

Dementia

A resident asks...

Why would a primary care physician want to know about the genetics of dementia?

Key Points:

- Genetic contributors to dementia include low penetrance and high penetrance mutations.
- A generic variant of apolipoprotein E (ApoE4) is a low penetrance mutation associated with an increased likelihood of Alzheimer's disease. A significant range of opinions exists regarding testing in these cases. Some experts have suggested testing for ApoE4 as part of the work-up of dementia. However, several expert panels have recommended *against* ApoE testing as a means to detect risk in asymptomatic people.
- In rare families, an autosomal dominant inheritance of early onset Alzheimer's disease occurs, due to high penetrance mutations. Genetic testing *may* be helpful in such families.
- Social implications of genetic testing for AD are significant.

Learning Objectives for the Dementia Module

Participants will be able to:

- Understand the clinical and social implications of ApoE testing.
- Recognize the family history indicators of autosomal dominant inheritance of early-onset dementia
- Consider the counseling implications for family members considering genetic testing.

Web Resources for Genetics of Dementia:

GeneClinics: <http://www.geneclinics.org>

GeneTests: <http://www.genetests.org>

CASE #1

Admission:

You are attending for an inpatient team. The team admitted an 80-year-old woman with acute confusion who is found by labs done in the ER to have a UTI. She improves slightly on antibiotic therapy but continues to be somewhat confused. A more complete history is obtained from her son who reports that she has been failing for some years, with progressive confusion and inability to manage her own affairs. A mini-mental status exam indicates dementia. The resident has found no focal abnormalities on neurologic exam except for mildly impaired hearing bilaterally. After confirmation of these physical exam findings, further work-up is discussed. The team orders a lab work-up to include basic blood chemistries, CBC, thyroid studies, liver function tests, and folate and vitamin B12 levels, and a head CT to rule out structural abnormalities.

Question for Discussion:

1. Should any additional etiologies be considered in this patient's work-up?

Second visit:

The patient's UTI resolves with treatment. She is discharged home and returns with a caretaker to see the resident in continuity clinic a week later. Lab and CT studies are negative. The resident has found out that the patient's father, an immigrant from Sweden, also developed Alzheimer's Disease (AD) at age 78. On the basis of an article in the New England Journal of Medicine (Mayeux et al. 1998), the resident has ordered an ApoE test. He did so in part because the family history suggests a genetic etiology and in part because the presence of a an ApoE4 allele will increase the likelihood that the patient's dementia is due to AD, while its absence will make AD less likely. You find out at this visit that the test results are available and that Mrs. P is homozygous for ApoE4.

Questions for Discussion:

2. How will the ApoE test result change work-up or management?
3. What are the risks and benefits of the ApoE test for Mrs. P?

Third visit:

Mrs. P is accompanied by her son for follow-up. The results of the work-up are discussed with Mrs. P's son. After the ApoE4 test result is explained as a finding consistent with a genetic predisposition to AD, Mr. P asks whether this test indicates that he too will get AD.

Questions for Discussion:

4. On the basis of Mrs. P's test results, what is Mr. P's risk of AD?
5. What are the risks and benefits of an ApoE test for Mr. P?
6. Does the interpretation of risks and benefits differ by ethnicity?

CASE #1 – Discussion

1. *Should any additional etiologies be considered in this patient's work-up?*

The initial work-up focused appropriately on treatable causes of dementia. Other common causes of dementia that should be considered include exposure to drugs or toxins and cerebrovascular disease. In addition to dementia, depression and delirium need to be considered (Ramsdell et al. 1990). Delirium may be caused by factors such as drug reactions, metabolic disorders, systemic illnesses (e.g. infection), cerebrovascular diseases and other CNS disease. Some neurological diagnoses, such as ALS and Parkinson's disease, present with dementia in combination with other focal neurological findings. Alzheimer's Disease (AD) accounts for about half of isolated dementia cases, with most of the remainder due to cerebrovascular disease. [Disclaimer: Experts may disagree about the menu of tests to be ordered in the initial work-up. Some would argue against a routine CT scan. The tests used in this case represent a common approach to work-up for treatable causes of dementia.]

2. *How will the ApoE test result change work-up or management?*

The ApoE4 result will not change work-up or management.

Three common variants of apolipoprotein E (ApoE) occur: ApoE2, ApoE3, and ApoE4. Epidemiological studies have documented ApoE4 as a risk factor for AD (see **Table 1**). ApoE2 appears to reduce risk.

In patients with suspected AD, the presence of one or more ApoE4 alleles has been shown to increase the specificity of the diagnosis in studies of white populations (Mayeux & Schupf 1995; Tsuang et al. 1999). Thus, knowing Mrs. P's ApoE4 genotype increases the probability of that her dementia is due to AD. The positive and negative predictive values of the ApoE4 testing (for the presence of one or more ApoE4 alleles) are estimated to be 88% and 40% respectively (Tsuang et al. 1999). These predictive values are not sufficiently high either to rule in or to rule out AD as a cause of the patient's dementia, and thus would not change work-up. In other

words, an ApoE4 homozygous genotype is not diagnostic for AD, and therefore does not remove the need to rule out causes of dementia, particularly those that are treatable.

There is no proven therapy for AD. Some studies suggest short-term benefit with tacrine, but this therapy remains controversial (Qizibash et al. 1998). The effect of ApoE status on response to tacrine has been evaluated in a few small studies with conflicting results (Rigaud et al. 2000; MacGowan, Wilcock & Scott 1998; Farlow et al. 1998). Thus, there is no scientific basis for determining management on the basis of ApoE status.

3. What are the risks and benefits of the ApoE test for Mrs. P?

Potential risks of the ApoE4 test result have to do with labeling: One could postulate that Mrs. P might experience anxiety or other adverse psychological effects as a result of knowing that she has a genetic susceptibility to AD. While these potential effects are likely to be of limited concern in a patient diagnosed with dementia, the patient's relatives could be quite troubled by their own risk for inheriting the disease susceptibility. The benefits to Mrs. P are likewise unclear.

4. On the basis of Mrs. P's test results, what is Mr. P's risk of Alzheimer's Disease?

Mr. P has an increased risk of AD. His risk is increased on the basis of his family history alone (see **Table 1**). In addition, he has an increased risk on the basis of his ApoE genotype (see **Table 2**). We know that he must have at least one copy of the ApoE4 allele, because his mother is homozygous for ApoE4. When family history and ApoE4 status are taken together, his risk to develop AD is at least 2 to 3 times higher than average. He also has a higher risk to develop AD before age 65 (see **Table 2**). His risk of developing AD by age 90 is estimated to be 61% (see **Table 3**).

5. What are the risks and benefits of an ApoE test for Mr. P?

It is not clear that this risk information provides any benefit to Mr. P. His mother's ApoE does not allow him to anticipate with certainty whether he will develop AD and, if so, at what age. There is no treatment available to carriers of ApoE4 alleles to prevent AD.

The risk information could cause harm, in the form of anxiety, stigmatization or discrimination. For example, if Mr. P were seeking a promotion and his employer knew of his increased risk for AD, that information could conceivably influence the promotion decision. Knowledge of an increased risk of AD could also make it harder for Mr. P to obtain life insurance or individually rated health insurance. These possibilities underscore the concerns many policymakers have expressed about the importance of preserving the confidentiality of predictive genetic information and preventing insurers and employers from using it (Hudson et al. 1995; Lapham, Kozma & Weiss 1996).

6. Does the interpretation of risks and benefits differ by ethnicity?

Only one study of ApoE4 status as a predictor of AD risk found no association for African-Americans or Hispanics (Tang et al. 1998). Another study found ApoE4 to be more predictive in whites than in Hispanics or African-Americans (Devi et al. 1999).

CASE # 2

Mr. Y comes to clinic with his wife to discuss an upsetting experience that occurred a week ago. Mr. Y is a 45-year-old computer engineer who manages a software development unit at a large company. He is well known within the industry as the developer of key components of several widely used programs. He had been under a great deal of stress at work, so he and his wife decided to take a vacation. They went to San Francisco to visit friends and attend the opera. On the first day of their trip, their 22-year-old daughter, Sue, who was at home, received a call from Mr. Y. He was in a telephone booth in Union Square. He could not remember what hotel he and Mrs. Y were staying at; he didn't know what to do. Sue gave him the name of the hotel and instructed him to take a taxi back. Shaken, he and his wife returned home. He denies drug use of any kind, drinks moderately, and recently underwent routine medical testing as part of an annual physical, with all results normal. He jogs 30 minutes a day.

Physical exam is unremarkable. There are no focal neurological signs. He is unable to remember three objects. He knows his name and telephone number but has trouble with his birthday, his address and the name of the President. Asked to describe the details of what happened in San Francisco, he says, "The same thing happened to my mother." Prompted, he tells a story that is difficult to follow, about his mother getting lost. Mrs. Y explains that Mr. Y's mother, aged 65, has been in a nursing home for the past 5 years, with a diagnosis of Alzheimer Disease. She also notes that Mr. P has been under considerable pressure at work, with his performance having been described by his boss as unsatisfactory and characterized by faulty management decisions.

Questions for Discussion:

1. How does the family history affect the patient's work-up?
2. What additional family history would be of value?
3. What options can be offered to the family?

Case # 2 – Discussion

1. *How does the family history affect the patient's work-up?*

Mr. Y requires a careful work-up for neurological and systemic illness, with attention to treatable causes of his recent onset of cognitive difficulties, particularly given his age and previous good health. However, his family history raises the possibility of an inherited early onset AD.

Approximately 10% of AD can be accounted for on the basis of mutations with high penetrance that cause an autosomal dominant early onset AD. The majority of these cases are due to mutations in the PSEN1 gene; mutations in two other genes, APP and PSEN2, have also been implicated (see **GeneClinics** review: <http://www.geneclinics.org>).

2. *What additional family history would be of value?*

A careful three-generation family history would be helpful in determining the likelihood of autosomal dominant early onset AD in Mr. Y's family.

This family history would reveal that Mr. Y's mother was diagnosed with AD at age 60, after at least 10 years of progressive memory problems. In addition, one of Mr. Y's two maternal uncles was noted to have memory problems before he died in an automobile accident at age 48. Mr. Y's maternal grandfather was institutionalized at age 52 and died at age 59; he was said to have "severe mental problems." This grandfather had a sister with memory problems, another sister who died at 72 without evidence of memory problems, and a brother who remained healthy and alert until age 90.

This family history is consistent with autosomal dominant inheritance of early onset AD in several respects:

1. Disease occurs in sequential generations.
2. Both males and females are affected.
3. In each generation, approximately equal numbers are affected and unaffected.

3. *What options can be offered to the family?*

Mr. Y in fact had early onset AD. His diagnosis and his family history confirm an autosomal dominant AD. The family may benefit from genetic counseling, to review autosomal dominant inheritance and to learn about options for genetic testing. Mr. and Mrs. Y have three children, aged 22, 20 and 17, each of whom has a 50% chance to inherit the condition. Genetic testing is available only for mutations in the PSEN1 and APP genes. These mutations have nearly 100% penetrance - that is, almost all people with a mutation develop early onset dementia. The age of onset is usually in the 40's or early 50's although onset in the 30's and early 60's has been reported. Onset after age 65 is thought to be very rare, with penetrance essentially complete by that age. However, testing for PSEN1 and APP mutations is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals (see **GeneClinics** and **GeneTests** reviews).

If Mr. Y were tested and found to have an identifiable mutation in the PSEN1 gene, testing could be offered to his adult children to determine whether they have inherited the predisposition to early onset AD. This option may or may not be of interest to different family members, and discussion of the implications of testing may be very difficult for the family. In addition to supervising the evaluation for Mr. Y, his primary care provider may play a crucial role in ensuring that family members' needs for information, counseling and emotional support are addressed over time.

Table 1
Risk of AD with Positive Family History

Risk assessed	Definition of “positive family history”	Odds Ratio (95% Confidence Interval) for positive family history versus negative
AD before age 65, in people with no ApoE4 allele (van Duijn 1994)	Report by at least two family members of first degree relative with dementia,	2.9 (1.6-5.6)
AD in HMO population (Jarvik 1996)	Report by subject or surrogate of parent or sibling with progressive memory problems interfering with daily activities	2.7 (1.8-4)
AD after age 85 (Payami 1997)	Report by subject or surrogate of parent or sibling with AD, dementia or progressive memory loss	3.8 (0.87-16.5)

Table 2
Risk of AD or Dementia According to ApoE Genotype

Risk assessed	Ethnicity	Odds Ratio (95% Confidence Interval) for:		
		1 or 2 ApoE4 alleles	1 ApoE4 allele	2 ApoE4 alleles
AD before age 65 AND positive family history (van Duijn)	White (Netherlands)	3.3 (1.6-7.0)	2.6 (1.2-5.7)	7.9 (1.7-36.0)
AD before age 65 AND negative family history (van Duijn)	White (Netherlands)	1.9 (1.0-3.7)	1.6(0.8-3.2)	4.9 (1.3-19.9)
AD after age 65 (Evans 1997)	Predominantly white (Boston)	2.3 (1.1-4.9)*		
AD after age 65 (Tang 1998)	White (New York)	2.5 (1.1-6.4)*		
AD in HMO population AND positive family history (Jarvik 1996)	White (Seattle)		5.0 (2-11)**	12.0 (3-59)
AD in HMO population AND negative family history (Jarvik 1996)	White (Seattle)		2.3 (1.4-4)**	No controls identified
Dementia after age 85 AND positive family history (Payami 1997)	White (Oregon)	9.13 (1.74-47.8)		
Dementia after age 85 AND negative family history (Payami 1997)	White (Oregon)	4.34 (0.99-1.04)		

* ApoE4/ApoE2 excluded from analysis

** ApoE3/ApoE4 only

Table 3
Lifetime Risk of AD in People with a Family History of AD
According to ApoE Genotype of Affected Relative (Martinez et al. 1998)

ApoE4 Genotype of Proband	Risk of AD by age 90 in First Degree Relative
ApoE4/ApoE4	61%
ApoE4/ApoE4 <i>or</i> ApoE4/ApoE3	50%
ApoE4/ApoE3	46%
ApoE3/ApoE3	29%

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