Genetic Testing for Early-Onset Alzheimer Disease

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ABSTRACT

The availability of testing for identified risk genes for Alzheimer disease (AD) in patients with clinically probable AD or their at-risk family members raises important questions for the neurologist. Because the potential benefits and risks of testing vary for each patient, physicians need to evaluate whether it is appropriate on a case-by-case basis. This article outlines the testing decision process and serves as a guide to assist clinicians with associated counseling and result disclosure. Because genetic testing is relatively new and preventive and therapeutic options for AD remain limited, it is important to remain sensitive to and understand the specific challenges associated with obtaining these tests in the routine clinical setting.

Continuum (Minneap Minn) 2013;19(2):475–479.

Case

NOTE: This is a hypothetical case.

A 60-year-old man is brought by his family for evaluation of several years of progressive memory loss and apathy. He recently became unable to balance his checkbook and has had several episodes of being unable to remember where he parked his car. His family history is notable for a paternal cousin and a maternal aunt who, by report, were also diagnosed with dementia (unknown ages). The patient and his family would like to clarify the diagnosis but are concerned because they have read about early-onset Alzheimer disease and its genetic linkages, and they are unsure whether genetic testing should be performed. Upon examination, the patient's speech is slow but fluent with some secondary naming errors (ie, referring to more specific parts of objects—the patient properly identified the wrist band of a watch but was unable to name the buckle of a belt) and normal repetition. His performance on the Trail-Making Test Part B is slow but accurate. The patient is unable to perform the serial 7's or serial 3's tasks and scores below normal when asked to name words beginning with the letters *F*, *A*, and *S*. He is able to follow two-step but not three-step commands. His abilities in both figure copying and clock drawing are inaccurate. The results of his routine dementia laboratory studies are normal, and the neurologist confirms that the presentation is most consistent with Alzheimer disease (AD). Should genetic testing be pursued?

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Relationship Disclosure:
Dr Tsao holds stock in Illumina and Biogen.

Unlabeled Use of Products/Investigational Use Disclosure:
Dr Tsao describes preliminary findings with genetic testing.

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DISCUSSION

Genetic Risk Factors

Several genetic risk factors for AD have been identified. The major susceptibility genes for early-onset AD (less than 65 years of age) are *PSEN1*, *PSEN2,* and *APP*. Mutations in each gene alter APP metabolism, resulting in increased production of a toxic form of the amyloid-β peptide.[1] The major susceptibility gene for late-onset AD (aged over 65 years) is the *APOE* gene, particularly the **E4* allele, although recently *TREM2* has been identified as another susceptibility gene. The presence of this allele is associated with increases in the risk of disease as well as a lower age of onset. Homozygous **E4* carriers have a greater risk and an earlier age of onset than heterozygous carriers.[2] Additionally, several common genes are linked to the development of AD, but individually hold less predictive value.[3] For people who live a normal lifespan, *PSEN1* or *APP* mutations are associated with complete penetrance, and *PSEN2* mutation is associated with 95% penetrance.[4,5]

Genetic Testing

Because AD treatment is currently focused on managing clinical symptoms rather than on affecting a cure, the issue of genetic testing is controversial. Physicians must evaluate the risk-to-benefit ratio of genotyping for patients and their families on a case-by-case basis. In the case example, it would first be important to obtain a detailed, three-generational family history to help determine whether a familial inheritance pattern exists. Generally, testing is conducted when there is evidence of autosomal dominant inheritance, as mutations are otherwise unlikely to be easily detected. Testing is preferred for symptomatic patients, such as the patient described in the case, rather than for those who are asymptomatic or only mildly symptomatic. Similarly, predictive testing is somewhat uncommon. Genetic tests are rarely used diagnostically because a positive autosomal dominant test can only confirm diagnosis in an affected patient. A negative test does not necessarily exclude disease, as tests can produce false negatives and positive biomarkers are not a prerequisite for AD diagnosis.

Because both known and presumed unknown mutations associated with AD exist, a negative test does not rule out genetic components to the dementia. A typical genetic test examines the three known autosomal dominant AD genes: *PSEN1*, *PSEN2*, and *APP*. *APOE* gene testing is generally not performed, as a mutation in this gene is neither necessary nor sufficient to cause AD, the testing has low sensitivity and specificity, and the role of *APOE*E4* has not been fully elucidated and is not subject to mitigation strategies.[6–9] However, the public seems to have an interest in this type of genotyping—15% of primary care physicians receive *APOE* genotyping requests from their patients with AD.[10,11] Pediatric and prenatal testing is not recommended because of the great variability in symptomology and age of onset.[8]

Nonetheless, genetic testing does hold the potential to help inform families of a possible cause of disease, to offer an explanation for the symptoms observed in the affected individual, and to give family members an answer regarding whether they might be affected in a similar manner, which allows for earlier life-planning decisions. People who test positive for various genetic mutations may become

eligible for therapeutic research studies, thereby allowing them the opportunity to contribute to general AD research.

A plethora of additional concerns need to be considered when advising on whether a patient should undergo testing. Results are not straightforward, as multiple genes are known to be associated with AD. The presence or absence of a mutation cannot serve to singularly confirm or exclude a disease diagnosis. Variability regarding phenotypic changes, age of onset, and disease course cannot be definitively explained or predicted by genetic testing. Further, the expense of testing, compounded with a general lack of insurance coverage for the tests, creates financial barriers to genotyping. Although the 2008 Genetic Information Nondiscriminatory Act (GINA) offers protection against genetic discrimination in relation to employment and health insurance, clinical testing is still relatively new, and problems with application of the law continue to exist.

Genetic Counseling

Physicians should always pair testing with genetic counseling. Sometimes, patients and their families may benefit from receiving such counseling even before the tests are performed. This facilitates a thorough discussion of all the risks and benefits and clarifies that there are currently no established methods for preventing the onset or halting the progression of AD. Clinicians are encouraged to serve as a source of information regarding progress with AD research and established and experimental treatments. It is beneficial to have at least one family member present for the patient's counseling, as informed consent for testing is required and decisions are likely to be especially difficult for patients with dementia.[12] Furthermore, positive test results may implicate family members as being at risk, and this impact should be discussed.

Patients should be advised to consider their course of action for each potential outcome, including how they will communicate the results to their family members. Physicians are advised to keep in mind that results cannot be rescinded and to thoroughly assess the psychosocial impact of testing. Testing positive for a genetic mutation may be especially overwhelming for patients or family members not experiencing disease symptoms. A follow-up appointment should be scheduled before initiating testing so that the patients will be assured that they have the opportunity to discuss next steps.

Disclosure of Results

Clinicians face social and ethical challenges when disclosing test results to patients. People who learn that they are genetically predisposed to developing AD may become anxious or depressed. They may undertake risky lifestyle changes, such as pursuing unsupported prevention or treatment efforts. Also, patients who test positive for *APOE* mutations have been recognized as being nearly 6 times more likely to alter their long-term care insurance than those who remain unaware of genotyping results.[13] Because there is a lack of conclusive evidence supporting the value of risk assessment and early intervention, any lifestyle change made by a patient is a cause for concern.

Physicians should be aware that their patients are likely to fear AD. A survey-based study conducted by the MetLife Foundation found that Americans fear AD more than heart disease, diabetes, and stroke.[14] For Americans of at least 55 years of age, AD is the most feared disease.[14]

The results can be beneficial when disclosure is handled properly; some studies indicate a lack of emotional distress in subjects who learn of their results. For example, in one study, *PSEN1*, *PSEN2*, and *TAU* genes were analyzed in 22 subjects at risk for AD or frontotemporal dementia.[15] All participants received genetic counseling and disclosure. One year after disclosure, participants who received negative results reported a level of testing-specific distress similar to those who received positive results. Consistent with these findings, the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) project conducted *APOE* genotyping in 162 asymptomatic adults who had a parent with AD and who were randomized to a disclosure or nondisclosure group.[16] The two groups did not differ on measures of anxiety, depression, or test-related distress after up to 1 year; however, participants in the disclosure group who received positive *APOE* results were more distressed than those who received negative results.[15,16] In addition, high levels of emotional distress before testing were correlated with emotional difficulties after disclosure, suggesting the value of psychological screening.[16]

The REVEAL methodology is a model for the AD community concerning the disclosure of results. It successfully demonstrates that separating education about the risks and benefits of disclosure from the actual disclosure, monitoring mood and anxiety after disclosure, requiring an emergency contact, and referring participants to mental health professionals when appropriate are all critical factors.[16,17] Although REVEAL is an excellent starting point, larger controlled studies examining possible disclosure methods may help further inform testing and disclosure.

CONCLUSIONS

Given the current general lack of therapeutic benefit from genetic testing, and the uncertain implications of results for patients and their families, the decision of whether to conduct testing for a patient who is clinically probable for AD remains uncertain. In the case example, depending on the perceptions of the patient and his family, a decision to either proceed or defer testing might be reasonable. The decision to proceed should be coupled with appropriate genetic counseling. The potential for future improvements in test sensitivity, specificity, and clinical utility holds promise for an increased understanding of AD mechanisms and application of genotyping efforts.

ACKNOWLEDGMENT

The author wishes to thank Briana Perry, BA for substantial contributions to this article.

REFERENCES

1. Hardy J. Amyloid, the presenilins and Alzheimer's disease. Trends Neurosci 1997;20(4):154–159.
2. Prasad KN, Cole WC, Prasad KC. Risk factors for Alzheimer's disease: role of multiple antioxidants, non-steroidal anti-inflammatory and cholinergic agents alone or in combination in prevention and treatment. J Am Coll Nutr 2002;21(6):506–522.
3. Alonso Vilatela ME, López López M, Yescas Gómez P. Genetics of Alzheimer's disease. Arch Med Res 2012; PII:S0188-4409(12)00299-8.
4. Sherrington R, Froelich S, Sorbi S, et al. Alzheimer's disease associated with mutations in presenilin 2 is rare and variably penetrant. Hum Mol Genet 1996;5(7):985–988.

5. Tanzi RE, Vaula G, Romano DM, et al. Assessment of amyloid beta-protein precursor gene mutations in a large set of familial and sporadic Alzheimer disease cases. Am J Hum Genet 1992;51(2):273–282.

6. Cohn-Hooke PE, Elting MW, Pijnenburg YAL, Swieten JCV. Genetics of dementia: update and guidelines for the clinician. Am J Med Genet B Neuropsychiatr Genet 2012;159B(6):638–643.

7. Burgunder JM, Finsterer J, Szolnoki Z, et al. EFNS guidelines on the molecular diagnosis of channelopathies,epilepsies, migraine, stroke, and dementias. Eur J Neurol 2010;17(5):641–648.

8. Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med 2011;13(6):597–605.

9. Mayeux R, Saunders AM, Shea S, et al. Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. Alzheimer's Disease Centers Consortium on Apolipoprotein E and Alzheimer's Disease. N Engl J Med 1998;338(8):506–511.

10. Roberts JS, LaRusse SA, Katzen H, et al. Reasons for seeking genetic susceptibility testing among first-degree relatives for people with Alzheimer disease. Alzheimer Dis Assoc Disord 2003; 17(2):86–93.

11. Neumann PJ, Hammitt JK, Mueller C, et al. Public attitudes about genetic testing for Alzheimer's disease. Health Aff (Millwood) 2001;20(5):252–264.

12. Goldman JS. New approaches to genetic counseling and testing for Alzheimer's disease and frontotemporal degeneration. Curr Neurol Neurosci Rep 2012;12(5):502–510.

13. Zick CD, Mathews CJ, Roberts S, et al. Genetic testing for Alzheimer's disease and its impact on insurance purchasing behavior. Health Aff (Millwood) 2005;24(2):483–490.

14. MetLife Foundation. MetLife Foundation Alzheimer's survey: what America thinks. New York, NY: MetLife Foundation, 2006.

15. Cassidy MR, Roberts JS, Bird TD, et al. Comparing test-specific distress of susceptibility versus deterministic genetic testing for Alzheimer's disease. Alzheimers Dement 2008;4(6):406–413.

16. Green RC, Roberts JS, Cupples LA, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. N Engl J Med 2009;361(3):245–254.

17. Karlawish J. Addressing the ethical, policy, and social challenges of preclinical Alzheimer disease. Neurology 2011;77(15):1487–1493.