No Worries! CAD Genetic Risk Disclosure Okay at Alzheimer's Genotyping

Marlene Busko | January 27, 2016

BOSTON, MA — Adults without Alzheimer's disease (AD) symptoms enrolled in an AD genetic-screening study, told they carried an gene linked not only with AD but also to coronary disease, didn't show more anxiety or depression after a year compared with those not told about the added CAD risk[1].

In fact, in the Risk Evaluation and Education for Alzheimer's Disease (REVEAL III) study, participants who learned that they were apolipoprotein E (*APOE*) ε4 carriers and that the genotype conferred a higher risk of both AD and CAD were *less* distressed than those who were not told about the second risk. The study was published January 25, 2016 in the *Annals of Internal Medicine.*

"Our data support the safety of disclosing secondary pleiotropic information about a modifiable condition, such as CAD, during genetic risk assessment for AD and counterintuitively suggest that such disclosure may mitigate test-related distress among persons who learn that they are at increased risk for not one but two life-threatening conditions," write Dr Kurt D Christensen (Brigham and Women's Hospital and Harvard Medical School, Boston, MA) and colleagues.

However, in an accompanying editorial[2] Dr Michael F Murray (Genomic Medicine Institute, Geisinger Health System, Forty Fort, PA) cautions that it is too early to recommend providing *APOE* ε4 results. For now, "I do not believe that *APOE* results would make it on to a list of healthcare priorities," he writes. "However, one can imagine a day soon when preventive interventions related to AD might become available," at which time *APOE* results would have a high predictive and preventive value.

"People are very interested in this [genetic] information, but without clinical utility, it's hard to imagine a scenario where physicians are going to start ordering [this test]," Christensen agreed, in a comment to **heart*wire*** from Medscape. However, "once more proven ways of reducing Alzheimer's disease risk emerge, then we might see [genetic] testing being implemented in clinical [settings]," he added. They are conducting this line of research anticipating a day when proven strategies for reducing AD risk emerge.

Does Knowing Incidental Risk of CAD Add Anxiety?

The ε4 allele of the *APOE* gene is strongly associated with risk for AD but is also weakly associated with CAD, according to Christensen. About one in four people have a form of *APOE* that increases their risk of late-onset AD (after age 60); but at the same time, "people who don't have *APOE* ε4 develop the disease, and people who have *APOE* ε4 often don't develop the disease."

Previously, the group showed that disclosing *APOE* status to participants in a genetic study of AD did not increase psychological distress, but participants were not informed of incidental CAD risk.

To investigate this, Christensen and colleagues enrolled 257 cognitively healthy adults in four cities (Boston, MA; Cleveland, OH; Ann Arbor, MI; and Washington, DC). They excluded those with relatives with early-onset AD or two or more first-degree relatives (parents or siblings) with AD, but aimed to enroll about 75% of participants with one first-degree relative with AD.

Participants were randomly assigned to receive or not receive unanticipated information about CAD risk in addition to information about AD risk. Those informed of the incidental risk were told that "some studies have shown that people who

carry ε4 also have a higher risk of developing heart disease," and that stopping smoking, maintaining a healthy diet and weight, treating high cholesterol, and exercising could lower their risk of CAD.

Participants were an average age of 58 years (range 21–83), 55% were women, 15% were African American, and 69% had a parent or sibling with AD.

After they had a telephone interview and filled in a questionnaire, participants received a brochure summarizing *APOE* test benefits (eg, possibly satisfying curiosity about the risk of AD), risks (possible difficulties coping with test results), and limitations ("there are no proven ways to prevent Alzheimer's disease from developing").

Participants then met with genetic counselors and had blood drawn for genotyping. About a month later, they received scripted information on their genetic risk, either in person or by telephone, from a genetic counselor.

One-third of participants (83 of 257; 32%) were *APOE* ε4 carriers.

Based on their *APOE* genotype, as well as race, gender, and presence or absence of a first-degree relative with AD, participants were informed of their risk of developing AD by the time they were 85 years old—which could range from 6% to 73%.

Women who were African American, had a sibling or parent with AD, and had an *APOE* ε4/ε4 genotype were at highest risk of developing AD, Christensen explained.

Anxiety, Depression, and Test-Related Distress

The primary study outcomes were 12-month Beck Anxiety Inventory scores (0–63; mild anxiety 9–15) and Center for Epidemiologic Studies Depression Scale scores (0–60; mild depression 11–16).

Secondary outcomes included 6-week and 6-month anxiety and depression scores and 12-month distress related to the genetic-risk assessment (based on Impact of Event Scale score) and changes in health habits.

At 12 months, both groups had mean anxiety scores of 3.5 (no anxiety), and mean depression scores in the AD-only and AD+CAD groups were 6.4 and 7.1, respectively (no depression).

Among *APOE* ε4 allele carriers, those who learned of the dual risk of AD and CAD had less distress and, regardless of genotype, were more likely to report that they had changed their diet and exercise habits. Possibly participants felt empowered to make changes about something that they could help prevent, Christensen acknowledged.

"The work should increase confidence that informing people of incidental genomic results that are associated with clear prevention strategies is well-tolerated," Murray summarized.

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References

1. Christensen KD, Roberts JS, Whitehouse PJ, et al. Disclosing pleiotropic effects during genetic risk assessment for Alzheimer disease. A randomized, controlled trial. *Ann Intern Med* 2016; 164:155-163. Abstract

2. Murray MF. Genomics: Prediction, prevention, priorities, and Punnett. *Ann Intern Med* 2016; DOI:10.7326/M15-2993. Editorial

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