Caregiver Connections
An Educational Webinar Series With The Experts

The presentation will begin shortly. Thank you for your patience!

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919-660-7510
The Genetics of Dementia & Genetic Testing

Daniel Parker, MD
Assistant Professor
Division of Geriatrics
Department of Neurology
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Disclosures

• No disclosures
Outline

• Background
• Is dementia genetic?
• Types of genetic testing
• Living with the results of genetic testing
What do we mean by mild cognitive impairment (MCI) and dementia?

**Normal Cognition**

- I notice subtle changes in my memory and thinking
- Cognitive assessment is normal.
- These changes **do not** interfere with my day to day activities.

**Subjective Cognitive Impairment (SCI)**

- There are changes in my memory and thinking that I and others notice.
- These changes are picked up on cognitive assessments.
- These changes **do not** interfere with my day to day activities.
- These changes aren’t caused by another medical or psychiatric problem.

**Mild Cognitive Impairment (MCI)**

- I need extra help with day to day activities.
- These changes aren’t caused by another medical or psychiatric problem.

**Dementia**

- There are changes in my memory and thinking that I and others notice.
- These changes are picked up on cognitive assessments.
- I need extra help with day to day activities.
- These changes aren’t caused by another medical or psychiatric problem.
MCI and dementia are “umbrella” terms

• MCI and dementia are syndromes or “umbrella” terms which describe a group of symptoms that occur together.
• They describe cognitive symptoms and their impact on function.
• They don’t tell us what’s going on in the brain that is causing the symptoms.
• There are different diseases that can cause MCI and dementia.
What diseases cause MCI/dementia?

**Alzheimer’s Disease**
- Accounts for 60-80% of dementia
- Progressive cognitive decline typically beginning with short-term memory
  - Amyloid β
  - Neurofibrillary Tau

**Lewy Body Disease**
- Accounts for 30% of dementia
- Progressive cognitive decline with cognitive fluctuations, visual hallucinations, REM sleep behavior disorder, and Parkinsonisms
  - α Synuclein
  - 80% Have AD Neuropathology

**Vascular Cognitive Impairment**
- Often co-occurs with AD
- Dementia primarily caused by cerebrovascular disease or impaired cerebral blood flow

**Frontotemporal Disease**
- Typically presents in 50s
- Accounts for ~10% of dementia in ≤65 years
- Includes behavioral variant and nonfluent and semantic primary progressive aphasia:
  - TDP-43
  - Tau
  - And Others
Genetics

• Genes are the “code” or “recipes” the body uses to make proteins.
• The human genome contains 20,000-25,000 protein coding genes.
• We have two copies of every gene, one from our mom and one from our dad.
Marfan Syndrome

Autosomal dominant

Unaffected parent

Affected parent

Unaffected child

Affected child

Autosomal recessive

Carrier parent

Affected child

Carrier parent

Unaffected child

Carrier child

Unaffected
Affected

Marfan Syndrome

Sickle Cell Disease

Marfan Syndrome

By Combination: SUM1File:Autosomal dominant - en.svg: Domaina, Angelito7 and SUM1File:Autosomal recessive - en.svg: Domaina, Kashmiri and SUM1


Sickle Cell Disease

By Combination: SUM1File:Autosomal dominant - en.svg: Domaina, Angelito7 and SUM1File:Autosomal recessive - en.svg: Domaina, Kashmiri and SUM1


Marfan Syndrome

Sickle Cell Disease

Marfan Syndrome

Sickle Cell Disease
Other Ways Genetics Influence Risk

• Chromosomal Disorders
  • Trisomy 21 (Down Syndrome)

• Risk Genes
  • Inheriting one or two "bad" versions of a gene increases the risk of developing the disease but doesn’t guarantee that you will develop the disease
  • The genetic contribution to most diseases is probably the result of mutations in multiple risk genes
Genetics of Alzheimer’s Disease

Early Onset Alzheimer’s Disease
- Onset before age 65. Autosomal Dominant.
- <10% of cases with a clear genetic cause
- Mutations in APP, PSEN1, PSEN2

Late Onset Alzheimer’s Disease
- Onset after age 65
- Increased risk due to APOE-ε4

Alzheimer’s Disease in Down Syndrome
- Extra copy of chromosome 21
- APP gene is on chromosome 21
APOE Genotype

- APOE genotype is the **strongest genetic risk factor** for Alzheimer’s disease that develops after age 65.
- There are three common APOE variants:
  - APOE-ε2 is the least common version and may provide protection against Alzheimer’s.
  - APOE-ε3 is the most common version and is considered to have a neutral effect on the Alzheimer’s — neither decreasing nor increasing the risk.
  - APOE-ε4 increases risk for Alzheimer’s and is associated with earlier onset in certain populations.

**Alzheimer’s Disease Risk**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>% US Population</td>
<td>1%</td>
<td>12%</td>
<td>60%</td>
<td>2%</td>
<td>21%</td>
<td>2%</td>
</tr>
<tr>
<td>Disease Risk</td>
<td>40% Less Likely</td>
<td>40% Less Likely</td>
<td>Average Risk</td>
<td>2.6x More Likely</td>
<td>3.2x More Likely</td>
<td>14.9 More Likely</td>
</tr>
</tbody>
</table>

The effect of APOE on Alzheimer’s risk is greater in women. The effect of APOE on Alzheimer’s risk is weaker in African-Americans.

<table>
<thead>
<tr>
<th>APOE Genotype</th>
<th>Sex</th>
<th>Age 65</th>
<th>Age 75</th>
<th>Age 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Male</td>
<td>&lt;1%</td>
<td>3%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>&lt;1%</td>
<td>3%</td>
<td>14%</td>
</tr>
<tr>
<td>No APOE-ε4</td>
<td>Male</td>
<td>&lt;1%</td>
<td>1-2%</td>
<td>5-8%</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>&lt;1%</td>
<td>1-2%</td>
<td>6-10%</td>
</tr>
<tr>
<td>One APOE-ε4 Copy</td>
<td>Male</td>
<td>1%</td>
<td>4-7%</td>
<td>20-23%</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>&lt;1%</td>
<td>5-7%</td>
<td>27-30%</td>
</tr>
<tr>
<td>Two APOE-ε4 Copies</td>
<td>Male</td>
<td>4%</td>
<td>28%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2%</td>
<td>28%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Prevalence of Alzheimer’s Disease Dementia by Age, Sex, and APOE Genotype
Figure HRs of AD according to the combination of healthy lifestyle factors in the prospective cohort studies

<table>
<thead>
<tr>
<th>Number of healthy lifestyle factors</th>
<th>N</th>
<th>% of AD</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 healthy factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAP 0–1</td>
<td>322</td>
<td>24.4</td>
<td>1.00 (1.00, 1.00)</td>
</tr>
<tr>
<td>MAP 0–1</td>
<td>123</td>
<td>31.7</td>
<td>1.00 (1.00, 1.00)</td>
</tr>
<tr>
<td>2–3 healthy factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAP 2–3</td>
<td>1,073</td>
<td>15.4</td>
<td>0.58 (0.37, 0.93)</td>
</tr>
<tr>
<td>MAP 2–3</td>
<td>507</td>
<td>26.4</td>
<td>0.66 (0.46, 0.94)</td>
</tr>
<tr>
<td>Combined (p for heterogeneity = 0.7)</td>
<td></td>
<td></td>
<td>0.63 (0.47, 0.84)</td>
</tr>
<tr>
<td>4–5 healthy factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAP 4–5</td>
<td>450</td>
<td>8.1</td>
<td>0.33 (0.18, 0.61)</td>
</tr>
<tr>
<td>MAP 4–5</td>
<td>290</td>
<td>19.3</td>
<td>0.43 (0.28, 0.66)</td>
</tr>
<tr>
<td>Combined (p for heterogeneity = 0.5)</td>
<td></td>
<td></td>
<td>0.40 (0.28, 0.56)</td>
</tr>
</tbody>
</table>

Model adjusted for age, sex, race, education, APOE ε4, and prevalence of cardiovascular disease (including heart disease or stroke). A random-effects meta-analysis was used to combine cohort-specific results. AD = Alzheimer dementia; CHAP = Chicago Health and Aging Project; CI = confidence interval; HR = hazard ratio; MAP = Rush Memory and Aging Project; N = number of participants in each group.

# FTD Genes

<table>
<thead>
<tr>
<th><strong>C9orf72</strong></th>
<th><strong>GRN</strong></th>
<th><strong>MAPT</strong></th>
</tr>
</thead>
</table>
| - Most common genetic variant in hereditary FTD and ALS  
- ~5-10% of apparently sporadic ALS & FTD | - ~20% of familial FTD  
- Small percent of apparently sporadic FTD | - ~20% of familial FTD  
- Small percent of apparently sporadic FTD |
| - Onset 20s-90s, with average of ~58 | - Onset 20s-90s, with average of ~61 | - Onset 17-80s, with average of ~50 |
| FTD, ALS, psychiatric illness, parkinsonism | FTD, parkinsonism, CBS | FTD, parkinsonism, CBS, PSP |

*There are other rare genes that can cause FTD and/or ALS such as VCP, TARDBP, FUS, CHCHD10, SQSTM1, CHMP2B, OPTN, etc., and we continue to discover more!*

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Types of Genetic Testing

Diagnostic Testing
I want to know if my disease is genetic

Predictive Testing
I want to know my risk of developing the disease

Approaches to Genetic Testing
- Specific Panel of Genes
- Exome or genome sequencing
- DNA banking
Why perform diagnostic testing?

- **Relief**
  - I knew there was something going on!

- **Accurate Diagnosis**
  - Avoid unnecessary testing.

- **Planning**
  - Know what to expect and anticipate future needs

- **Family Planning**
  - PGT & prenatal diagnosis

- **Alleviates Guilt**
  - If only I had quit smoking...

- **Research**
  - Participate in clinical trials.
Why perform predictive testing?

**Relief**
Reduce uncertainty about the future.

**Planning**
Career, finances, family goals

**Family Planning**
Assisted reproductive therapy

**Research**
Join a clinical trial
Potential Downsides of Genetic Testing

Anxiety
Anticipating the development of symptoms

Relationships
How might this information affect your spouse, kids, friends?

Treatment Options
Few effective treatments

Insurance
Required to disclose for long term care, life, and disability insurance

CCRCs
Health requirements for entry
My parent has dementia. Should I get tested?

What’s the probability their dementia was genetic?
• Depends on subtype, age of onset, family history

No test is perfect!
• Risk of false positives, false negatives, the significance of some genetic variants isn’t clear

What are the goals of testing?
• How are you going to use this information?

How might testing affect your family?
APOE Genotyping

• Insurance typically doesn’t cover APOE testing
• Direct to consumer testing options are available
  • 23andme Health Report assesses presence and number of APOE-ε4 variants
  • EmpowerDx (www.empowerdxlab.com) offers APOE genotyping for $99
Living with the Results of Genetic Testing

• Few family members of people with early-onset AD choose to be tested. Those who do usually cope well with the results, but some cases of depression have been reported.

• APOE testing in asymptomatic individuals is generally not recommended.
Summary: Alzheimer’s Disease Genetic Testing

Early Onset Alzheimer’s Disease
APP, PSEN1, PSEN2
Rare <1% of AD Dementia & <10% of Early Onset Dementia

Late Onset Alzheimer’s Disease
APOE-ɛ4
Modestly Affects Risk
Relatively Common
Risk Varies by Sex/Ethnicity
Summary

• Most cases of dementia do not have a single genetic cause and not all genetic variants that cause or contribute to dementia risk have been identified.

• Early onset Alzheimer’s disease can be due to mutations in the APP, PSEN1, and PSEN2 genes.

• \textit{APOE-ɛ4} modestly increases the risk of late onset Alzheimer’s disease in some populations.

• FTD can be caused by mutations in C9orf72, GRN, and MAPT.

• Generally best to test the person with the disease.

• You can meet with a genetic counselor without undergoing genetic testing.
Resources

- Find a genetic counselor near you - https://findageneticcounselor.nsgc.org/
- AFTD genetics page: https://www.theaftd.org/ftd-genetics/ftd-genetics-and-you-learning-more/
- FTD Disorders Registry genetics page: https://ftdregistry.org/genetics-ftd
- Dementia Society of America: https://www.dementiasociety.org/
- Alzheimer’s Association: https://www.alz.org/
- NIH resources: https://www.nia.nih.gov/health/early-onset-alzheimers-disease-resource-list
- Dominantly Inherited Alzheimer’s Network or DIAN: https://dian.wustl.edu/
- Clinical trials and other research search tool: http://clinicaltrials.gov/
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Thank you for joining us today!

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