GENE MESSENGER

☆Topic: Alzheimer Disease

☆Summary: Informative genetic testing is currently available to only a small number of families with a history of early-onset (younger than 60 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.

☆Bottom line: Genetic testing is not feasible for most cases of Alzheimer disease (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 years of age and older) might be eligible to participate in AD research studies.

✓ The Disease[1]

- AD is an adult-onset progressive dementia.
- AD is relatively common and the overall lifetime risk of developing dementia is 10-12%.
- 75% of cases are sporadic and of unknown cause – usually have late onset of symptoms.
- 25% of cases are familial and there are two types of familial cases:
  - (1) Early-onset familial AD with a mean age of onset of under 60 years (<2%)
  - (2) Late-onset familial AD (15-25%)

✓ The Genes[1]

- Early-onset familial AD:
  - 3 genes identified – amyloid precursor protein (APP), presenilin 1 (PSEN1), presenilin 2 (PSEN2)
  - Autosomal dominant inheritance
  - Each of the identified genes is involved in production of the amyloid ß (Aß) peptide, a major component of amyloid plaques.
- Late-onset familial AD:
  - Apolipoprotein E (APOE) gene variations have been associated with AD and are considered a risk modifier, especially APOE ε4.
  - Approximately 1% of the general population are APOE ε4 homozygotes (carry 2 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, risk of AD is approximately 20-25%.

✓ Consequences of having a faulty gene

- Inheriting a mutation in APP, PSEN1 or PSEN2 gene causes early-onset AD.
- Information about the genetic risks involved in late-onset AD is limited; individuals with APOE ε4, especially if they have two copies, have lower age of onset of AD.

✓ Who should be offered referral for genetic counselling?[1]

(Genetic testing eligibility depends on family history)

Patients with:

- AD with age of onset under 60 years.
- Late-onset AD and multiple affected close relatives.
- Closely related family members of the above two types of patients.
- A family member who has an identified mutation in the APP, PS1 or PS2 gene.

✓ Testing - for the faulty gene

- Genetic testing for AD is only available for a small number of families.
  - Testing may be available for early-onset cases. In this case, testing is likely to be initiated in a living affected relative; if a gene mutation is found, other family members would be eligible for testing for the identified family mutation.
  - Clinical testing is currently not available for late-onset or sporadic cases but, 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]

✓ Benefits of genetic testing

- Positive test result or a negative test result for a known family mutation
  - Relief from uncertainty
  - Increased feeling of control
  - Opportunity to plan life decisions given this additional information
- Negative test result for a known family mutation
  - Relief from fear of developing the disease
  - Knowledge that children are not at risk

✓ Harms/limitations of genetic testing

- Positive test result
  - Adverse psychological reaction, family issues/distress
  - Insurance/job discrimination, confidentiality issues
  - Currently no cure or effective preventive therapy if a gene mutation found
- Negative test result for a known family mutation
  - Survivor guilt
- Negative test result for the patient in whom genetic testing is initiated
  - Not a definitive answer and cannot offer testing to other family members because no mutation found

☆Web Resource: www.geneclinics.org

☆References:

1. www.geneclinics.org, Select "Gene Reviews", At "Search by Disease," type in "Alzheimer disease." Written by Thomas D. Bird, MD.
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.

☆Review Article:

Bertram L, Tanzi R. Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses. *Nature Reviews: Neuroscience*. 2008;9:768-778.

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GenetiKit KNOWLEDGE IN TRANSLATION

Dr Carroll is Principal Investigator of the GenetiKit Project and is the Sydney G Frankfort Chair in Family Medicine at Mount Sinai Hospital and an Associate Professor in the Department of Family Medicine at the University of Toronto.

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