative 51% less decline in memory compared to the isoleucine homozygotic reference group after adjusting for gender, race/ethnicity, education, medical comorbidities, and APOE status. After controlling for these same variables, the hazard ratios for any dementia and for Alzheimer’s disease specifically were less among both valine homo- and heterozygotes compared to the isoleucine homozygotic group. However, the results were statistically significant only among the valine homozygotes. Importantly, the protective effect remained after adjusting for APOE status.

## THE CHOLESTEROL HYPOTHESIS

Carter has suggested that there is a convergence of polymorphic genes implicated in Alzheimer’s disease, including those associated with the amyloid precursor protein, cholesterol, lipoproteins, and atherosclerosis.<sup>5</sup> Cholesterol and its transport system have also been associated with amyloid production as well as tau hyperphosphorylation and neurofibrillary tangles.<sup>6</sup> Thus, both of the signature pathologic findings of Alzheimer’s disease are related in some way to cholesterol homeostasis.

Moreover, a number of retrospective and case control studies comparing individuals prescribed statins for hypercholesterolemia have detected a small but statistically reliable protective effect against Alzheimer’s disease.<sup>6</sup> Statins have anti-inflammatory effects and reliably prevent cardiovascular disease and stroke which has a direct impact on dementia.<sup>7</sup> Yet, despite the hypothetical appeal of cholesterol as a target

for intervention, large-scale prospective studies of two statins, simvastatin and pravastatin, failed to prevent dementia. In both studies, total cholesterol and LDL cholesterol were significantly and substantially decreased compared to placebo. But there were no differences in cognitive performance over time or in the incidence of dementia.<sup>8</sup> However, both studies were designed to examine cardiovascular events rather than dementia as the primary outcome. The sample sizes and periods of observation may not have been sufficient to detect protection against dementia.<sup>7</sup> In his 2008 Public Policy forum for the Alzheimer’s Association, Dekosky<sup>9</sup> described the challenge of finding a protective effect of any medication against Alzheimer’s disease. The requisite sample size would approach 3,000 individuals and require a 5-year period of observation in order to detect a difference between drug and placebo. In contrast, the Cholesterol Lowering Agent to Slow Progression of Alzheimer’s disease study [CLASP] included 400 people with mild to moderate Alzheimer’s disease randomized to receive placebo or simvastatin. People with vascular disease and those whose cholesterol level met criteria for lipid-lowering medications were excluded. Change measured by the cognitive portion of the Alzheimer’s Disease Assessment Scale is the primary outcome. The CLASP study<sup>10,11</sup> is the only double-blind, randomized controlled trial specifically designed to detect reduced cognitive decline among people with Alzheimer’s disease who would not have been prescribed a statin for cardiovascular indications. Prior studies have examined whether the cerebral cholesterol shuttle plays a role in initiating dementia. CLASP, if positive, will determine whether it sustains the disease.

## CONCLUSION

Studies of longevity genes such as CETP and APOE add to the argument that aggressively targeting cardiovascular risk factors may be the most effective public health approach against Alzheimer’s disease at present. Cardiovascular mortality declined substantially between 1970 and 2000 representing nearly 800,000 lives saved from heart disease.<sup>9</sup> If this trend continues and if the CLASP study is positive, the threatened pandemic of disability due to dementia may well be abated. Use of the current Food and Drug Administration-approved medications to combat the symptoms of dementia combined with lipid-modifying agents could then push the disability of Alzheimer’s disease to the end of the naturally occurring life span. The personal and societal benefit would then be similar to that observed for interventions which postpone the disability of diabetes. If genetic polymorphisms associated with

exceptional longevity are associated with lessened incidence of dementia, their characterization may suggest novel pharmacologic interventions to prevent Alzheimer's disease as well. **PP**

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