FOCUS ON ALZHEIMER'S DISEASE AND RELATED DISORDERS

In This Issue: Genetics, Cholesterol, and the Risk of Alzheimer's Disease

In recent years, researchers have made significant progress in understanding factors that may modify the risk of Alzheimer's disease (AD). Known genetic risk factors include mutations of the presenilin 1 (PS1), presenilin 2 (PS2), and amyloid precursor protein (APP) genes and the apolipoprotein E (APOE) ε4 allele. The relatively uncommon PS1, PS2, and APP mutations cause a form of the disorder typically characterized by dementia onset before the age of 60 and autosomal dominant inheritance. In contrast, the APOE ε4 allele is a polymorphism found in almost one fourth of the population that increases the susceptibility to (but is not a sufficient cause of) many cases of AD with dementia onset after the age of 60 and is, indeed, the best-established genetic risk factor for any common psychiatric disorder.

While variants of the E APOE protein (i.e., the product of different APOE alleles) may influence accumulation of the amyloid protein in the formation of neuritic plaques, phosphorylation of tau protein in the formation of neurofibrillary tangles, vulnerability of neurons to these AD-related processes, and other potentially disease-causing processes, APOE is best known as the major cholesterol transporter in the blood and central nervous system. This finding, as well as several other epidemiologic, neurobiological, and clinical studies has raised the possibility (but not yet proved) that higher cholesterol levels may increase the risk of AD and that the statins and other cholesterol-lowering medications may decrease the risk and progressive course of the disorder.

In this issue of *The Journal of Clinical Psychiatry*, Papassotiropoulos and colleagues investigated the relative contributions of a cluster of cholesterol-related genes to the risk of AD in a European sample of AD cases and controls. They found that a cluster of 9 single nucleotide polymorphisms (SNPs) contributed to the risk of AD. While the APOE ε4 allele had the greatest contribution to this risk (accounting for about 65% of the discrimination between the cases and controls), the cluster of 8 other cholesterol-related SNPs had a similar contribution (also accounting for about 65% discrimination), and altogether the cluster of 9 SNPs accounted for about 75% discrimination. On the basis of their findings, the researchers proposed a cholesterol-related genetic risk score to assess each individual's risk for AD, and they supported the biological relevance of their proposed score by showing that these scores were correlated with levels of the major cholesterol metabolite in the cerebrospinal fluid of an independent sample of nondemented individuals.

This study is potentially important for several reasons: First, it implicates a cluster of genes, including but not limited to the APOE ε4 allele, in the susceptibility to late-onset AD. This kind of information is needed to further understand pathogenic mechanisms. Indeed, it provides further support for the role of higher cholesterol levels in the pathogenesis of AD and the potential role of cholesterol-lowering strategies in the treatment and prevention of this disorder.

Second, this study illustrates the potential power of set association genetic analyses, which examine the *combined* contribution of candidate SNPs. Unlike the more traditional analysis of individual SNPs, this approach considers the polygenic nature of AD and other common psychiatric disorders, may prove more powerful than previous methods, and may be less prone to chance findings.

Finally, the authors propose the computation of an aggregate cholesterol-related score (currently for research purposes only) to assess an individual's genetic risk for AD. If confirmed or extended to include additional susceptibility genes, this approach could help identify suitable candidates for disease-slowing and prevention therapies. For instance, this information could help choose individuals most likely to benefit from disease-slowing treatments or prevention therapies that target processes involved in the cholesterol pathway, and it could be used to help healthy persons consider the risk-benefit ratio of prevention therapies in light of the intervention's potential side effects and cost, their individual risk of AD, and their individual likelihood of responding to the proposed treatment.

Like all genetic studies, these findings should be considered preliminary until replicated in independent samples. While the proposed cholesterol-related genetic risk score is not yet clinically indicated to predict a healthy person's risk of dementia, we can all take heart in the progress that geneticists and other researchers continue to make in the scientific creation of a world without AD.

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