IS IT GENETIC? CURRENT PRACTICE OF GENETIC COUNSELING FOR ALZHEIMER'S DISEASE

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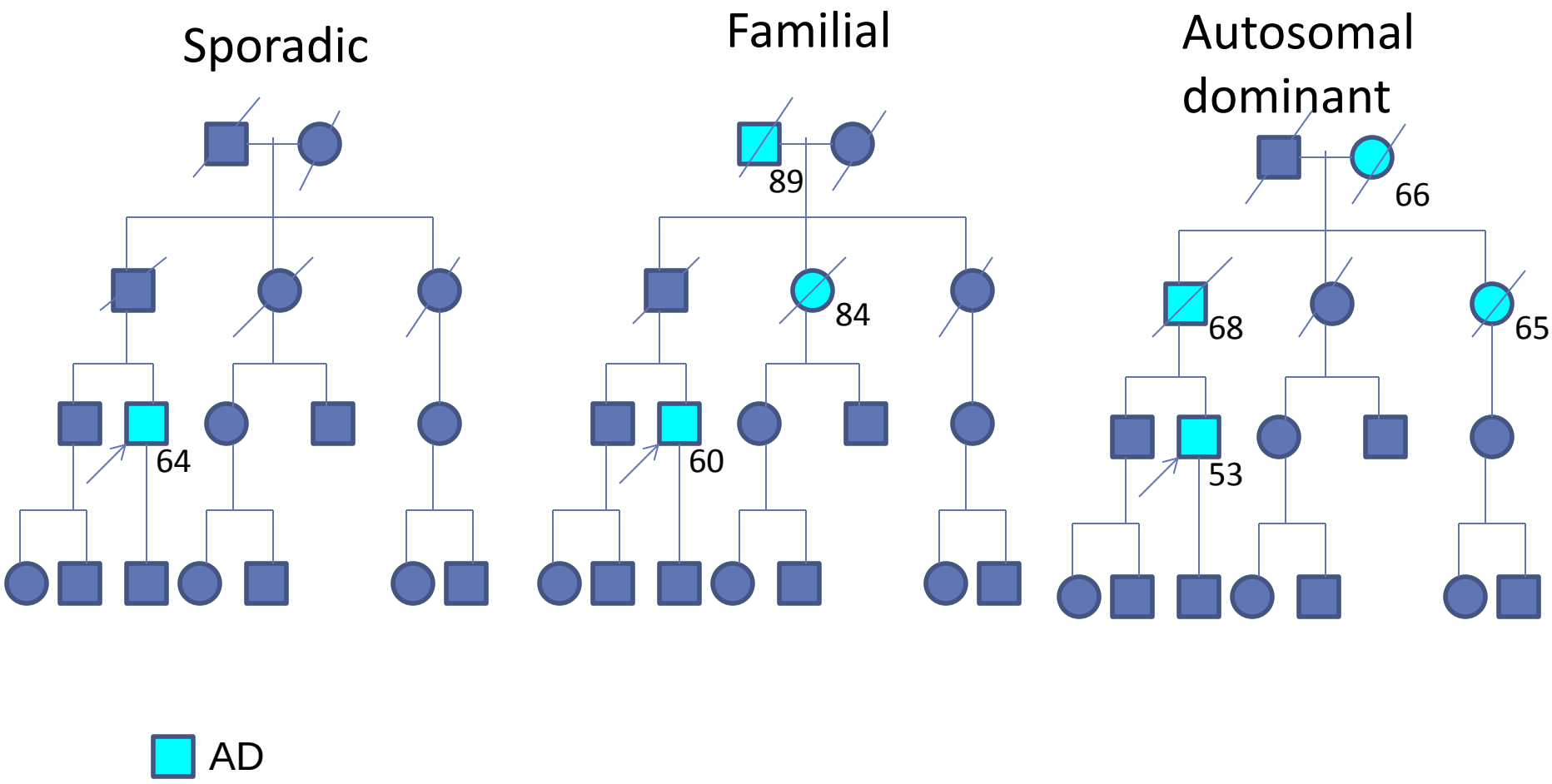
Outline

- 1. Looking at family histories.
- 2. When do you consider genetic testing?
- 3. Genetic testing for DIAD (dominantly inherited AD)
- 5. APOE and other risk genes.
- 6. DTC for AD
- 7. What to do for your patients who test positive?

Scary numbers

- 5.7 million people in the US have AD in 2015.
  - 5.5 million people ≥ 65 (1/9)
  - 200,000 people < 65
  - ~2/3 of these are women
- ~ 1/3 people ≥ 85 have AD
- That's why almost every pedigree has someone with dementia
- But genetic testing is rarely appropriate!!

Family History



So when do you consider genetic counseling/testing?

Gold standard:

- Affected person with onset under 60 and a family history consistent with dominantly inherited AD (DIAD)
- Unaffected at-risk individual with known family mutation

New possibilities using next-gen ???

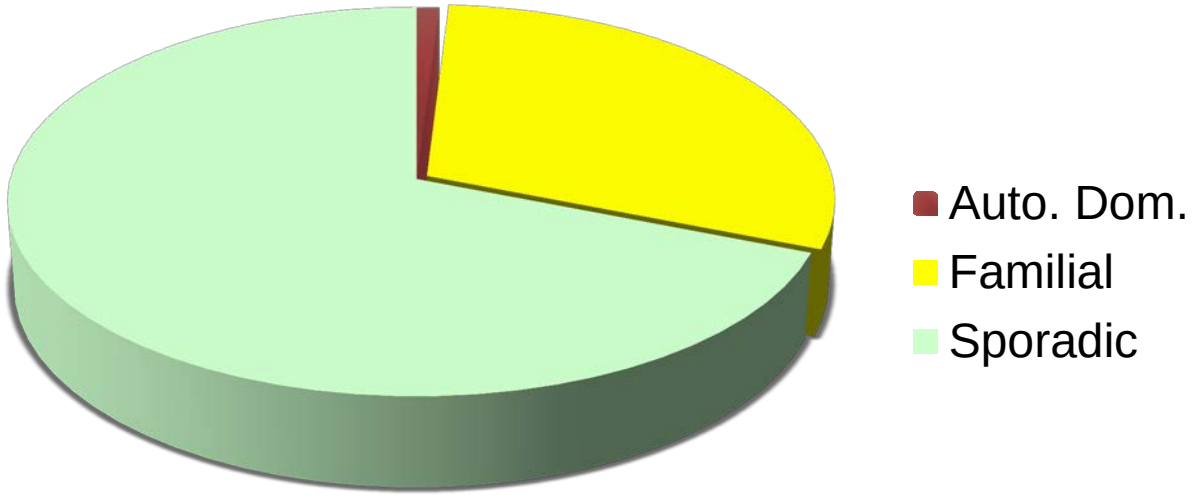
- Affected person with family history of *dementia*
- Unaffected at-risk individual with family history consistent with autosomal dominant dementia

? How do we know which dementia? *Be careful!*

Genetic *counseling* is appropriate for anyone with family history of dementia

Family history

Empiric risk of having a first degree relative with AD : lifetime risk 2-3-fold



AD Genetics: Genetic heterogeneity

Inheritance Type	Alzheimer's Type	Chromosome Location	Gene Product
Autosomal Dominant	Early onset familial	21q21.3	Amyloid Precursor Protein
	Early onset familial	14q24.13	Presenilin 1
	Early onset familial (Volga)	1q31.42	Presenilin 2
Genetic Susceptibility Factor	Late onset familial and ~50% sporadic	19q13.2	APOE -ε4

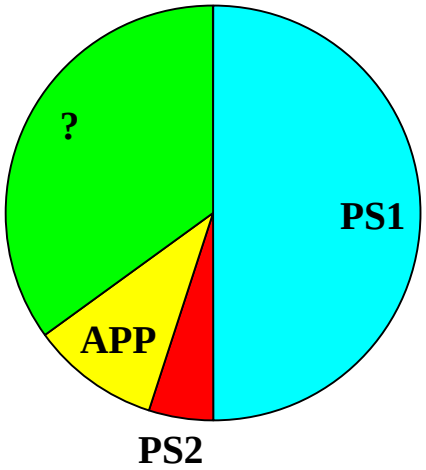
Autosomal Dominant Genes

- Result in early onset
  - Presenilin 1 (*PSEN1*): 30s-60s usually 40s,50s
  - Presenilin 2 (*PSEN2*): 40-75, < 100% penetrant
  - Amyloid precursor protein (*APP*):

    40s-50s

    duplications, promotor mutations
- Rapid progression

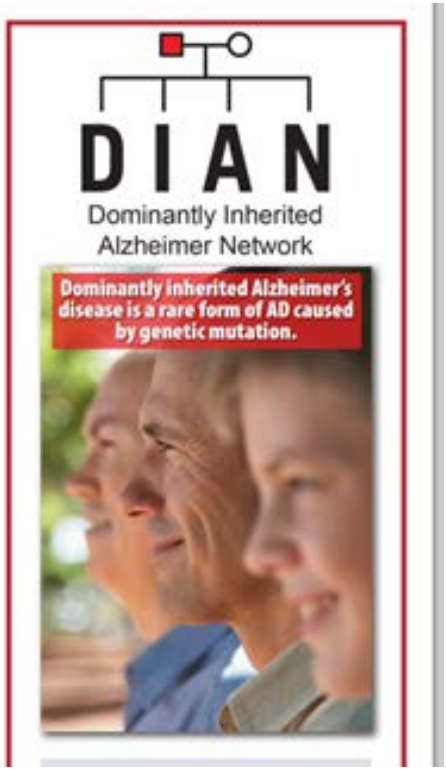
  (usually 8-10 yrs)



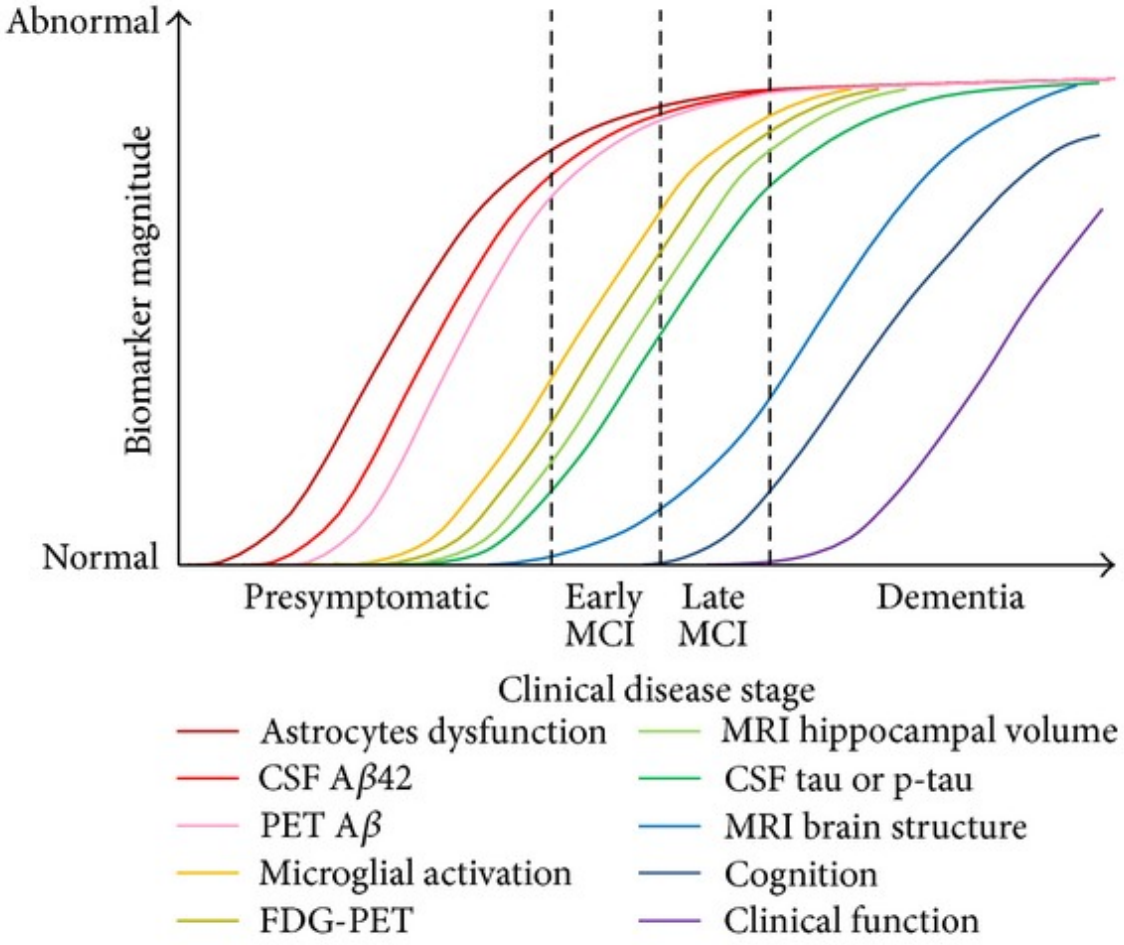
DIAN
(Dominantly Inherited Alzheimer's Network

- Observational study
- DIAN-TU: randomized drug study

Central site: Washington University in St. Louis



DIAN Study



Risacher S, Saykin AJ. Annu Rev Clin Psychol. 2013;9:621-48.

Case 1

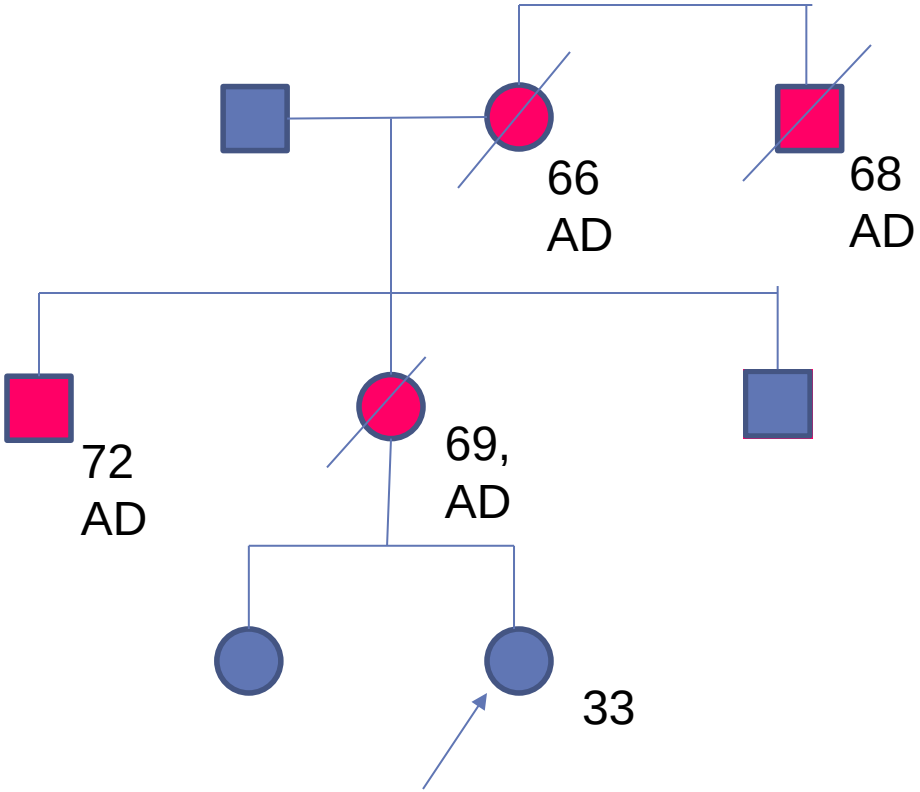
- A 44-yr-old man was referred by his neurologist so that he could have genetic testing to qualify for the DIAN-TU drug study.
- He was desperate for treatment because he had already been diagnosed with early-onset AD.
- Family hx revealed that his mother and multiple other people in the family had been affected but were not available for testing (India).

Case 1

- After counseling and a neuro. eval., blood was draw and sent for a dementia panel. With no documentation of relatives, team felt that a generalized dementia panel was appropriate.
- Results: 2 Variants of unknown significance (VUS)
  - 1 in recessive ALS genes
  - 1 in *PSEN2. Classified as conserved, amino acid change, likely pathogenic*
- Was not accepted into DIAN-TU

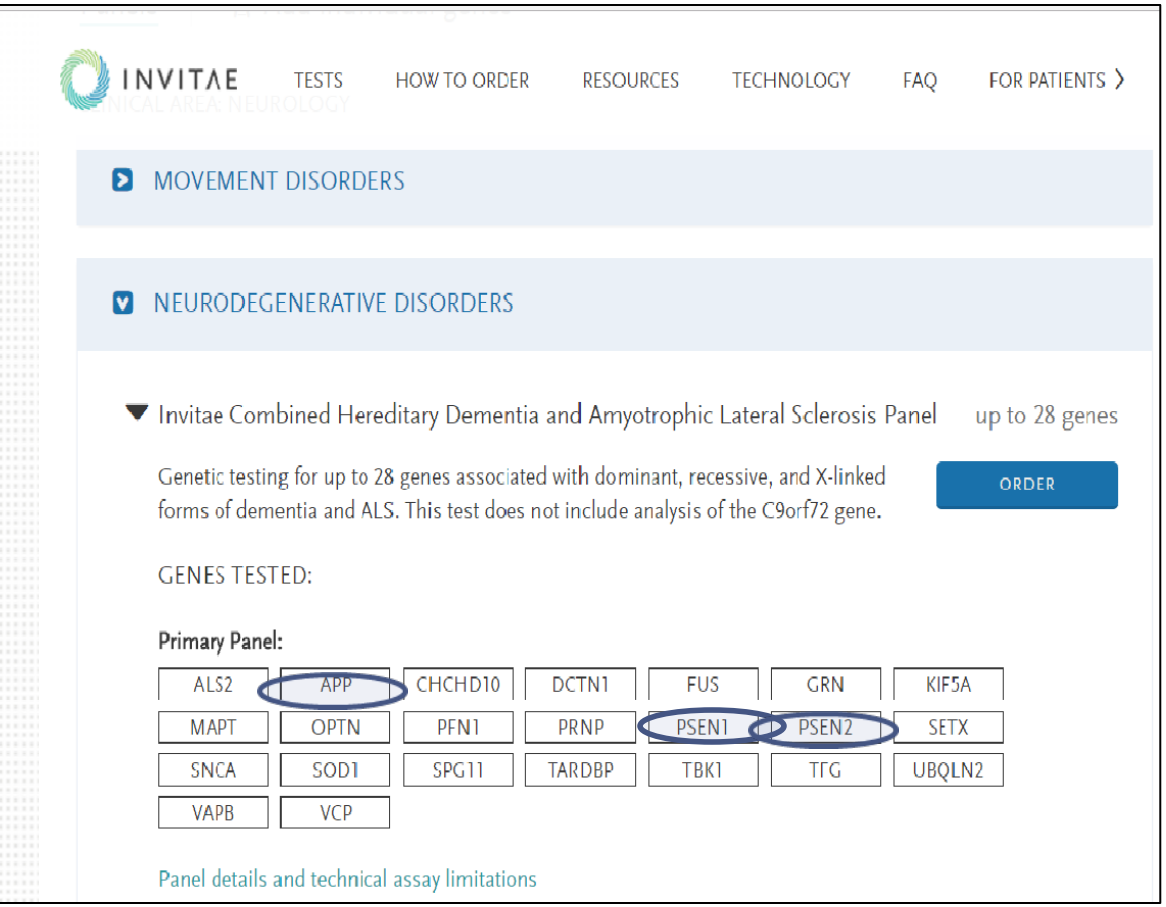
- VUS: growing problem with genetic testing

Case 2



33-yr-old woman was referred for genetic counseling by outside physician after he ran a next-gen sequencing panel for dementia. Upon speaking with her on the phone, she said she carries a mutation for AD.

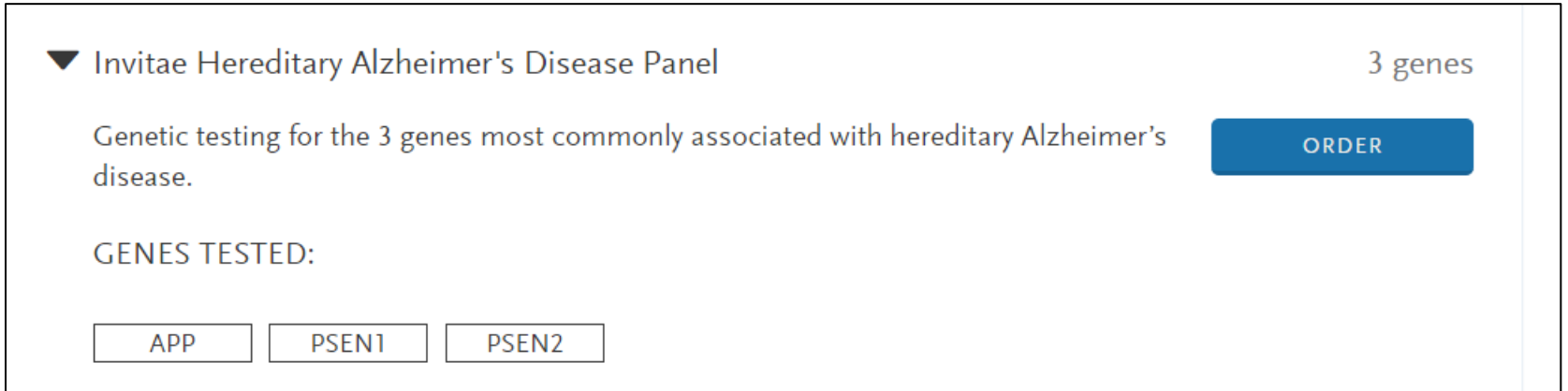
She was asked to send her test result to the genetic counselor and also see if she could obtain medical records on her relatives with AD.



What do you order?

Large panel: covers multiple conditions

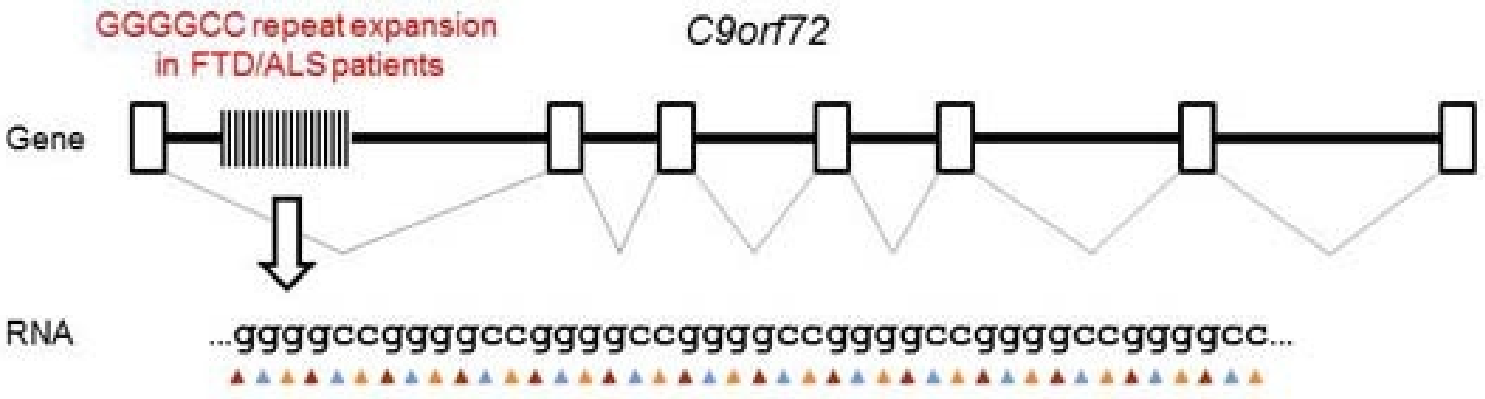
Small panel: use when sure of diagnosis



Case 2 differential dx

- AD
- FTD

Consider *C9orf72*: FTD gene which can present as a memory disorder



Hexanucleotide repeat not detected by next-gen sequencing

Case hx results

- Test results indicate 3 VUS:
  - 2 are in autosomal recessive ALS genes
  - 1 is in very rare autosomal dominant FTD/ALS gene
    - Important to clarify whether family diagnoses are probable AD
    - Would it be possible to test uncle?

- Special issues with genetic testing for dementia
  - Does person have the capacity to consent?
  - Next of kin may be at-risk relative with own agenda

❖This is why genetic counseling is necessary BEFORE testing!

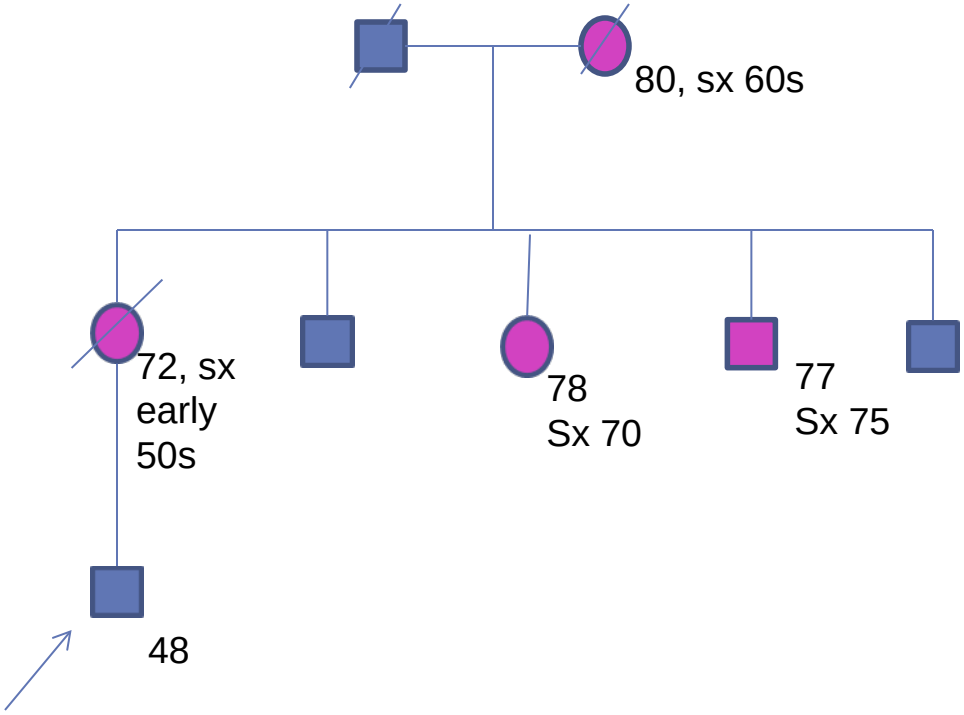
Genetic counseling and testing for DIAD

- Use modified HD protocol
  - Telephone screen: family hx, motivation, GINA
  - In person genetic counseling with support person
    - Examine family hx further
    - Education on genetics of AD
    - Anticipatory guidance
  - Psychiatric (MD) assessment
  - Consent and blood draw
  - In person results with support person

What do you need to think about?

- If I knew my genetic status, is there anything I could do to prevent or delay the disease?
- How would learning my results help or harm my life?
- With whom would I share my results?
- How would my results effect my family?

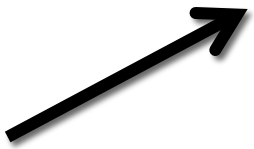
“I want testing for early-onset Alzheimer’s.”



Susceptibility Gene: APOE

The 3 ApoE alleles: ε2, ε3, & ε4

	General population	Alzheimer's Disease
ε 2	8%	4%
ε 3	78%	60%
ε 4	14%	36%



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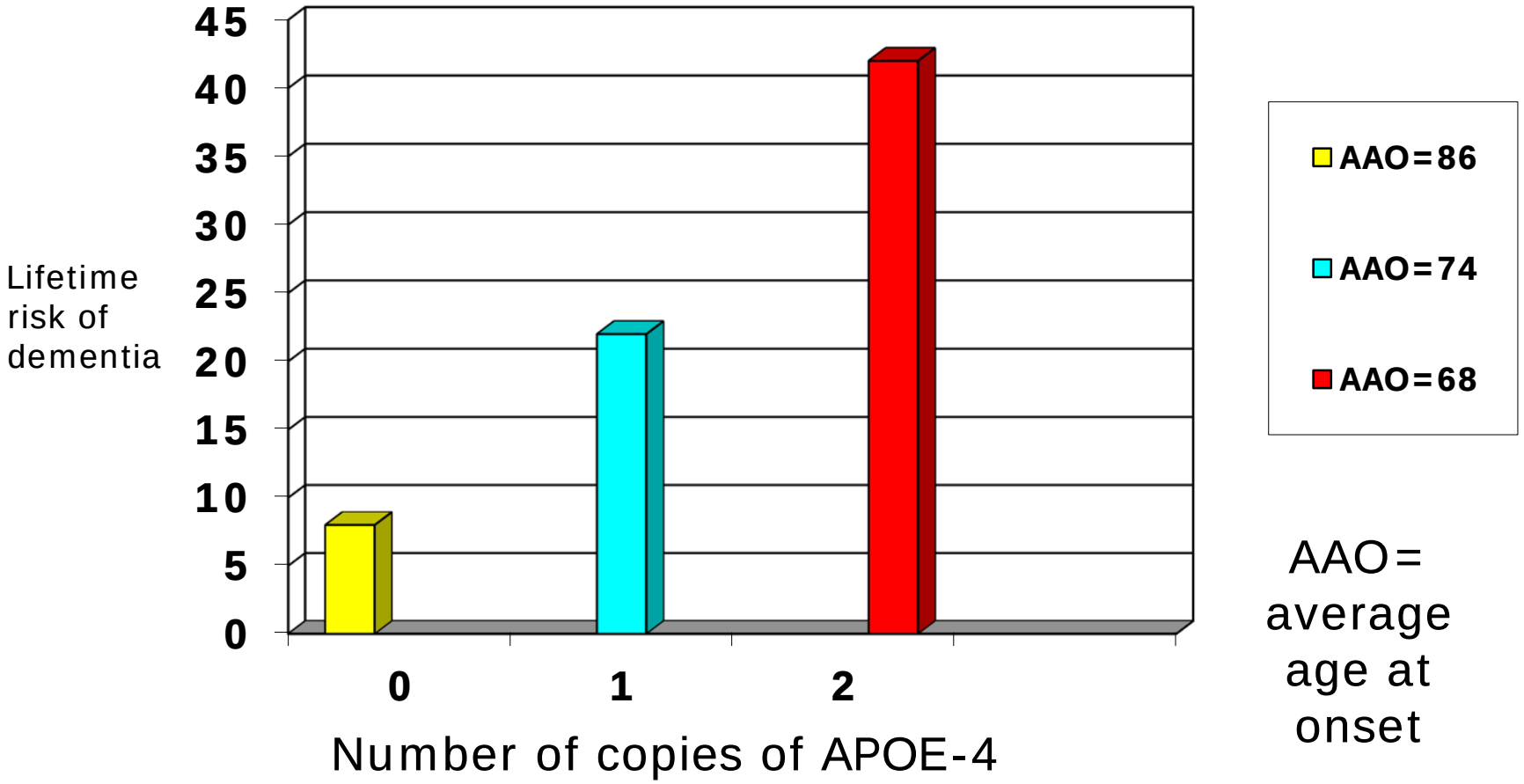
Risk and Age of Onset of AD Depends on APOE allele dosage



AAO= average age at onset

Qian et al., 2017

Pleiotropic effects of APOE

- APOE e4 associated with increased risk of coronary heart disease
- APOE e2 possible risk factor for primary macular degeneration
- How much do you say in counseling?

- REVEAL Study concluded that talking about CHD actually helps because there is something you can do about it.

APOE Testing Guidelines

- insufficient sensitivity or specificity to be used for diagnostic testing
- Neither necessary nor sufficient for the development of AD so not recommended for predictive testing

Ethnic group	Relative Risk	95% CI
Caucasians	**2.5**	[1.1-6.4]
African Americans	**1.0**	[0.6-1.6]
Hispanics	**1.1**	[0.7-1.6]

New susceptibility gene in African Americans

- *ABCA7*

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April 10, 2013, Vol 309, No. 14 >

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Original Contribution | April 10, 2013

Variants in the ATP-Binding Cassette Transporter (*ABCA7*), Apolipoprotein E ε4, and the Risk of Late-Onset Alzheimer Disease in African Americans FREE

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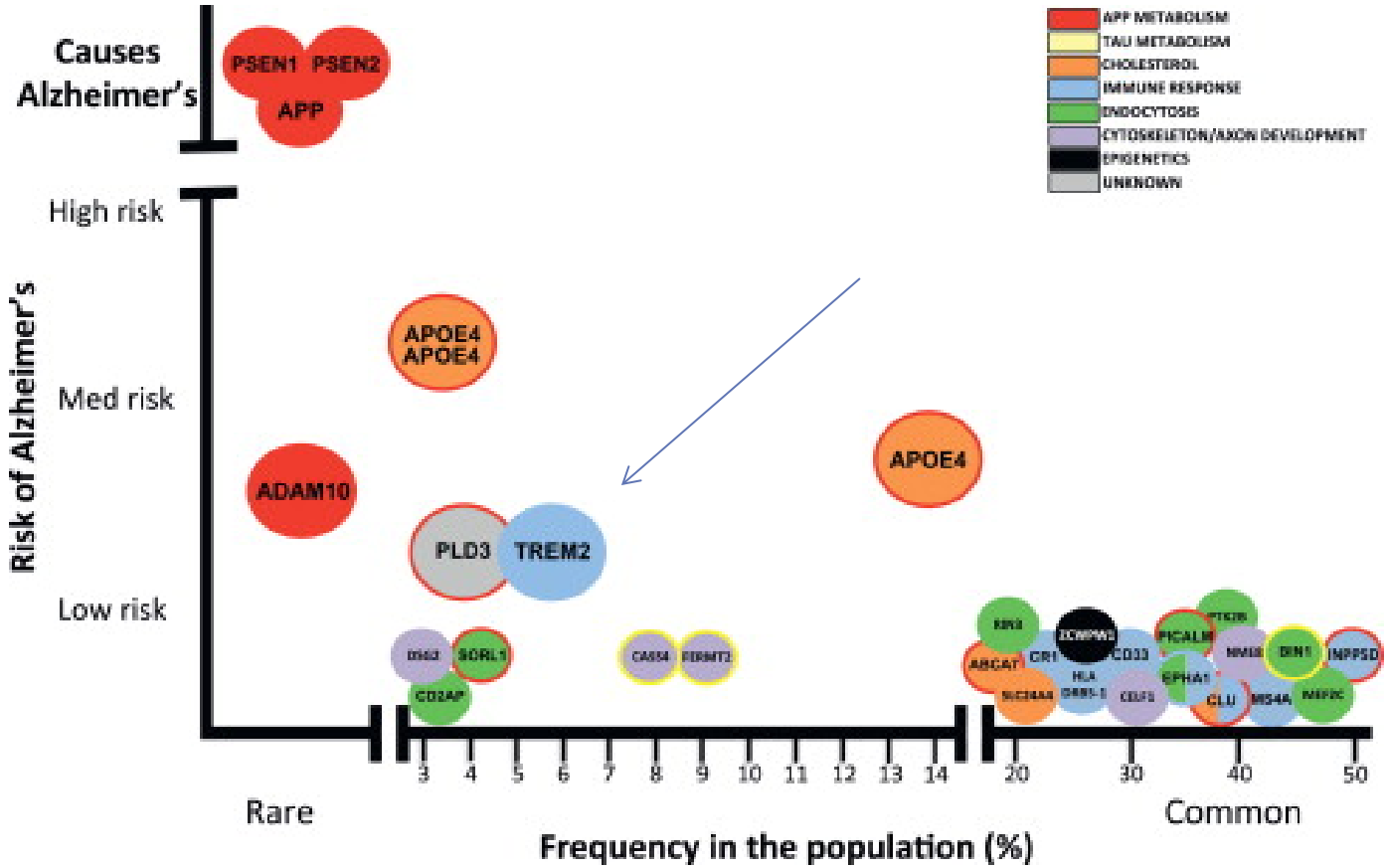
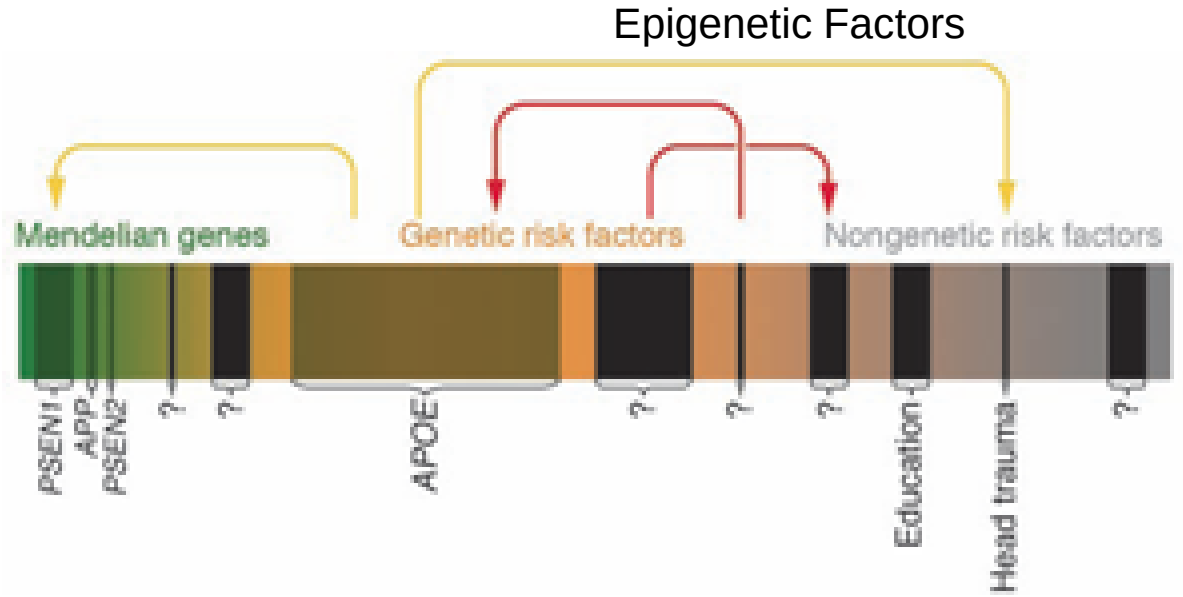


Figure 1. Rare and common variants contribute to Alzheimer's disease risk. GWAS, genome-wide associated studies.

TREM2 R47H variant also associated with increased risk for Parkinson's disease, frontotemporal dementia, and amyotrophic lateral sclerosis-is this a general risk of neurodegeneration common to all these diseases?

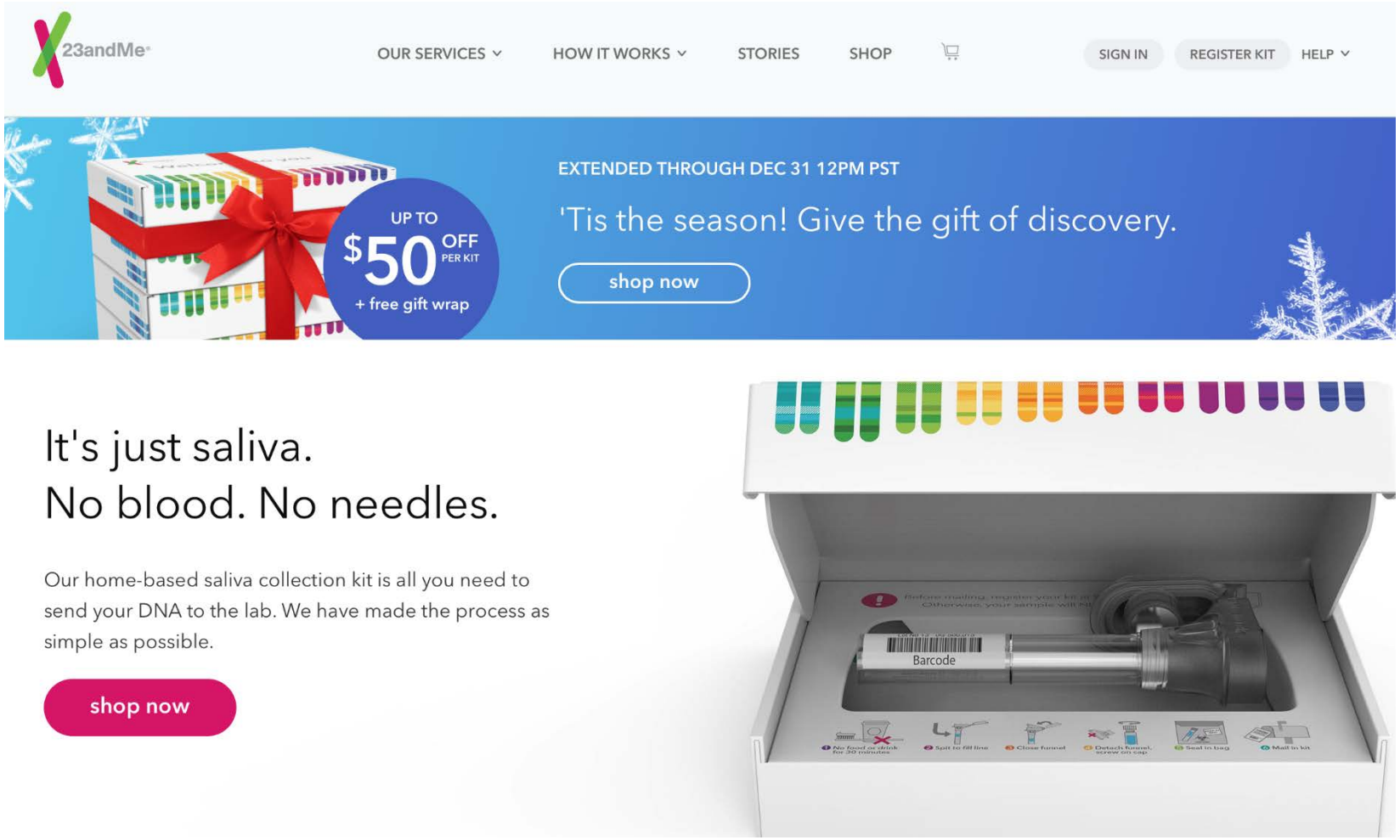
Karch CM, Goate AM. Biological Psychiatry, 2015, 77(1) :43–51

Overall Risk for AD…Multifactorial!!



Lars Bertram,L and Tanzi RE. The genetic epidemiology of neurodegenerative disease
JCI. 2005; 115(6):1449-1457

The Reality of 23andme



Wellness reports

5+ reports

Alcohol Flush Reaction
Caffeine Consumption
Deep Sleep
Genetic Weight
Lactose Intolerance
Muscle Composition
Saturated Fat and Weight
Sleep Movement

See sample report

Traits reports

15+ traits

Asparagus Odor Detection
Back Hair (available for men only)
Bald Spot (available for men only)
Bitter Taste Perception
Cheek Dimples
Cleft Chin
Earlobe Type
Earwax Type
Eye Color
Finger Length Ratio
Freckles
Hair Curliness
Light or Dark Hair
Male Hair Loss (available for men only)

Carrier Status reports*

40+ reports

ARSACS
1 variant in the SACS gene; relevant for French Canadian descent

Agenesis of the Corpus Callosum with Peripheral Neuropathy
1 variant in the SLC12A6 gene; relevant for French Canadian descent

Autosomal Recessive Polycystic Kidney Disease
3 variants in the PKHD1 gene

Beta Thalassemia and Related Hemoglobinopathies
10 variants in the HBB gene; relevant for Cypriot, Greek, Italian, Sardinian descent

Bloom Syndrome
1 variant in the BLM gene; relevant for Ashkenazi Jewish descent

Canavan Disease
3 variants in the ASPA gene; relevant for Ashkenazi Jewish descent

Congenital Disorder of Glycosylation Type 1a (PMM2-CDG)
2 variants in the PMM2 gene; relevant for Danish descent

Cystic Fibrosis
28 variants in the CFTR gene; relevant for European, Hispanic/Latino, Ashkenazi Jewish descent

D-Bifunctional Protein Deficiency
2 variants in the HSD17B4 gene

Dihydrolipoamide Dehydrogenase Deficiency
1 variant in the DLD gene; relevant for Ashkenazi Jewish descent

Familial Dysautonomia
1 variant in the IKBKAP gene; relevant for Ashkenazi Jewish descent

How To Use This Test

This test does not diagnose Alzheimer's disease or any other health conditions.

Please talk to a healthcare professional if this condition runs in your family, you think you might have this condition, or you have any concerns about your results.

Review the Genetic Health Risk tutorial

See Scientific Details

See Frequently Asked Questions

Intended Uses

- Tests for the **ε4** variant in the APOE gene.
- Identifies if someone has the ε4 variant associated with an increased risk of developing late-onset Alzheimer's disease.

Limitations

- Does **not** include all possible variants or genes associated with late-onset Alzheimer's disease.
- Does **not** include any variants or genes linked to early-onset Alzheimer's disease.
- Does **not** determine a person's full APOE genotype.

Important Ethnicities

- The ε4 variant included in this test is found and has been studied in many ethnicities. Detailed risk estimates have been studied the most in people of **European** descent.

The New York Times

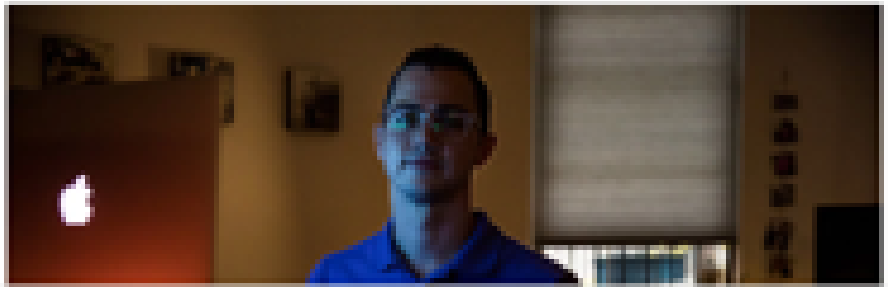
Opinion

23andMe Said He Would Lose His Mind. Ancestry Said the Opposite. Which Was Right?

By Laura Hercher

Ms. Hercher is a genetic counselor.

Sept. 15, 2019



Story

- Matt Fender, age 32, IT coder
- Decided to do 23andMe because his sister had died of a pulmonary embolism at age 23
- Found out that he was ApoE 4/4 which put him at risk for Alzheimer’s disease
- Wanted to find out ways that he could stave off AD so tried to talk with doctor who wasn’t helpful

Story continued

- Then decided to have raw data analyzed in Prometheus and discovered a *PSEN1* mutation
- Contacted me by email
- I called him back and talked about having CLIA testing and the protocol that we would do prior to testing.
- He said that he already sent a 2nd sample to Ancestry and would wait till it came back

Story conclusion

- Ancestry result negative
- Resent 23andMe which again showed mutation
- Eventually convinced doctor to test him
- CLIA testing negative

Bottom line

- Encourage patients to get genetic counseling BEFORE and testing (even DTC)
- Examine family history to determine probable risk
- Do not assume reported family hx has correct dx-get med records if possible
- Consider which genes should be tested for differential dx
- When ordering testing, make sure that lab tests for all possible disease-associated genes for AD and other possible dementias (consider *C9orf72*) and performs duplication/deletion analysis
- Discourage *APOE* testing
- Refer for research

How do you help people who test positive?

- Refer to research:
  - DIAN for DIAD
  - Generation study for APOE4 carriers
    - ≥ 65

Generation Program
ALZHEIMER'S PREVENTION INITIATIVE

Cornell researchers to launch early trial of gene therapy aimed — ultimately — at preventing Alzheimer's

- Support groups
- Psychiatric referral as needed

- What's good for the

is good for the