Explaining The Role Of Genetics As A Risk Factor For Dementia To Patients In The Primary Care Setting

1. Overview

Families are often concerned about the possibility that genetics may play some role in the pathogenesis of Alzheimer’s disease (AD). Genetic mechanisms impact the risk for dementia via inherited risk factors, age-related damage to otherwise healthy genes or medical/environmental damage to genes. Genetic factors can impact risk for Alzheimer’s disease, Frontotemporal dementia and other less common dementia, such as Creutzfeldt’s-Jacob disease (500).

Genetic factors also impact baseline intellect including global intellect, verbal IQ and working memory (521). Socioeconomic status and other non-inheritable factors such as SES can also impacts intellect (See Table 1).

A positive, family history for dementia may increase a patient’s risk for developing dementia; however, monozygotic twin studies show concordance less than 100% and significant variation in age of onset (12). Individuals who have a parent or sibling with AD may have 3.5x increased risk of developing the disease. The autosomal dominant variant of Alzheimer’s disease is present in only 1-2% of all Alzheimer’s disease cases. Many other forms of dementia, such as vascular dementia and diffuse Lewy body disease have a substantially reduced genetic predisposition in comparison to AD. A variety of genes are associated with familial/early onset AD that include chromosomes 1, 2, 14, and 21, as well as late onset or sporadic disease that includes chromosomes 6, 19, and 21 (1), (2), (3) (See Table 2).

The early onset familial AD accounts for less than 2% of dementia and may involve genes that impact the amyloid precursor protein gene. About half of the late-onset cases may be related to the APOE gene which is located on chromosome 19. Unlike the amyloid gene on chromosome 21, the APOE gene is a susceptibility gene that may accelerate the age of onset for symptoms (11), (12). Based on studies in elderly twins, genetic liability in late onset disease accounts for 48% of variation in the risk of developing dementia (3).

| Table 1 | Effect of Genetics on Baseline Intellect |
|-----------------|-----------------|-----------------|-----------------|
| SES – up to 50%  |  VIQ – up to 57%  | Working memory – 33 to 64%  |

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| Table 2 | Important Genes for Dementia |
|-----------------|-----------------|-----------------|-----------------|
| Chromosome | Disease | Function | Ref. |
| 1 | FAD | PSEN 2 | 11/500 |
| 14 | FAD | PSEN 1 | 11/500 |
| 17 | FTD | Tau MATP | |
| 19 | LOAD | APO E | 9 |
| 19 | MCI to AD | APOE | 503 |
| 21 | Down’s LOAD | APP | 500 |
| Telomeres | Vascular Dementia | Shortening increases risk | 501 |

FAD – familial AD  PSEN – Presenilin  FTD – Frontotemporal Dementia  LOAD – Late onset AD  APP – Amyloid Precursor Protein
2. Interpretation of the Family History for Dementia
A family history of Alzheimer’s disease requires a post-mortem confirmation of the reported premortem diagnosis, as studies report a 10% discrepancy between clinical and pathological diagnosis. Many clinical conditions can produce confusion in the older patient and the family history is only as accurate as either the premortem diagnosis or postmortem confirmation.

3. Assessing the Genetic Risk Factors for Alzheimer’s Disease
The relative genetic risk for developing Alzheimer’s disease can be crudely assessed by determining how many family members were affected by the disease and what age these individuals developed symptoms. Individuals who develop dementia early in life, i.e., below age 60, are more likely to have a genetic variant of the disease. Proximity in the family tree may be helpful. For example, an individual with a father and uncle who both develop dementia before age 60 might have a significantly increased risk for developing dementia in comparison to a woman who had a maternal aunt develop the disease after age 80 producing the same risk factors as the general population.

4. Genetic Risk Factors in Common Dementias Other Than AD
Familial studies in Frontotemporal dementia suggest 25% to 50% of affected individuals have a first degree relative with dementia. Abnormalities of Chromosome 17 associated with the microtubule associated protein tau may explain some inheritance (12). The genetics of Parkinson’s disease and diffuse Lewy body dementia remain controversial. Certain rare disorders such as Huntington’s disease have specific genetic deficits.

5. Predictive Value of Available Genetic Testing
Predictive genetic testing is not presently available for Alzheimer’s disease or any other form of dementia except for Huntington’s chorea. APO lipoprotein E (APO-E) genes are often discussed because the presence of two E4 alleles will increase the risk while homozygote E2 may be protective (See Table 3). For example, females with two APOE-4 alleles are at significantly greater risk for developing dementia than individuals with E3 or E2 (See Table 4). The APOE-4 allele risk is greatest in the 60- to 70-yr age group and decreases after age 80. The APOE-4 allele is associated with the greatest risk in white females between the age of 60 and 70 (12). APOE genetic typing is now offered as a routine clinical laboratory test by some commercial laboratories. The APOE-4 gene is important but not necessary for dementia (1), (9) and certain ethnic groups, such as pygmies and others, have high rates of APOE-4 without identified increased risk (5), (6), (7), (8). It is unlikely that a single specific gene will be identified for late onset Alzheimer’s disease or most other types of dementia, as the genetic risk may be predicted by a variable mixture of independent and inter-related genetic factors. Assessment of multiple genetics risk factors will probably be required to predict the risk in the future.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>A Meta-Analysis of 33 Studies for APOE Risk Effect in Caucasians with Clinical and Pathological AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE Genotype</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>3/4 vs 3/3</td>
<td>3.2</td>
</tr>
<tr>
<td>4/4 vs 3/3</td>
<td>14.9</td>
</tr>
<tr>
<td>2/2 vs 3/3</td>
<td>0.6</td>
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<table>
<thead>
<tr>
<th>Table 4</th>
<th>Estimates for Risk of Dementia Based on Age, Gender, and APO Typing</th>
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<tbody>
<tr>
<td>Gender/Age</td>
<td>3/3 (%)</td>
</tr>
<tr>
<td>M/65</td>
<td>&lt;5</td>
</tr>
<tr>
<td>F/65</td>
<td>&lt;5</td>
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<tr>
<td>M/75</td>
<td>10</td>
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<tr>
<td>F/75</td>
<td>10+</td>
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</tbody>
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6. **Understanding the Interaction of Genes, Environment, and Health Behaviors**

A variety of health behaviors, e.g., exercise, weight control, or intellectual vitality may interact with medical conditions, e.g., diabetes or hypertension, to amplify the role of genetic predispositions, such as the presence of the APOE 4 allele. For example, diabetics with APOE-4 typing have higher density of senile plaques at autopsy. This complex relationship will require years of further research to clarify and quantitate as a “genetic risk assessment”. FOR ADDITIONAL INFORMATION, CLICK HERE 2515.12, 2515.15, 2515.15-1.

International studies comparing African Americans from Indianapolis to genetically similar individuals from their homeland in Nigeria show that APOE typing is less predictive of dementia in native Africans. The reduced risk of dementia in the Nigerian group may result from better health behaviors, such as a better diet and increased physical exercise.

7. **Molecular Genetics of AD**

Many publications, i.e., over 875, have studied many polymorphisms (1055) of at least 355 genes. At least 12 genetic loci are associated with AD in addition to PSEN 1,2 and APOE. These other loci have a “modest” effect on susceptibility (520). Telomeric shortening is linked to accelerated aging and increased risk of dementia following stroke. Genetic loci are associated with a range of neural proteins including insulin degrading enzyme, tumor necrosis factor, presenilins, and sortilin-related receptor SORL-1 (520), (532).

8. **Impact of APOE Testing Results on Patients Undergoing Testing**

Individuals who are informed about a positive test for APOE-4 are more likely to alter cognitive health behaviors and adjust long-term care insurance (505), (506). Informed individuals did not appear to exhibit a false sense of reassurance from an APOE-3 or APOE-2 result (2). Adverse psychological consequences are not reported among individuals with APOE-4 test results but current national consensus recommendations still advise against testing (4). Most tested subjects were concerned about: 1) their risk (71.9%), 2) children’s risk (70%), 3) best treatment (79%), and 4) future planning (92%) (506).

9. **Impact of Genetics on the Natural History of Alzheimer’s Disease**

The presence of a single APOE-4 allele may advance the age of onset of AD by about eight years in those individuals who will develop dementia. The APOE-4 gene predicts diminished cognitive performance in some individuals between age 50 and 60, as well as conversion from MCI to AD (504), (531) in younger patients. APOE-4 testing is not predictive of natural history in older patients, i.e., over age 80 (532). In brain imaging, APOE-4 allele may predict early onset of cortical volume loss (535) and diminished blood flow (536). An individual’s clinical course cannot be predicted by APOE typing although this allele is more commonly associated with delusions in LOAD (odds ratio 3.11) (539). Response to treatment seems unrelated to APOE-4 typing (540).

**Recommendations**

APOE testing is not recommended as a predictive test for dementia. Individuals, who are concerned about having Alzheimer’s disease in the family, should be encouraged to engage in health practices that protect the brain. Although the value of cognitive fitness programs for persons with strong genetic loads for Alzheimer’s disease is unproven, conventional wisdom suggests that reducing other associated brain injury would prolong the duration of cognitive fitness. Much or most dementia may result from a complex interaction between susceptibility genes, environment and life choices. Future genetic therapy will be complex and require therapeutic techniques not presently available to clinicians.
Summary
1. Some families may request “genetic” testing for Alzheimer’s disease, i.e., APOE typing.
2. Genetic testing for dementia is imprecise.
3. Genetic testing does not presently assist with treatment strategies.
4. Testing may encourage healthy behaviors that may reduce risk factors for dementia.
5. Testing may assist patients to engage in advanced planning.
6. Adverse APOE test results are not shown to provoke patient distress.
7. Physicians should counsel patients who request APOE testing.
8. Physicians should explain predictive limitations of testing.
9. Physicians should offer to counsel children of tested individuals.
10. Physicians should advise about potential adverse impact on health insurance.
11. Physicians should document each interaction.
12. Genetic testing for dementia should be discouraged except for specific diseases such as Huntington’s disease.
References


