ALZHEIMER DISEASE

Informative genetic testing is currently available to only a small number of families with a history of early-onset (younger than 60-65 years of age) Alzheimer disease (AD). For these families, the benefits of genetic testing are limited and are mainly related to the individual's perception of the psychological advantages of knowing whether or not he or she is predisposed to develop AD. There remains no cure or effective preventive therapy for AD.

Genetic testing is not feasible for most cases of AD at this time. Apolipoprotein E gene variations alone cannot be used to predict future disease occurrence. Rare families with a history of early-onset AD might be eligible for genetic testing, while families with multiple relatives affected with late-onset AD (60-65 years of age and older) might be eligible to participate in AD research studies.

WHAT IS ALZHEIMER DISEASE? [1]

Alzheimer disease (AD) is an adult-onset progressive dementia. It is relatively common and the overall lifetime risk of developing dementia is 10-12%. Seventy-five percent of AD cases are sporadic, of unknown cause and usually have late onset of symptoms. Twenty-five percent of AD cases are familial (i.e. ≥ 2 persons in family have AD) and are composed of two types:

- Early-onset familial AD (EOAD) with a mean age of onset < 60-65 years (<2%)
- Late-onset familial AD (LOAD) with a mean age of onset of >60-65 years (15-25%)

Three genes have been associated with early-onset familial AD (EOAD) – amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*). Each of the identified genes is involved in production of the amyloid ß (Aß) peptide, a major component of amyloid plaques. EOAD follows an autosomal dominant inheritance pattern. [1]

Late-onset familial AD (LOAD) has been associated with apolipoprotein E (APOE) gene variations. These are considered a risk modifier, especially APOE ε4. Approximately 1% of the general population are APOE ε4 homozygotes (carry two copies of ε4). Approximately 42% of persons with AD do NOT have an APOE ε4 allele.[1]

Inheritance of AD is a complex interaction between genetic and environmental factors. With one affected first-degree relative, the risk of AD is approximately 20-25%.[1]

RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION

Genetic testing for AD is only available for a small number of families with EOAD, with testing likely to be initiated in a living affected relative. If a gene mutation is found, other family members are eligible for testing for the identified family mutation. Clinical testing is currently not available for LOAD or sporadic cases. When there are multiple related affected individuals, research testing may be available. APOE ε4 testing is not recommended for risk assessment because of low sensitivity and specificity; APOE ε4 is neither necessary nor sufficient for the disease[2].

Consider a genetics consult for patients with:

- AD with age of onset <60-65 years
- Late-onset AD and multiple affected close relatives
- Close relatives of the above two types of patients
- A family member who has an identified mutation in the *APP, PSEN1* or *PSEN2* genes

See www.geneticseducation.ca for how to connect to your local genetics centre.

WHAT DOES THE GENETIC TEST RESULT MEAN?[1]

Inheriting a mutation in *APP*, *PSEN1* or *PSEN2* gene causes EOAD. Information about the genetic factors involved in LOAD is limited; for example, data suggest that a young asymptomatic person with two copies of the APOE ε4 allele may have an increased lifetime risk of developing AD and a lower age of onset of AD compared to persons who have only one or no copies of the APOE ε4 allele.

HOW WILL GENETIC TESTING HELP YOU AND YOUR PATIENT?

In the case of genetic testing for EOAD, a positive test result for a known family gene mutation can result in:

- Relief from uncertainty
- An increased feeling of control
- Opportunity to plan life decisions given this additional information

A negative test result for a known family gene mutation for EOAD can result in:

- Relief from fear of developing early-onset AD
- Knowledge that children are not at risk for early-onset AD

ARE THERE HARMS OR LIMITATIONS OF GENETIC TESTING?

Currently no cure or effective preventive therapy is available if a gene mutation is found. A positive test result for a known EOAD family gene mutation can result in:

- Adverse psychological reaction, family issues/distress
- Insurance/job discrimination, confidentiality issues

A negative test result for a known family EOAD gene mutation can result in survivor guilt.

When an individual with no known familial gene mutation has genetic testing, a negative result is not a definitive answer.

For recent review articles on AD see Alonso Vilatela ME *et al.,* Genetics of Alzheimer's disease. *Arch Med Res.* 2012; 43(8): 622-31 and Goldman JS *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

References

[1] Bird TD. Alzheimer Disease Overview. 1998 Oct 23 [Updated 2014 Jan 30]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1161/

[2] American College of Medical Genetics/American Society of Human Genetics Working Group on *APOE* and Alzheimer's disease (1995) Statement on use of apolipoprotein E testing for Alzheimer's disease. *JAMA* 1995; 274(20): 1627-1629

Other AD resources: http://www.alzheimer.ca/en (Alzheimer Society)

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