

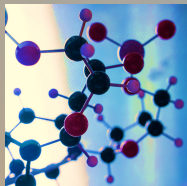
Genetics and Alzheimer Disease

Practical knowledge and emerging insights

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Learning objectives



- Define the genetic basis of inherited and familial AD
- List considerations for genetic risk assessment in AD
- Describe insights from the latest genetic research in AD

Introduction



+
Genetic counselors..

..help families understand and adapt to the
**psychological,
familial,
&
medical**
aspects of genetic disease.



Image <https://www.nsgc.org>

AUDIENCE POLL

polleverywhere.com

(link updated day of conference; results displayed live) ◦ + •

Q. If you could take a test that will tell you with 100% certainty if you will develop AD, would you take that test?

A.
YES / NO

AUDIENCE POLL

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Q. Instead, if the test could only tell that you have either a 55% or a 12% chance to develop AD, would you take that test?

A.
YES / NO



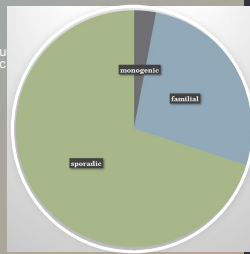
Genetics of Alzheimer Disease

Monogenic, familial, or sporadic?

Cases of AD

Most cases of AD are **sporadic** and occur with no clear family or identifiable genetic cause.

Only 1-5% of cases are monogenic



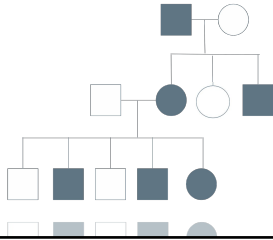
Monogenic AD

Gene name	Avg age of onset
PSEN1	43
PSEN2	57
APP	52

All three genes are involved in the production of amyloid.

Harmful variants in these genes are **rare** but are inherited in the **dominant** pattern.

Dominant inheritance pattern



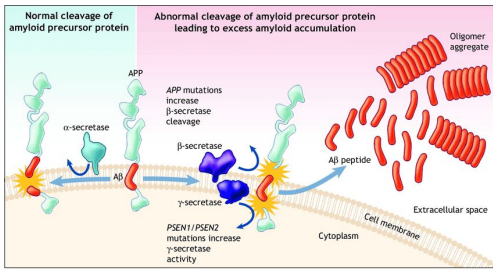


Image courtesy of Patterson C, Feightner JW, Garcia A, Hsiong GY, MacKnight C, Sadosvnick AD. Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease. CMAJ. 2008; 180(15):1648-56. doi: 10.1503/cmaj.071076. PMID: 18250545. Epub 2008-08-24; PMCID: PMC2244657.

Beta amyloid

Much of AD research has targeted the beta amyloid (Aβ) protein.

- Reducing production of Aβ
- Suppressing β-secretase activity
- Clearing existing Aβ plaques

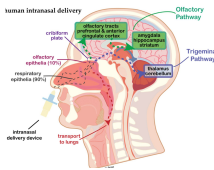
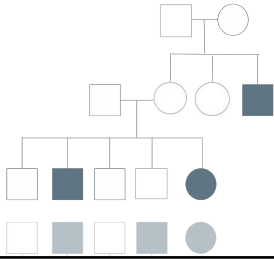
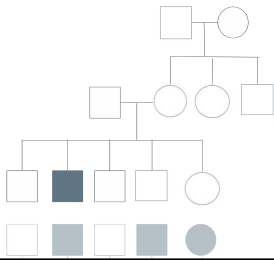


Image Brossi M, Farias Duplidor G, Ehrlich ME, Sator R. Intranasal Peptide Therapeutics: A Promising Avenue for Overcoming the Challenges of Traditional CNS Drug Development. Cells. 2022; 11(2):2623. https://doi.org/10.3390/cells11222623

Familial inheritance



Sporadic disease



Familial AD

Gene	Avg age of onset
Many different risk genes including APOE	It depends!

APOE gene is involved with lipid transport in the brain.

APOE gene comes in different "versions" or alleles.

APOE e4 is a **risk factor** for AD, not a cause.

APOE

APOE versions "alleles"	Effect
APOE e2	Decreases risk for AD
APOE e3	Average risk for AD
APOE e4	Increases risk for AD

Humans have two copies of the APOE gene. A person may be born with any combination of these alleles.

Example:
2/4 3/3 3/2 4/4

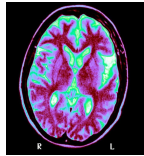
APOE and Lecanemab (Leqembi)

FDA approved July 2023. Lecanemab is an antibody meant to clear A β plaques in the brain.

Data shows slower cognitive decline than placebo.

Side effects might include small bleeds and swelling in the brain tissue

People with the APOE 4/4 genotype have the highest risk of side effects.



AD risk genes

Genome-wide association studies (GWAS) have identified at least 100 normal versions of genes that each contribute a very small amount to risk for AD.

These variants are common in the population.

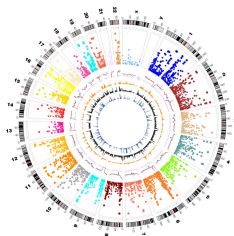


Image: Li, M., Shao, P. & Wang, J. Genetic variant representation, annotation and visualization. *Hereditas* 144: 192–200 (2012). <https://doi.org/10.1111/hdi.12110>

AD risk genes

An aggregated risk number is known as "polygenic risk score" (PRS).

Currently, clinical genetic testing cannot provide accurate PRS scores for patients.



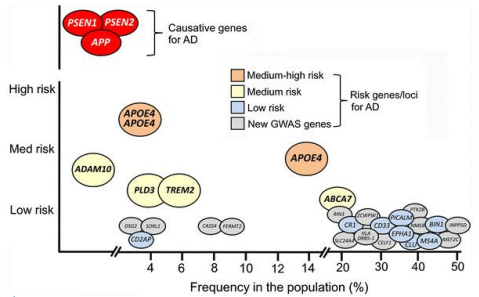


Image: Yamazaki Y, Painter MM, Bu G, Kawakami T, Apolipoprotein E as a Therapeutic Target in Alzheimer's Disease: A Review of Basic Research and Clinical Evidence. CNS Drugs. 2016; Sep;30(9):773-808. doi: 10.1007/s00265-016-0361-4. PMID: 27328971. PMCID: PMC4826196.

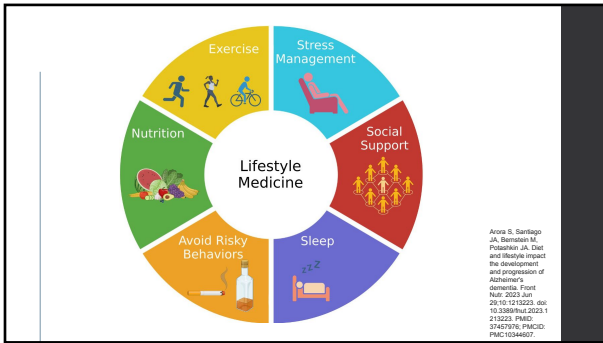
Multifactorial Inheritance

Multifactorial refers to the many factors that influence a person's risk for a disease over the course of their entire life:

- Genetics (many genetic factors and their interactions)
- Environment (air, water, toxins, medications)
- Personal factors (gender, age, experiences)




Image: Caputo-Kiley D, Austin J, Weeks L. (2021). Journey into Genes: Cultural Values and the (Near) Future of Genetic Counseling in Mental Health. In: Skowron D, Fildes B, Singh-Mani G, Van Steen W, Woods BT, eds. International Perspectives in Value-Based Mental Health Practice. Springer, Cham. https://doi.org/10.1007/978-3-030-47862-0_28



Gene therapy for Alzheimer Disease?

Examples:

- CRISPR/CAS9 systems used in mice to delete mutations in APOE, APP, PSEN1 and prevent Alzheimer disease.



Viral vector delivery of an outside gene (NF- α 1/CPE) to mouse brain prevents neurodegeneration and Alzheimer Disease.

Genetic risk assessment in Alzheimer disease

to test or not to test?



Genetic testing

- Single gene testing
- Panel testing
- APOE genotyping

Can be done through a blood draw, saliva sample or cheek swab.

Cost range \$0 - \$400 per test



Before genetic testing..

- Consider your family history
- Review your insurance options
- Consider the impact of a positive result



Family history considerations

- **KNOW, ASK, and TELL** about medical conditions in your family.
- Learn about age of onset, details of diagnosis.
- Use a pedigree diagram to visualize inheritance patterns.



Review insurance options

BEFORE you seek a referral to genetics.



Protected:

- Health insurance
- Most types of employment



Not Protected:

- Life insurance
- Long term care insurance
- Disability insurance

Consider the impact of results

What benefit do you expect from testing?

How would a positive result impact your

- Life plans
- Family members
- Employment

Who can support you during this process?

Who have you told? Who will you tell?



Personalized Care For Your Genetic Health



Find a Genetic Counselor

www.nsgc.org

11/2017

CONCLUSION

AD is usually polygenic and multifactorial.



Family history is a powerful tool for estimating risk.

Genetic research and gene therapy are developing quickly - Talk to a genetic counselor and stay tuned!

THANK YOU!!



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Resources

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