DUKE DEMENTIA FAMILY SUPPORT PROGRAM

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

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September 19, 2023

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

Subjective Cognitive Impairment (SCI)

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

Mild Cognitive Impairment (MCI)

- 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.

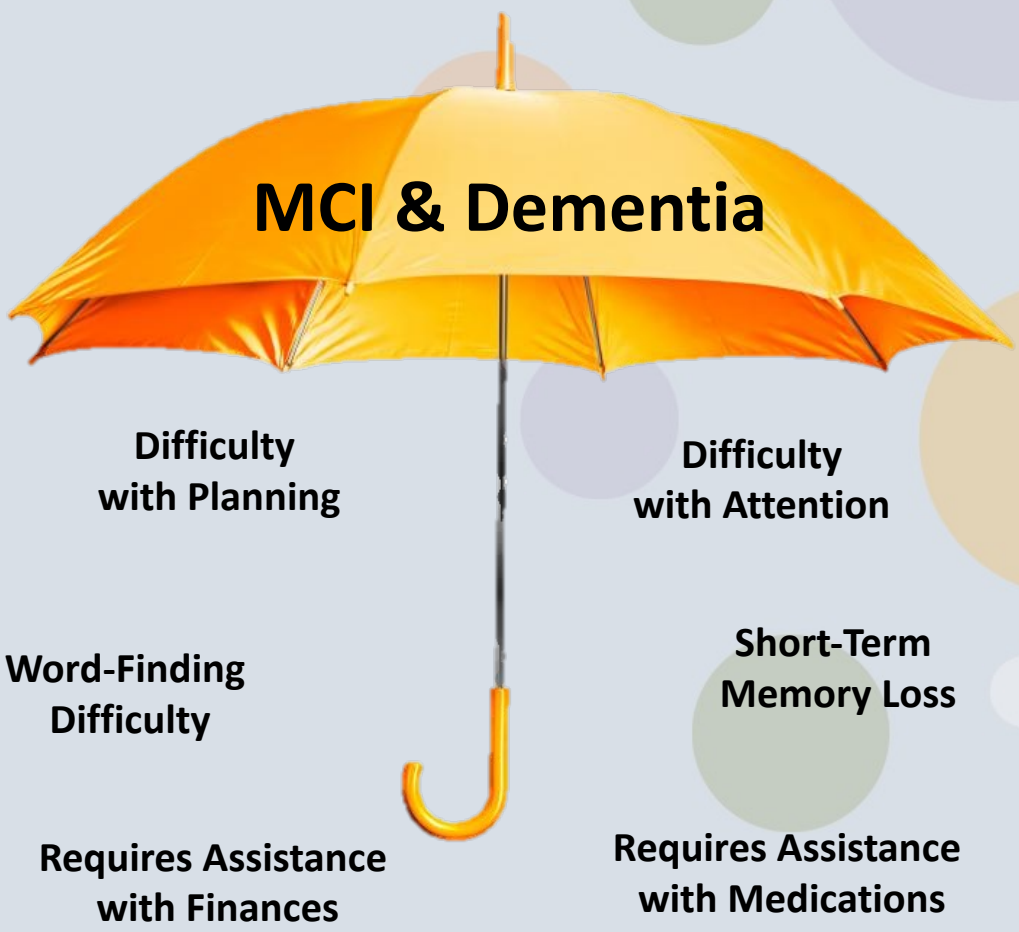
Dementia

- 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.

Syndromes or “Umbrella” Terms

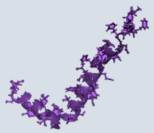


What diseases cause MCI/dementia?

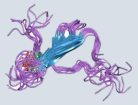
Alzheimer's Disease

- Accounts for 60-80% of dementia
- Progressive cognitive decline typically beginning with short-term memory

Amyloid β



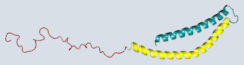
Neurofibrillary Tau



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

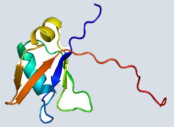
Vascular Cognitive Impairment

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

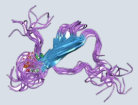
Frontotemporal Disease

- Typically presents in 50s
- Accounts for ~10% of dementia in ≤65 years
- Includes behavioral variant and nonfluent and semantic primary progressive aphasia.

TDP-43



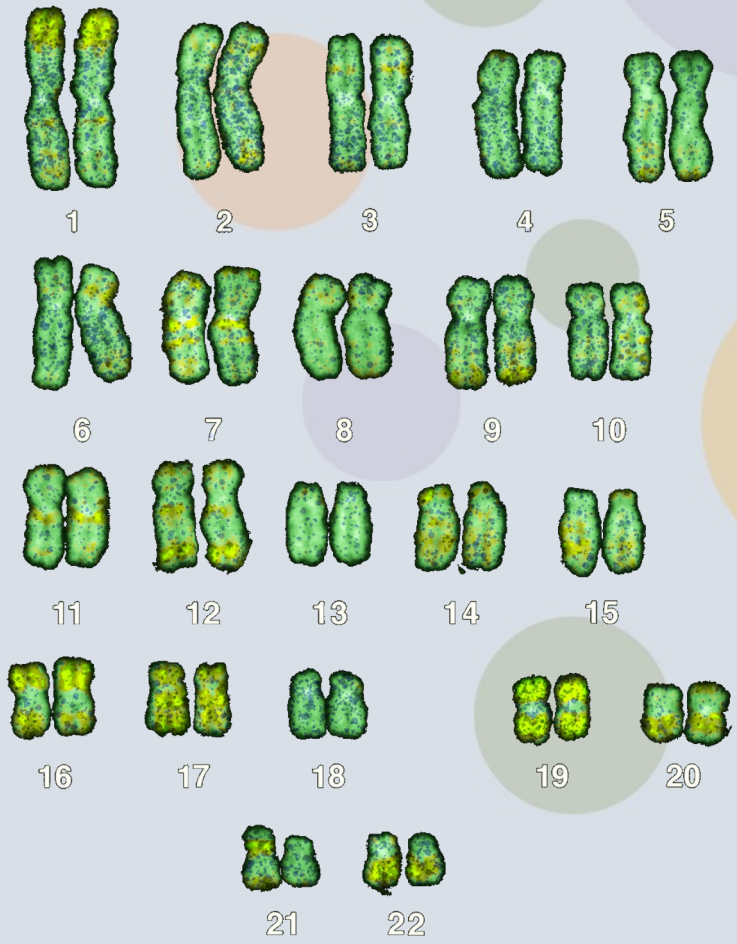
Tau



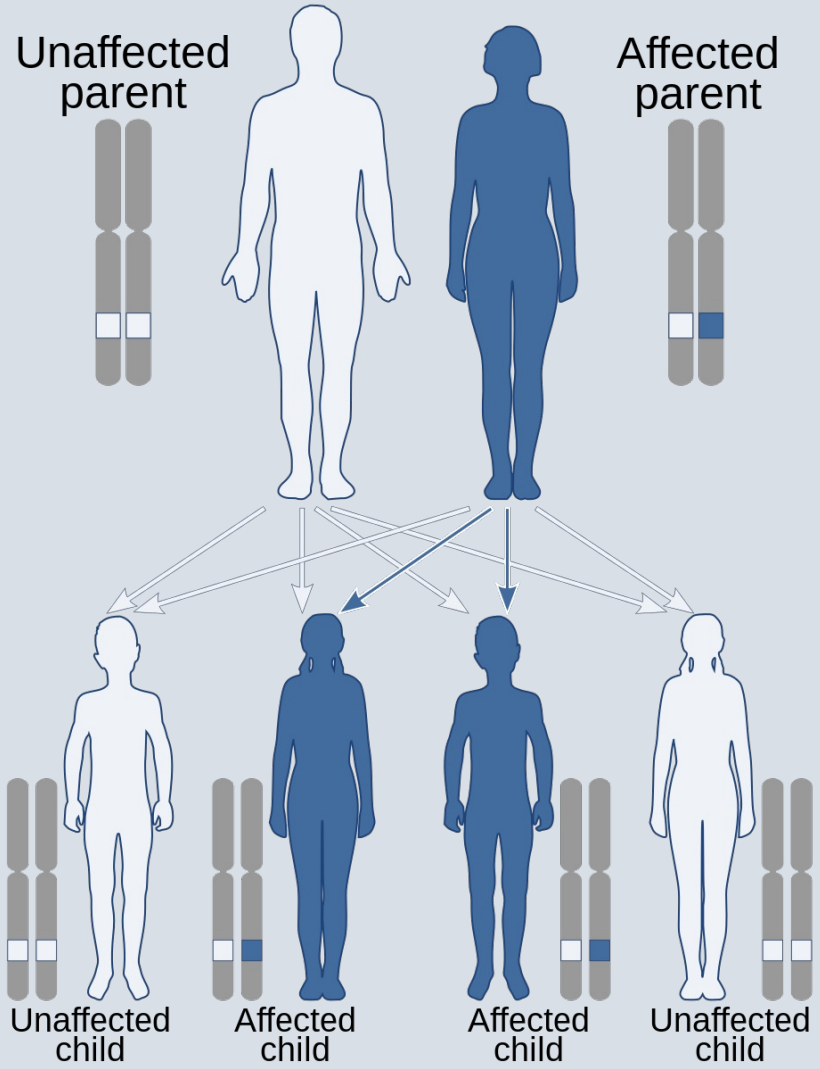
And Others

Genetics

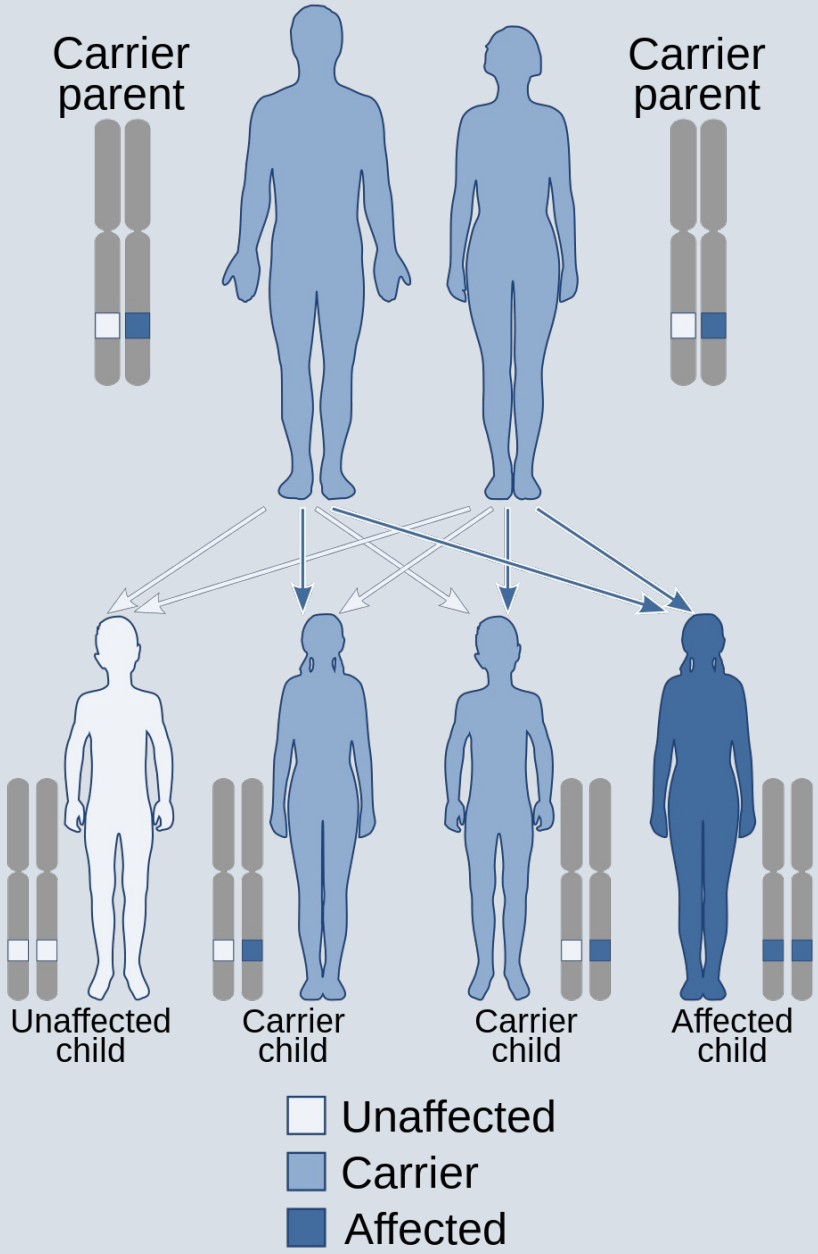
- Genes are the “code” or “recipes” the body uses to make proteins.
- The human genome contains 20,000-25,000 protein coding genes.
- We have two copies of every gene, one from our mom and one from our dad.



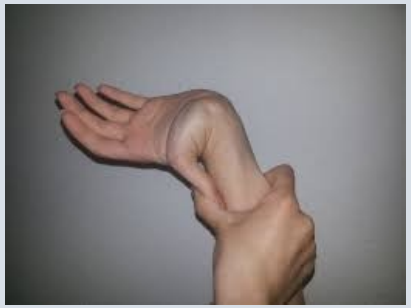
Autosomal dominant



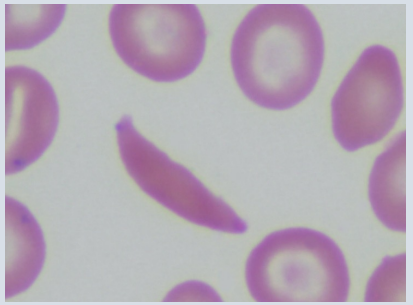
Autosomal recessive



Marfan Syndrome

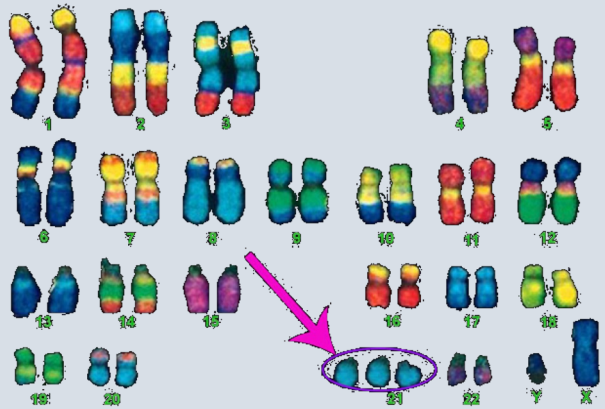


Sickle Cell Disease



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

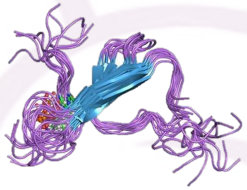
Late Onset Alzheimer's Disease

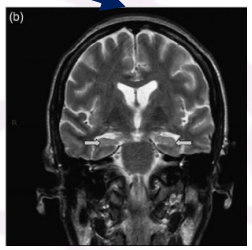
- Onset after age 65
- Increased risk due to *APOE*-ε4

***APOE*-ε4**

Amyloid β

Tau





Neurodegeneration

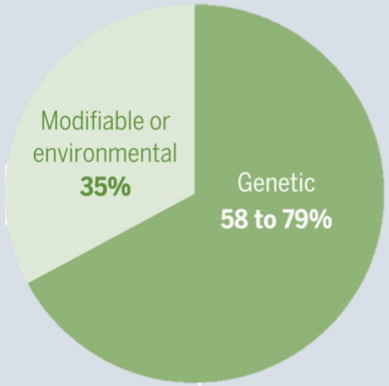
MCI, Dementia

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.



Modifiable factors (blood pressure, lifestyle, exercise, diet, smoking) account for 35-40% of risk! APOE genotype accounts for 5-10% of the genetic risk. Other genes play a role too.

Alzheimer's Disease Risk

APOE-ε2/ε2 *APOE-ε2/ε3* *APOE-ε3/ε3* *APOE-ε3/ε4* *APOE-ε4/ε4*

APOE Genotype

Lower Risk ***Higher Risk***

APOE Genotype	ε2/ε2	ε2/ε3	ε3/ε3	ε2/ε4	ε3/ε4	ε4/ε4
% US Population	1%	12%	60%	2%	21%	2%
Disease Risk	40% Less Likely	40% Less Likely	Average Risk	2.6x More Likely	3.2x More Likely	14.9 More Likely

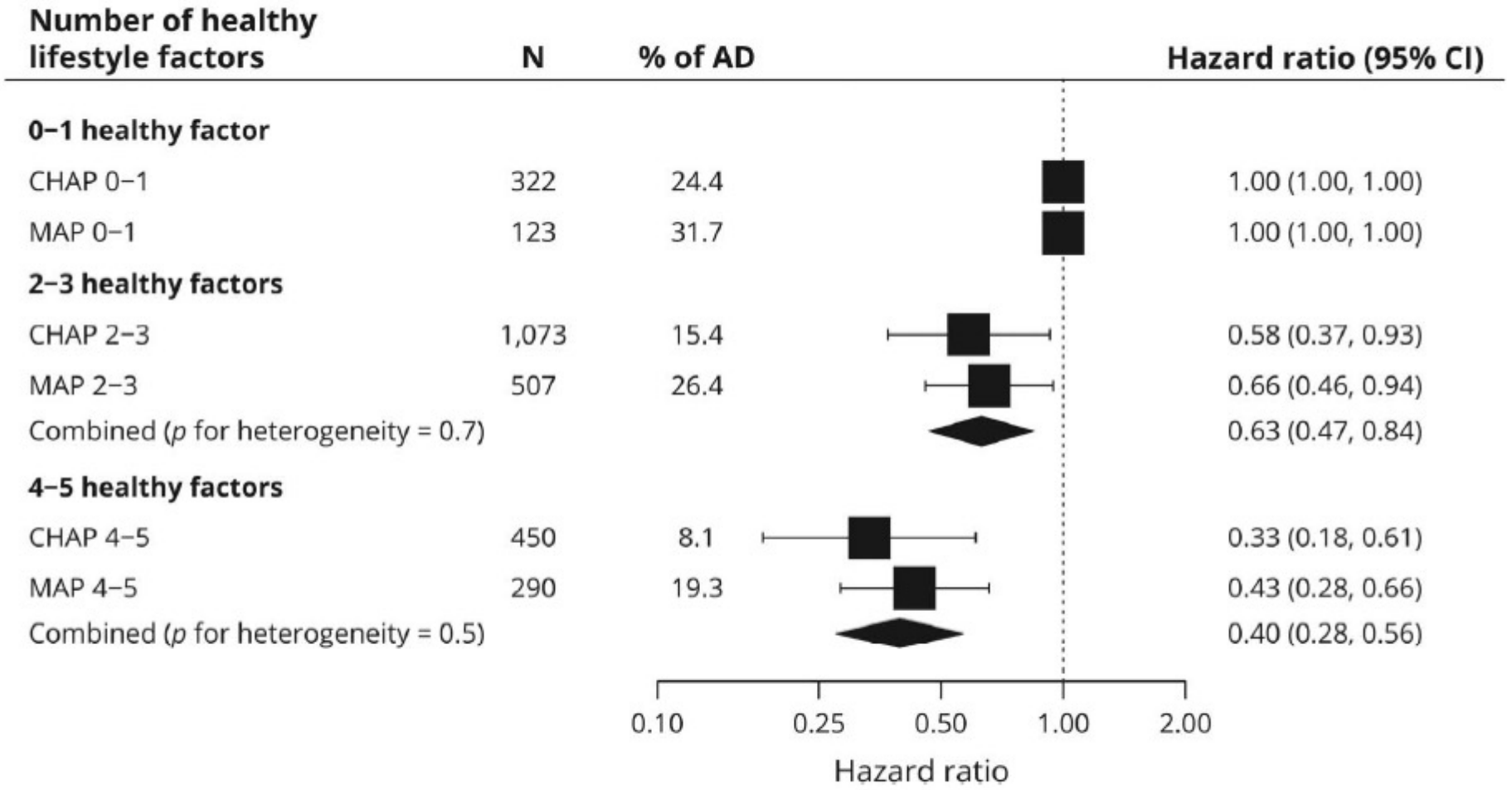
The effect of APOE on Alzheimer's risk is greater in women.
The effect of APOE on Alzheimer's risk is weaker in African-Americans

Serrano-Pozo, et al. "APOE and Alzheimer's Disease: Advances in Genetics, Pathophysiology, and Therapeutic Approaches." *The Lancet Neurology* 20, no. 1 (January 2021): 68–80. https://doi.org/10.1016/S1474-4422(20)30412-9.

Prevalence of Alzheimer's Disease Dementia by Age, Sex, and APOE Genotype

APOE Genotype	Sex	Age 65	Age 75	Age 85
All	Male	<1%	3%	11%
	Female	<1%	3%	14%
No APOE-ε4	Male	<1%	1-2%	5-8%
	Female	<1%	1-2%	6-10%
One APOE-ε4 Copy	Male	1%	4-7%	20-23%
	Female	<1%	5-7%	27-30%
Two APOE-ε4 Copies	Male	4%	28%	51%
	Female	2%	28%	60%

Figure HRs of AD according to the combination of healthy lifestyle factors in the prospective cohort studies



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.

Dhana, Klodian, Denis A. Evans, Kumar B. Rajan, David A. Bennett, and Martha C. Morris. "Healthy Lifestyle and the Risk of Alzheimer Dementia: Findings from 2 Longitudinal Studies." Neurology, June 17, 2020, 10.1212/WNL.0000000000009816.

FTD Genes

C9orf72	*GRN*	*MAPT*
• 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!		

Moore, K. M., Nicholas, J., Grossman, M., McMillan, C. T., Irwin, D. J., Massimo, L., ... & Freedman, M. (2020). Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. *The Lancet Neurology*, *19*(2), 145-156.

Hsiung GYR, Feldman HH. GRN Frontotemporal Dementia. 2007 Sep 7 [Updated 2020 Feb 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1371/

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

Alleviates Guilt
If only I had quit smoking…

Family Planning
PGT & prenatal diagnosis

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

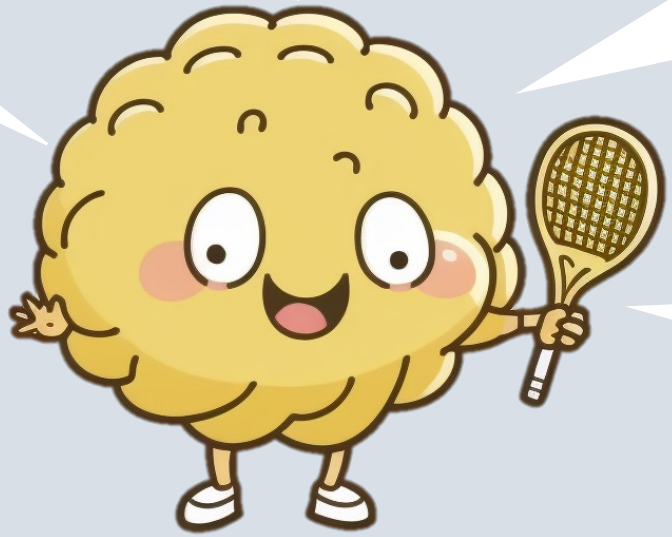
Research
Join a clinical trial

Potential Downsides of Genetic Testing

Anxiety
Anticipating the development of symptoms

Treatment Options
Few effective treatments

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



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

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-ε4

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.
- *APOE*-ε4 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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