A Family Matter: Genetics & Alzheimer's Disease

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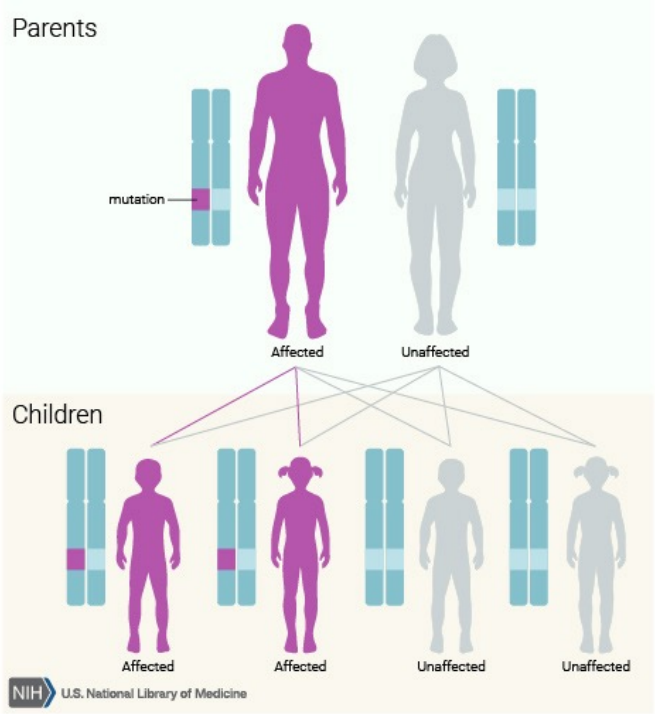
The first case of Alzheimer's disease

Auguste Deter was first seen by Dr. Alois Alzheimer when she was 51.

Dr. Alzheimer reported Auguste had a "peculiar disorder of the cerebral cortex" and admitted her to his hospital unit due to her substantial forgetfulness and hallucinations.

Dementia progressed rapidly and she died 5 years later, in 1906, at age 56.

Hereditary (autosomal dominant) Alzheimer's disease



A parent with an autosomal dominant Alzheimer's causing gene has a **50%** chance of passing down the mutated gene to their biological child

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Genes involved in autosomal dominant Alzheimer's

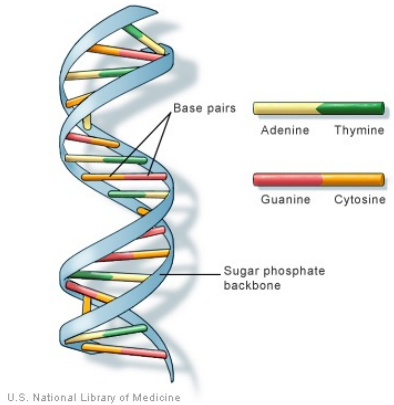
Gene	Chromosome	# of mutations*
PSEN1	14	150
PSEN2	1	11
APP	21	50

Source: https://ghr.nlm.nih.gov/gene/

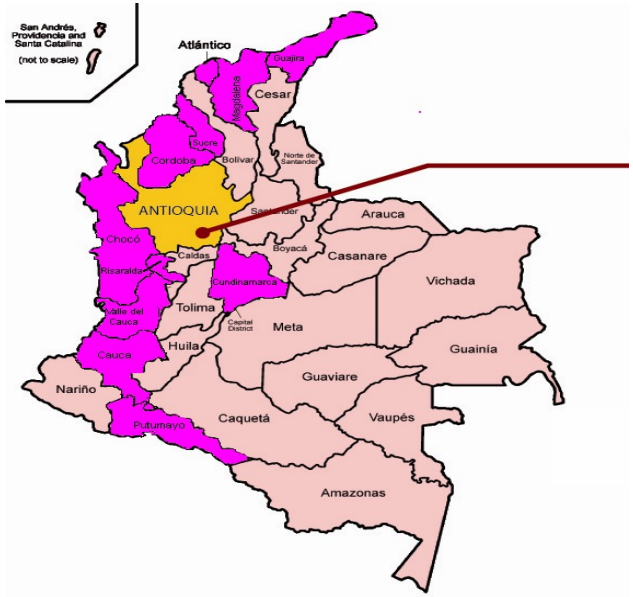
Nearly all these mutations lead to the overproduction of a longer, toxic version of amyloid-β peptide. Copies of this protein fragment stick together and build up in the brain, forming clumps called amyloid plaques that are a characteristic feature of Alzheimer disease. A buildup of toxic amyloid-β peptide and the formation of amyloid plaques likely lead to the death of neurons and the progressive signs and symptoms of this disorder.

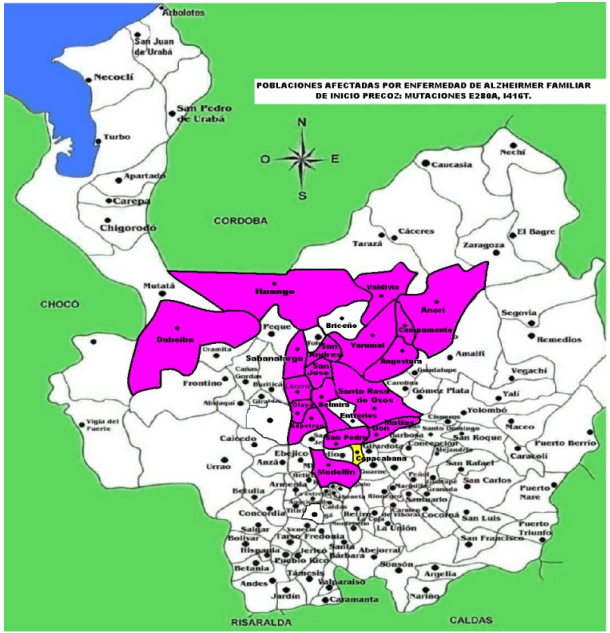
Genetics and Alzheimer's

- **Alzheimer's disease-causing genetic mutations**
  - *PSEN1, PSEN2 & APP*
- **Alzheimer's disease protective genetic mutations**
  - *A673T (on APP gene)*
- **Alzheimer's disease susceptibility genes**
  - *APOE ε4 allele*
  - *Trisomy 21*
  - *Others*



Colombia: Home to World's Largest ADAD Population





E280A

I416T

P117A

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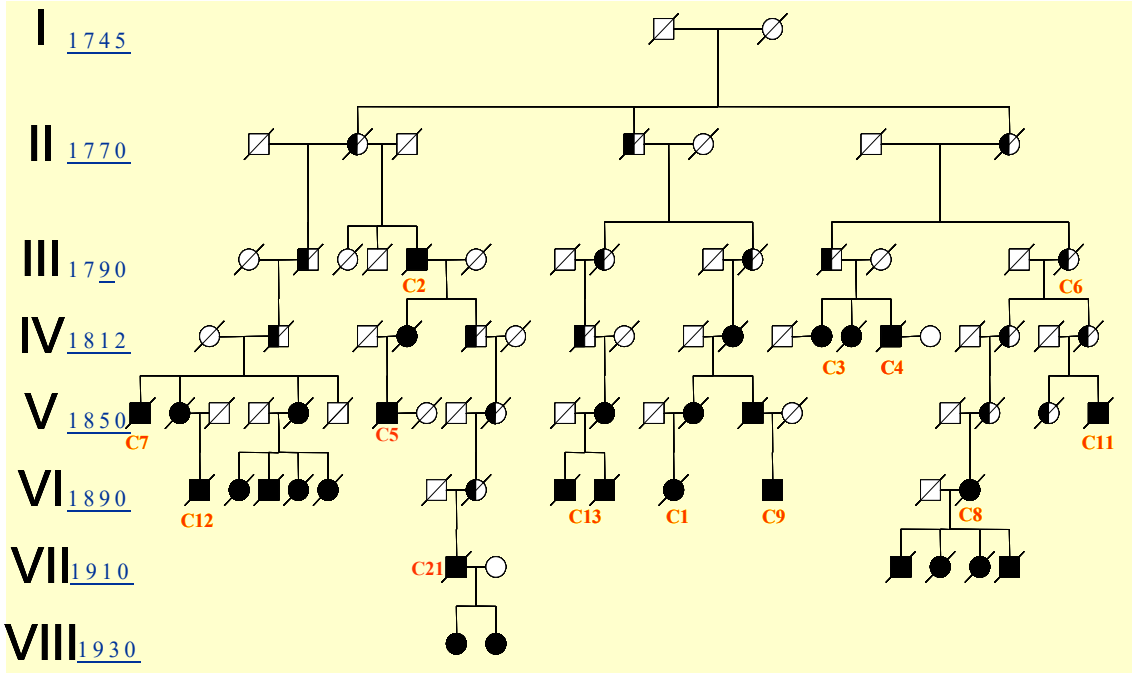
Founder effect and common ancestry of 14 families



Individual II 1: originates families C2, C5, C7, C12, C21
Individual II 2: originates families C1, C9, C13
Individual II 3: originates families C3, C4, C6, C8, C11

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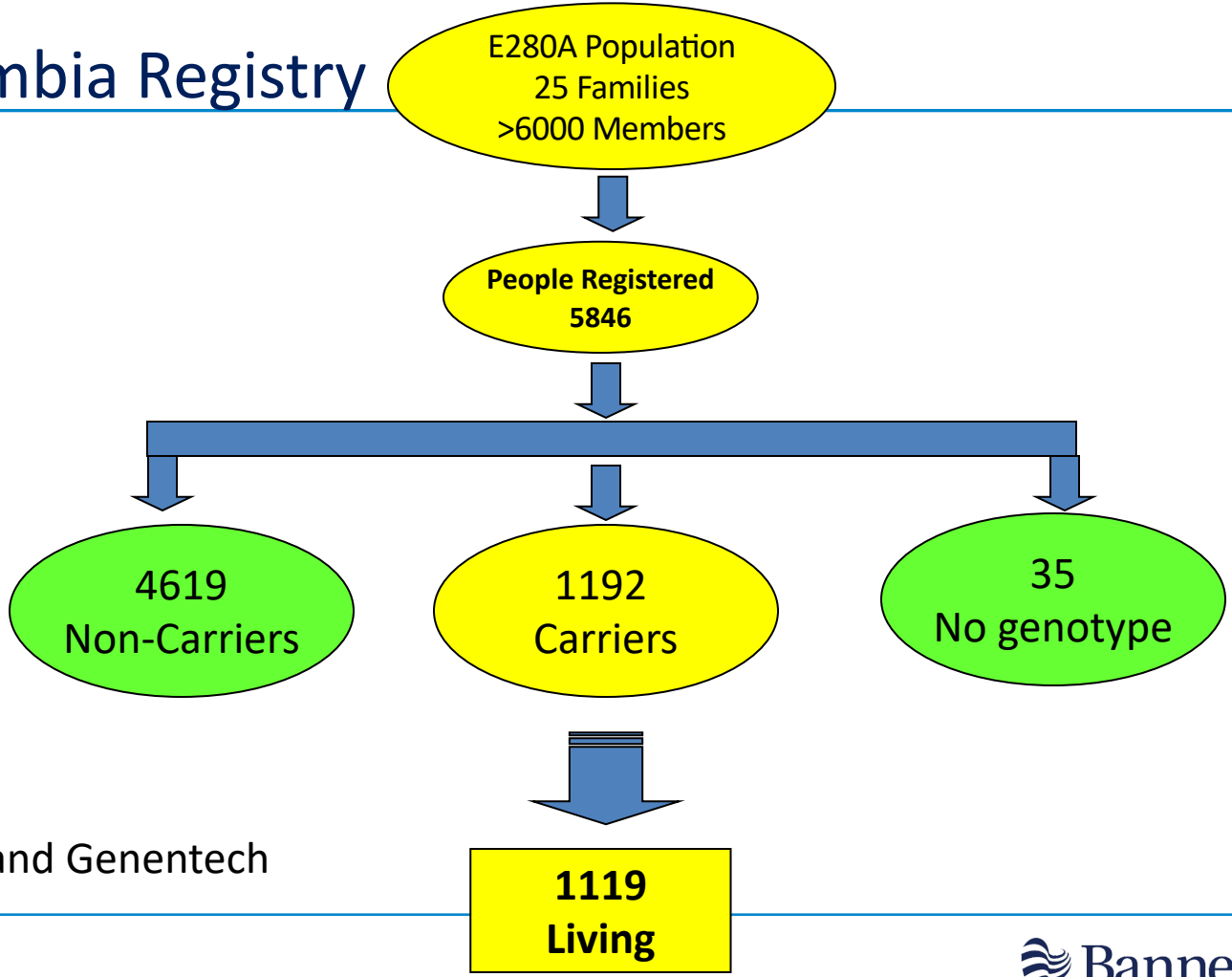
Field work to identify the families

API Colombia Registry



GNA, Banner and Genentech

GNA: Neuroscience Group of Antioquia

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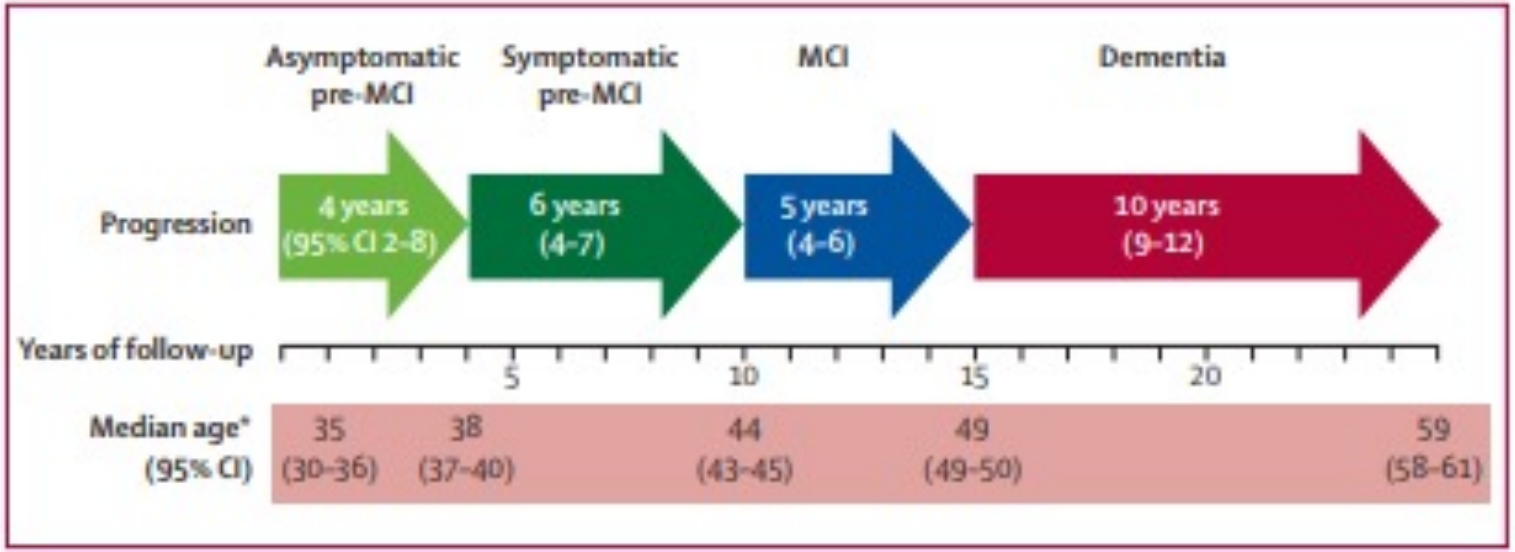
Progression of Disease in *PSEN1* E280A Carriers



Acosta-Baena et al, Lancet Neurol 2011

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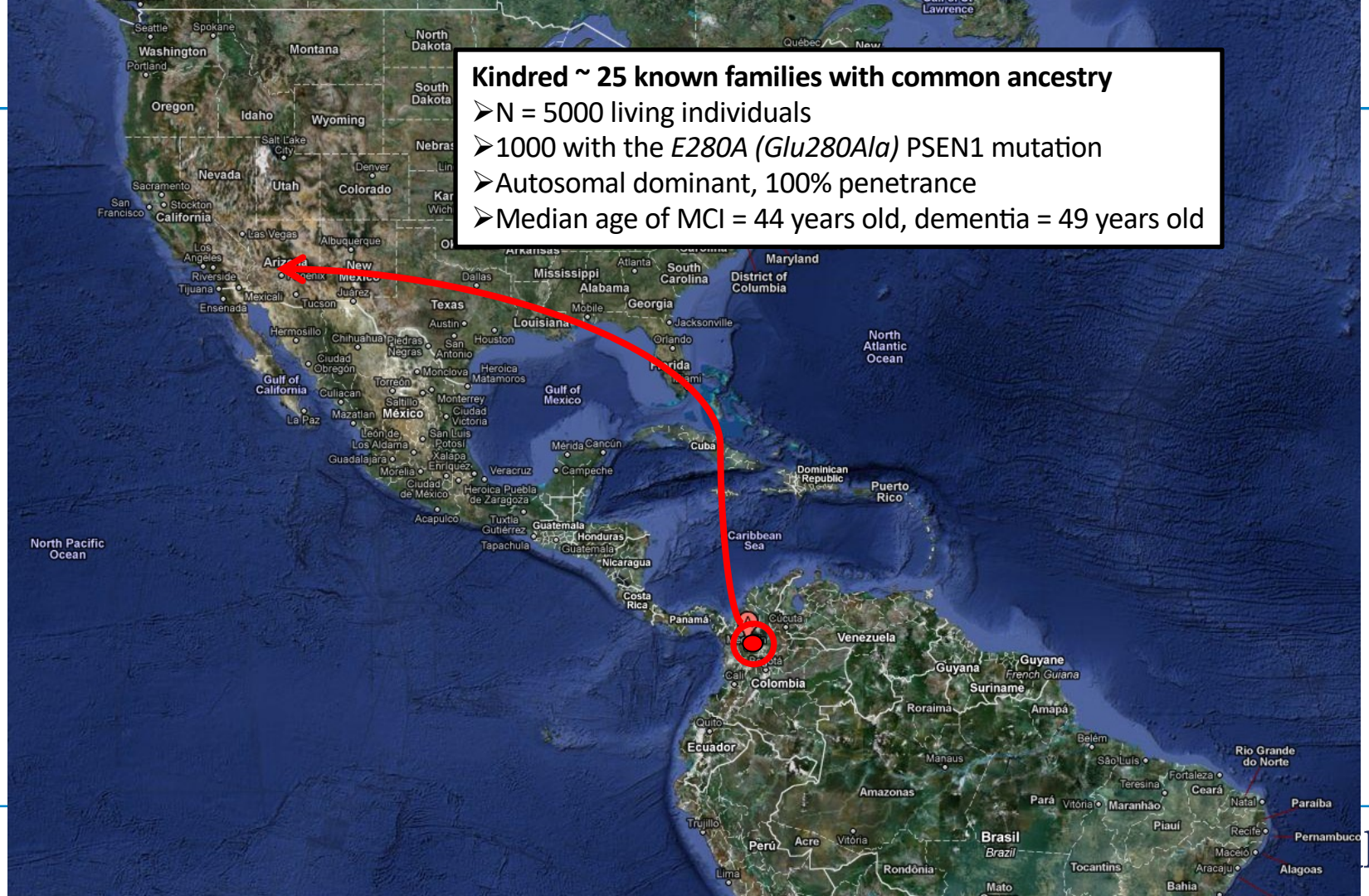
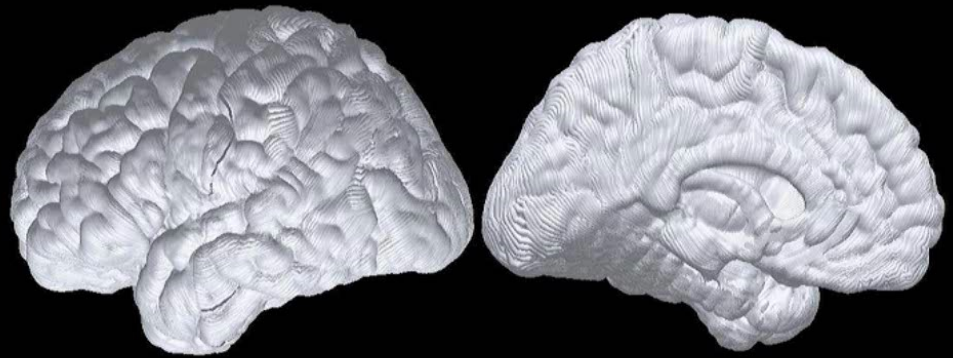
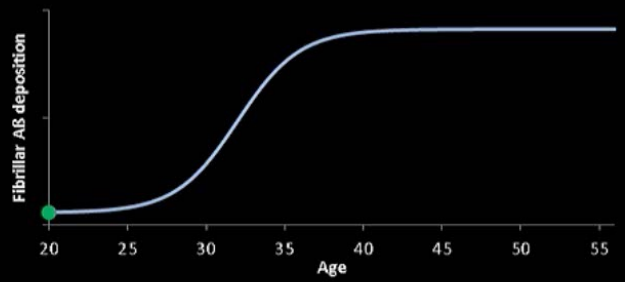
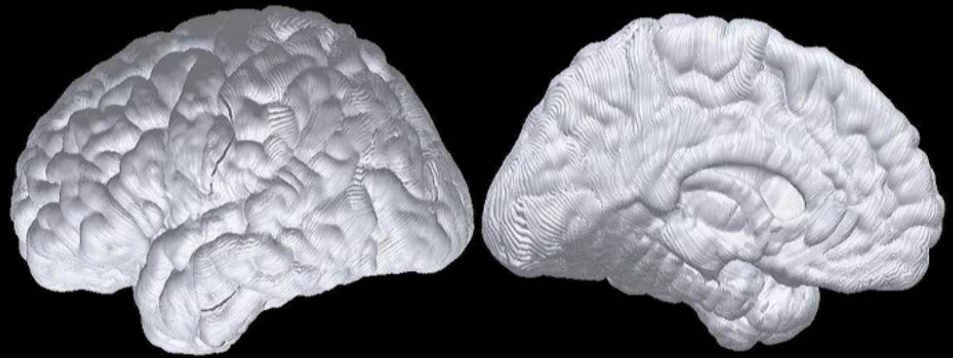

Kindred ~ 25 known families with common ancestry
➢N = 5000 living individuals
➢1000 with the *E280A (Glu280Ala)* PSEN1 mutation
➢Autosomal dominant, 100% penetrance
➢Median age of MCI = 44 years old, dementia = 49 years old
North Pacific Ocean
North Atlantic Ocean
Caribbean Sea
Gulf of Mexico
Gulf of California
Washington
Oregon
California
Nevada
Idaho
Montana
Wyoming
Utah
Colorado
Arizona
New Mexico
Texas
Louisiana
Mississippi
Alabama
Georgia
South Carolina
Maryland
District of Columbia
México
Cuba
Dominican Republic
Puerto Rico
Guatemala
Honduras
Nicaragua
Costa Rica
Panamá
Venezuela
Colombia
Ecuador
Perú
Brasil
Brazil
Guyane
Guyana
French Guiana
Suriname
Roraima
Amapá
Amazonas
Pará
Maranhão
Piauí
Ceará
Rio Grande do Norte
Paraíba
Pernambuco
Alagoas
Tocantins
Rondônia
Acre
Bahia
Seattle
Spokane
Portland
Sacramento
San Francisco
Stockton
Los Angeles
Riverside
Las Vegas
Albuquerque
Tijuana
Mexicali
Ensenada
Tucson
Juárez
Hermosillo
Chihuahua
Ciudad Obregón
Culiacan
Mazatlan
La Paz
Monterrey
Saltillo
Torreón
Piedras Negras
San Antonio
Houston
Austin
Dallas
Atlanta
Mobile
Jacksonville
Orlando
Miami
Heroica Matamoros
Ciudad Victoria
San Luis Potosí
León de los Aldama
Guadalajara
Morelia
Veracruz
Campeche
Mérida
Cancún
Ciudad de México
Heroica Puebla de Zaragoza
Acapulco
Tuxtla Gutiérrez
Tapachula
Cucuta
Call
Quito
Manaus
Belém
São Luís
Fortaleza
Teresina
Natal
Recife
Maceió
Aracaju
Vitória
Trujillo
Lima
Mato
Denver
Salt Lake City
Nebraska
South Dakota
North Dakota
Québec
Lawrence



25 years before kindred's median age at clinical onset

mutation carriers, healthy





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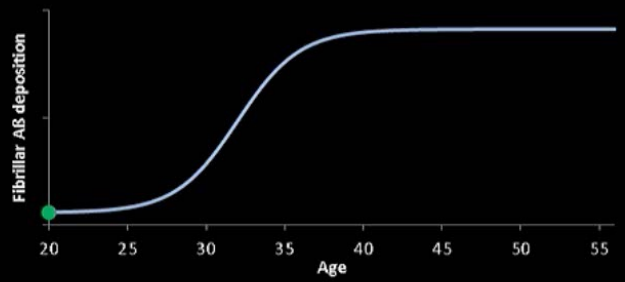

Rationale for Launching the API Program in 2008

- The public health need
- A “preclinical stage” of Alzheimer’s disease exists during which silent brain changes occur
- We had plausible experimental therapies
- We had biomarkers of Alzheimer’s disease progression
- We needed to develop improved cognitive/clinical endpoints
- Earlier treatment may have a better chance to slow the progression of the disease

Reiman et al., 2010 *Biomarkers Med*

API ADAD Trial: “A top 10 world changing idea”

Early Treatment for Alzheimer's

A drug trial of 300 Colombians could reveal a way to prevent the disease from ever starting

Alzheimer's disease remains virtually untreatable. More than 100 experimental drugs have failed to halt the condition that robs people of their memories, their relationships and, ultimately, their identity. Now scientists will be testing a new strategy for preventing this horrific condition from starting in the first place. Just as healthy people take statins to lower their cholesterol and avoid heart disease, people at risk for Alzheimer's could conceivably pop pills to keep the disease at bay.

Researchers will be investigating a drug that flushes away an intrusive protein called amyloid, suspected as a primary contributor to Alzheimer's. Until recently, amyloid clumps could only be seen by dissecting the brain after death. Yet advanced positron-emission tomography scans of living people's brains, a recent innovation, show that by the time symptoms appear, amyloid has been silently accumulating for up to 20 years. Perhaps by then the brain is irreversibly damaged, making any drug useless. No one knows for sure, however, whether amyloid causes Alzheimer's or is merely a by-product of the disease. The new study may provide an answer to this mystery.

Set to start early in 2013 if all approvals are granted, the investigation will involve 300 members of distantly related families in Colombia whose rare and particularly devastating form of Alzheimer's strikes in the prime of life. By their 50s and 60s, many are as helpless as infants. Normally it is impossible to predict who will

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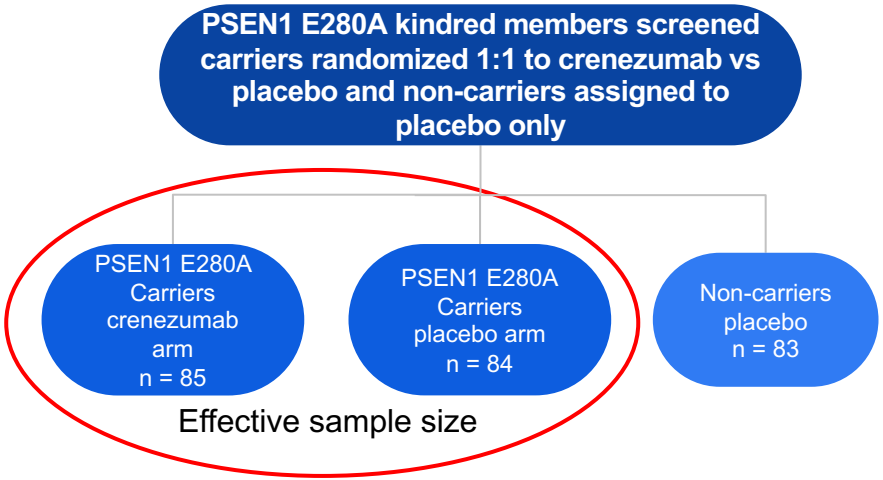
Study design and inclusion/exclusion criteria

ADAD Colombia Trial
ALZHEIMER'S PREVENTION INITIATIVE



Key Inclusion/Exclusion Criteria

Inclusion	Exclusion
• Member of PSEN1 E280A kindred	• Sig medical, neurologic, or psychiatric condition
• 30-60 years old	• Body weight < 45 or > 120 kg
• Does not meet criteria for MCI or dementia	• Medications that impair cognition
• MMSE ≥ 24 (< 9 yrs educ) or ≥ 26 (≥ 9 yrs educ)	• Strokes, ARIA-E or >4 microhemorrhages
• Study partner	• Pregnancy

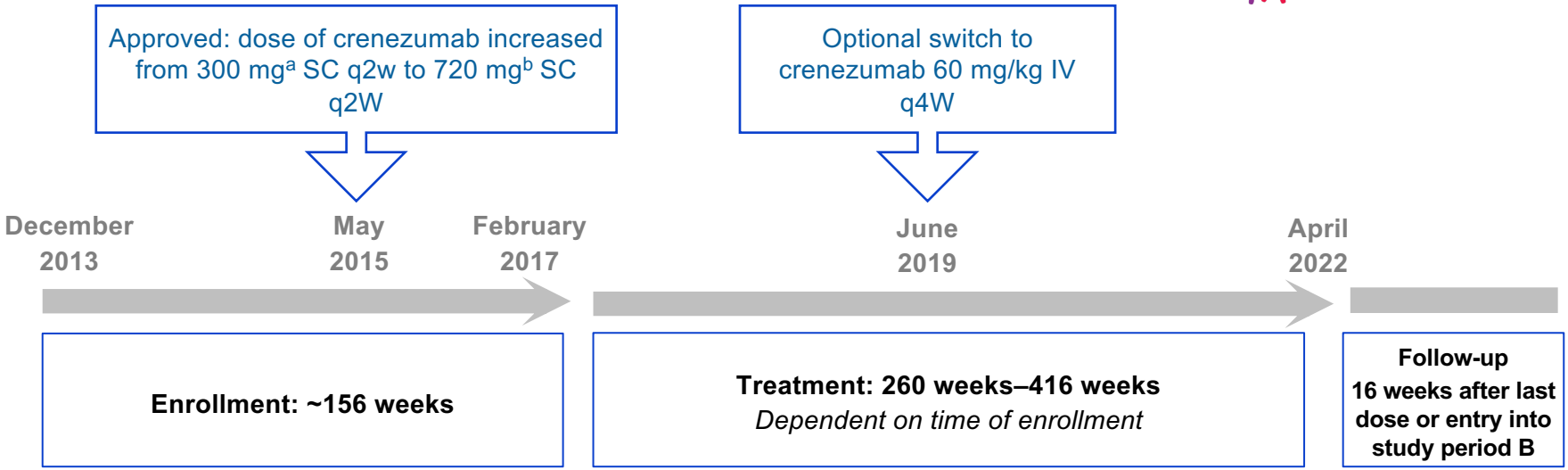
Study Duration	5-8 years in the double-blind study period A (common-close design; all participants stay on treatment until the last randomized participant reaches 5 years (w260))
Treatment	Crenezumab vs placebo (720 mg* SC q2w or 60 mg/kg IV q4w)
Primary Outcome Family	Annualized rate of change in (1) API ADAD composite score and (2) episodic memory assessed by the Free and Cued Selective Reminding Test (FCSRT) cueing index (both outcomes assessed every 6 months)
Key Secondary Outcomes	Amyloid PET SUVr –> Time to MCI/dementia due to AD –> CDR-SB –> Time to non-zero in CDR-GS –> RBANS total score

* initially 300 mg; see next slide

AD, Alzheimer's disease; ADAD, autosomal dominant Alzheimer's disease; API, Alzheimer's Prevention Initiative ARIA-E, amyloid-related imaging abnormalities-edema; CDR-GS, Clinical Dementia Rating – Global Score; CDR-SB, Clinical Dementia Rating – Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Evaluation; PET, positron emission tomography; PSEN1, presenilin-1; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SUVr, standard uptake value ratio; q2w, every two weeks; q4w, every four weeks.

Protocol evolution to meet emerging science

ADAD Colombia Trial
ALZHEIMER'S PREVENTION INITIATIVE



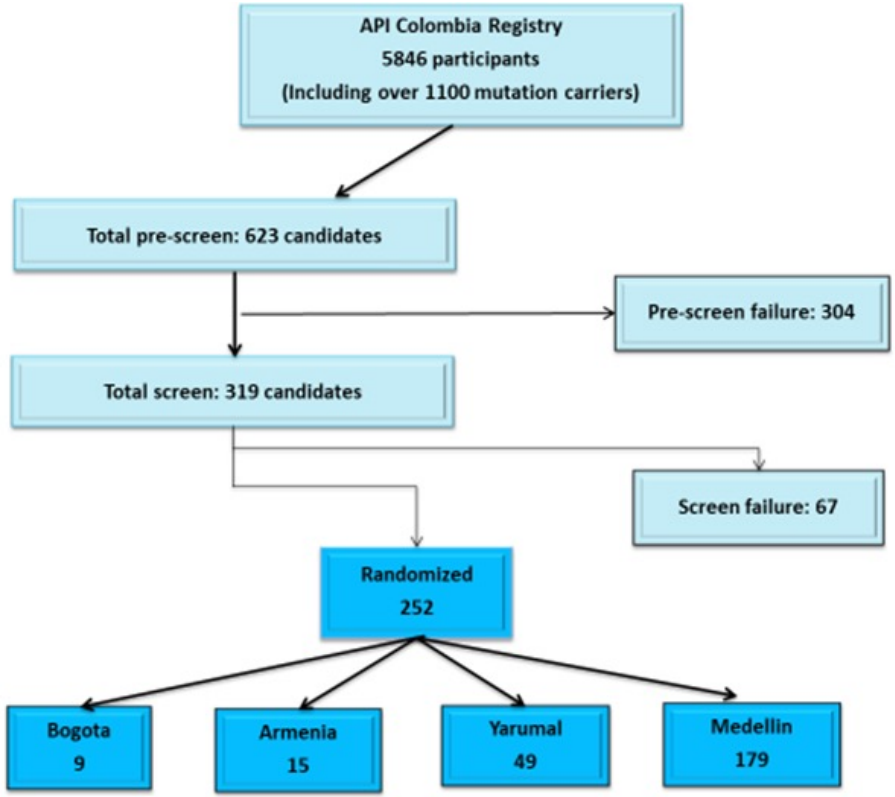
The evolving science of AD led to modifications to the API trial where the dose of crenezumab increased more than 7-fold over the duration of the study, from 300 mg every 2 weeks to ~4200 mg[c] a month

[a]2 x 1 mL SC injections; [b]2 x 2.2 mL SC injections; [c]60 mg/kg is equivalent to 4200 mg for an average 70 kg person.
AD, Alzheimer's disease; ADAD, autosomal dominant Alzheimer's disease; API, Alzheimer's Prevention Initiative; IV, intravenous; q2W, every two weeks; q4W, every 4 weeks; SC, subcutaneous.

Pre-screening and screening of the API Colombia participant recruitment

ADAD Colombia Trial
ALZHEIMER'S PREVENTION INITIATIVE

- Launched in December 2013
- Last randomization in February 2017



API, Alzheimer's Prevention Initiative
Rios-Romenets S, Lopera F et al. Alzheimers Dement. 2020;16:1023–30.

Baseline characteristics

Baseline characteristics were generally well balanced across the arms

ADAD Colombia Trial
ALZHEIMER'S PREVENTION INITIATIVE

	Crenezumab - Carrier (n = 85)	Placebo - Carrier (n = 84)	Placebo - Non-carrier (n = 83)
Age, mean (SD)*	36.8 (5.3)	36.9 (6.3)	43.3 (7.2)
Female sex	51.8%	70.2%	68.7%
Education >=9 years*	56.5%	56.0%	45.8%
>=1 APOE4 allele*	22.4%	20.2%	22.9%
CDR-GS=0*	90.6%	88.1%	94.0%
CDR-SB, mean (SD)	0.16 (0.38)	0.14 (0.43)	0.05 (0.17)
API Composite, mean (SD)	81.9 (8.8)	80.4 (11.3)	83.7 (9.8)
FCSRT CI, mean (SD)	0.78 (0.16)	0.76 (0.20)	0.83 (0.14)
MMSE Total Score, mean (SD)	28.9 (1.3)	28.8 (1.5)	29.2 (1.0)
NPI, mean (SD)	0.26 (0.89)	0.64 (2.16)	0.37 (1.95)
FAST, mean (SD)	1.09 (0.29)	1.13 (0.37)	1.01 (0.11)
^Amyloid PET Positive, Amyloid PET SUVr, mean (SD)	61.2% 1.15 (0.15)	48.8% 1.11 (0.12)	0 0.96 (0.04)

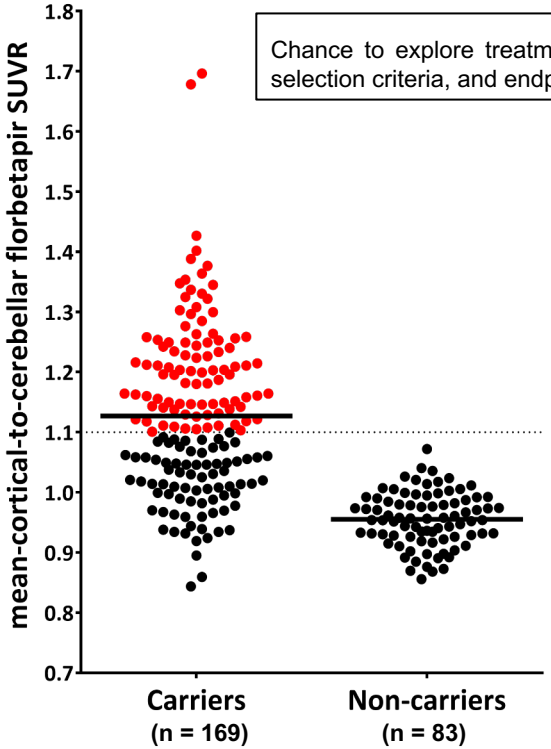
Data on file. *stratification variables, ^Whole cerebellum used as the reference region; threshold > 1.1 defined as positive

API, Alzheimer's Prevention Initiative; APOE4, apolipoprotein E4; CDR-GS, Clinical Dementia Rating – Global Score; CDR-SB, Clinical Dementia Rating – Sum of Boxes; FAST, Functional Assessment Staging Tool; FCRST, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Evaluation; NPI, Neuropsychiatric Inventory; PET, positron emission tomography; SD, standard deviation; SUVr, standard uptake value ratio.

Baseline Aβ PET measurements

ADAD Colombia Trial
ALZHEIMER'S PREVENTION INITIATIVE

Chance to explore treatment effects in A+ and A- carriers and inform the design, size, selection criteria, and endpoints in future secondary and primary prevention trials



55% A+ and 45% A- using a 1.10 SUVR (24.3 Centiloid) Threshold

Aβ, amyloid-beta; AD, Alzheimer's disease; PET, positron emission tomography; SUVR, standard uptake value ratio.

Participant disposition

Excellent adherence and retention rates over 8-year study

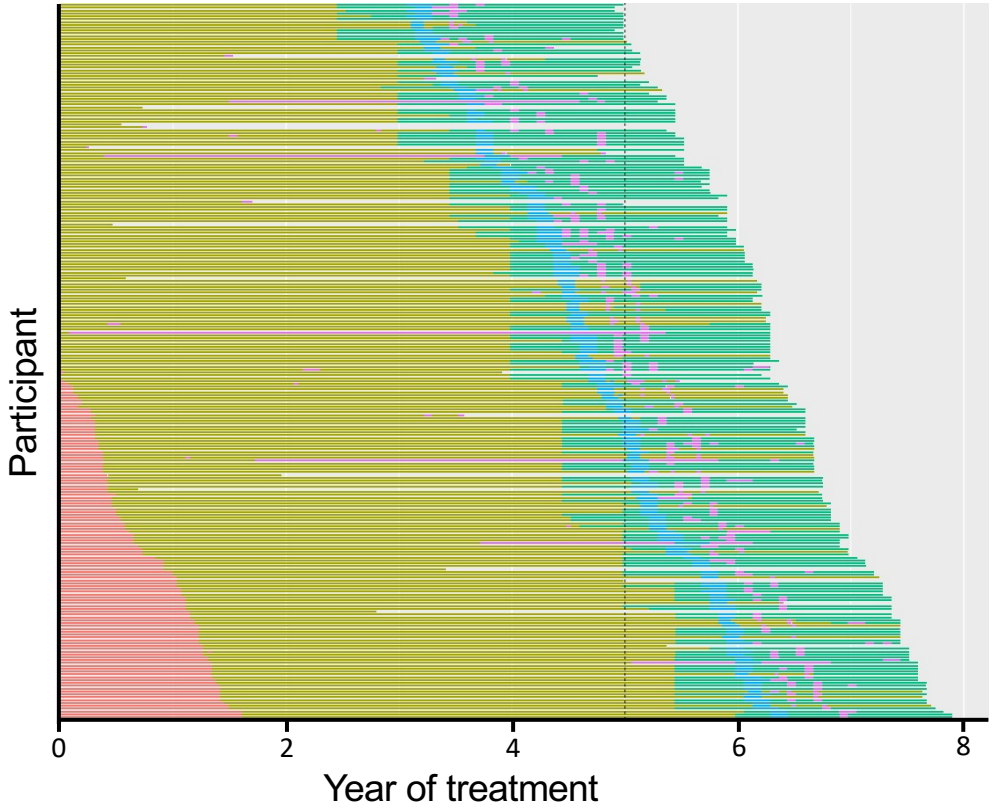
ADAD Colombia Trial
ALZHEIMER'S PREVENTION INITIATIVE

	Crenezumab - Carrier (n = 85)	Placebo - Carrier (n = 84)	Placebo - Non-carrier (n = 83)	All Participants (N = 252)
Completed study period A	**79 (92.9%)**	**78 (92.9%)**	**80 (96.4%)**	237 (94.0%)
Completed treatment in period A	**76 (89.4%)**	**75 (89.3%)**	**77 (92.8%)**	228 (90.5%)

The primary reason for treatment discontinuation was participant decision (n = 12)

Treatment exposure

Mean 6.1 years of treatment, up to 7.9 years, low impact of COVID-19



- Average SC treatment duration 4.3 years
- Average IV treatment duration 2 years
- Average SC dose intensity 99%
- Average IV dose intensity 88%

SC 300 mg
SC 720 mg
IV 60 mg/kg
MISSING DUE TO COVID-19 SITE CLOSURE
MISSING

ADAD Colombia Trial
ALZHEIMER'S PREVENTION INITIATIVE

All participants including both carriers and non-carriers who received at least 1 dose of study drug are included in this plot. IV, intravenous; SC subcutaneous.

Main outcomes

ADAD Colombia Trial
ALZHEIMER'S PREVENTION INITIATIVE

- Analyzed using random coefficient regression model (RCRM)[1] in mutation carriers receiving at least 1 dose of study drug
  - Provides a simple and holistic measure of average clinical benefit over full duration of trial
- **Dual primary outcomes**
  - API ADAD Composite Test total score assessing overall cognitive function (α=0.04) **and/or**
  - Free and Cued Selective Reminding Task (FCSRT) Cueing Index assessing episodic memory (α=0.01)
  - Trial positive if either or both were significant
- **Key secondary outcomes**
  - Amyloid PET SUVr
  - Time to MCI or dementia due to AD
  - Change in Clinical Dementia Rating Sum of Boxes (CDR-SB)
  - Time to CDR Global >0
  - RBANS Total Score

The RCRM adjusts for age, education, APOE4 and CDR-GS at baseline and adjusts for treatment assignment for slope; both random intercept and slope terms are added to the model.
AD, Alzheimer's disease; ADAD, autosomal dominant Alzheimer's disease; API, Alzheimer's disease; APOE4, apolipoprotein E4; CDR-GS, Clinical Dementia Rating – Global Score; CDR-SB, Clinical Dementia Rating – Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; MCI, mild cognitive impairment; PET, positron emission tomography; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RCRM, random coefficient regression model ; SUVr, standard uptake value ratio.
1. Hu N, et al. Biom J. 2021;63:806–24.

Results for primary outcomes

Mutation carriers only

ADAD Colombia Trial
ALZHEIMER'S PREVENTION INITIATIVE

	API Composite (Range 0 – 100)		**FCSRT Cueing Index (Range 0 – 1)**	
	Crenezumab (n = 84)	Placebo (n = 84)	Crenezumab (n = 84)	Placebo (n = 84)
Annualized rate of change (SE) points per year	-1.10 (0.29)	-1.43 (0.29)	-0.03 (0.004)	-0.04 (0.004)
Difference in annualized rate of change, 95% CI	0.33, (-0.48, 1.13)		0.008, (-0.003, 0.019)	
P-value	**0.43**		**0.16**	
Relative reduction, 95% CI*	22.9%, (-53.1%, 61.1%)		19.9%, (-9.3%, 42.2%)	

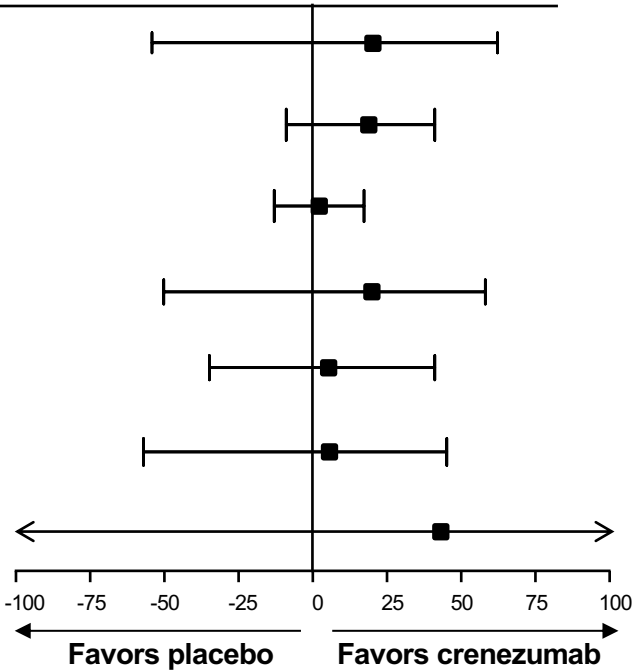
API, Alzheimer's Prevention Initiative; CI, confidence interval; FCSRT, Free and Cued Selective Reminding Task; SE, standard error.
*95% CI for relative reduction is based on the bootstrap method with replacement.

Dual primary and key secondary outcomes

ADAD Colombia Trial
ALZHEIMER'S PREVENTION INITIATIVE

Results numerically favor crenezumab across primary and secondary outcomes in relative reduction scale

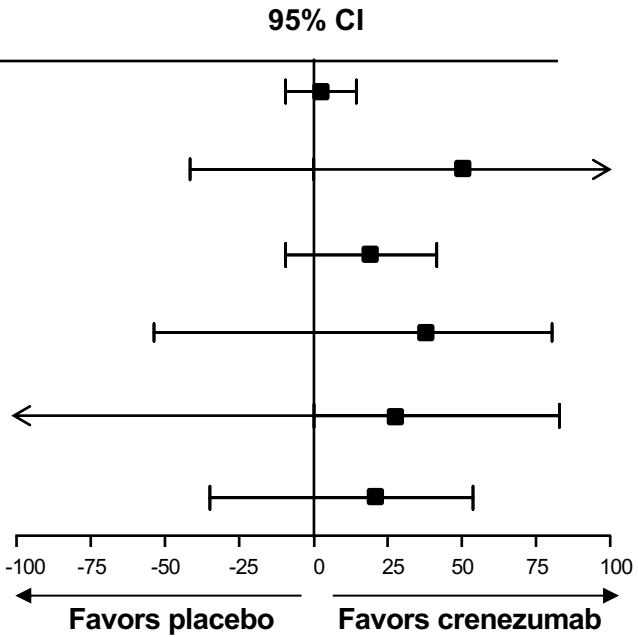
Endpoint	Carrier	Relative Effect	P value*
API ADAD Composite	168	22.9%	0.43
FCSRT Cueing Index	168	19.9%	0.16
Amyloid PET SUVr	168	3.6%	0.69
Time to MCI/dementia due to AD	168	20.8%	0.48
CDR Sum-of-Boxes	168	8.8%	0.64
Time to non-Zero in CDR-GS	150	8.1%	0.76
RBANS Total Score	168	43.8%	0.55



Biomarker outcomes

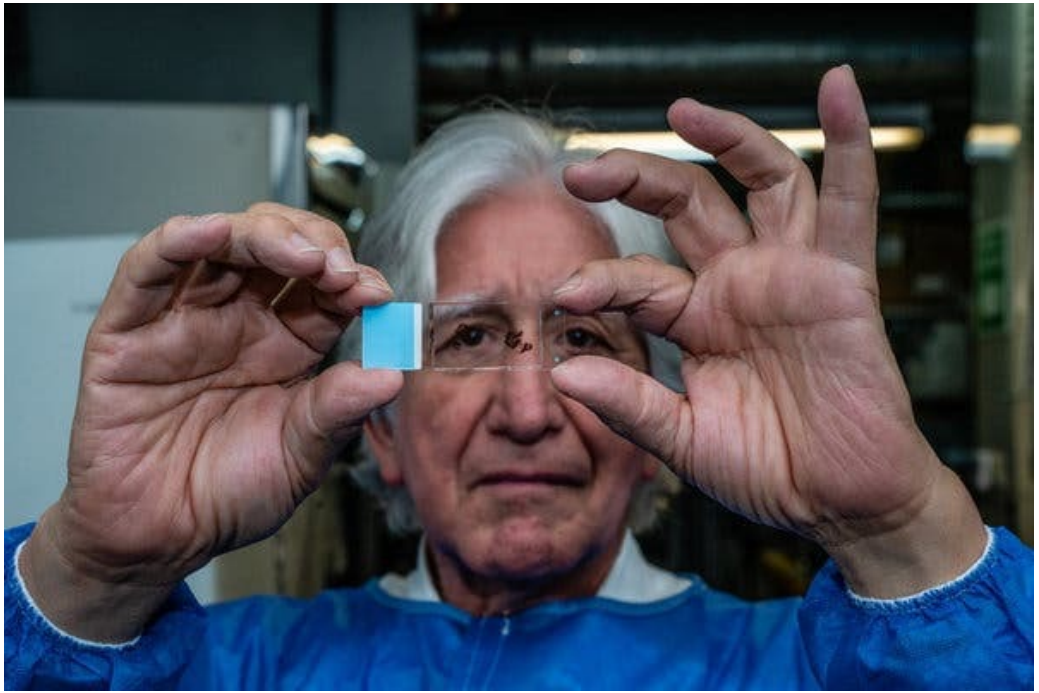
ADAD Colombia Trial
ALZHEIMER'S PREVENTION INITIATIVE

Biomarker outcome	Carriers	Relative reduction	P value*
Aβ PET (Florbetapir SUVR)	168	3.6%	0.69
Tau PET (ERC GTP1 SUVR)	83	51.1%	0.20
FDG PET (sROI FDG SUVR)	168	18.1%	0.25
CSF pTau181	84	37.4%	0.28
CSF tTau	90	28.7%	0.53
CSF NfL	90	18.2%	0.46



* P-values are uncorrected for multiple comparisons.
Continuous outcomes were modeled by the RCRM. Models were stratified for age, group, education, APOE4 and CDR-GS
Forest plots show mean reductions in biomarker progression in the crenezumab carrier group compared to those in the placebo carrier group and 95% CIs.
Aβ, Alzheimer's disease; APOE4, apolipoprotein E4; CI, confidence interval; CSF, cerebrospinal fluid; ERC, entorhinal cortex; FDG, fluorodeoxyglucose; GTP1, Genentech Tau Probe 1; NfL, neurofilament light chain; PET, positron emission tomography; pTau, phosphorylated Tau; RCRM, random coefficient regression model; sROI, statistical region of interest; SUVR, standard uptake value ratio; tTau, total Tau.

Where do we go from here?



The New York Times

Why Didn't She Get Alzheimer's? The Answer Could Hold a Key to Fighting the Disease

Researchers have found a woman with a rare genetic mutation that has protected her from dementia even though her brain has developed major neurological features of the disease.

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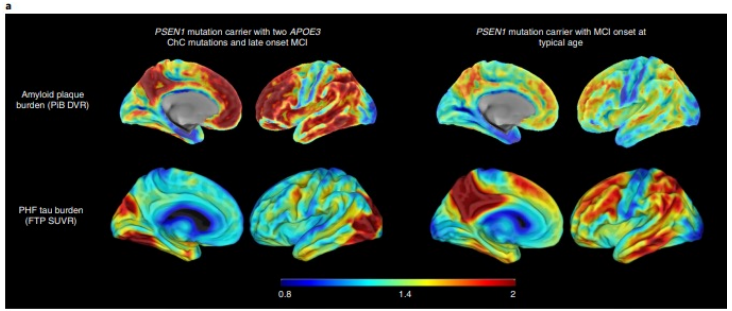
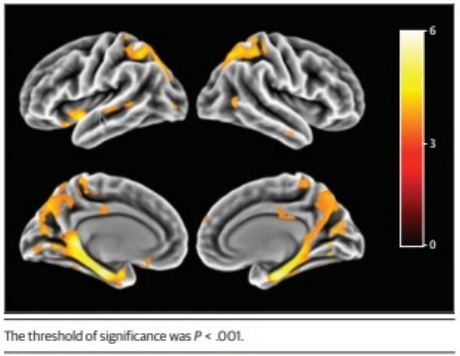
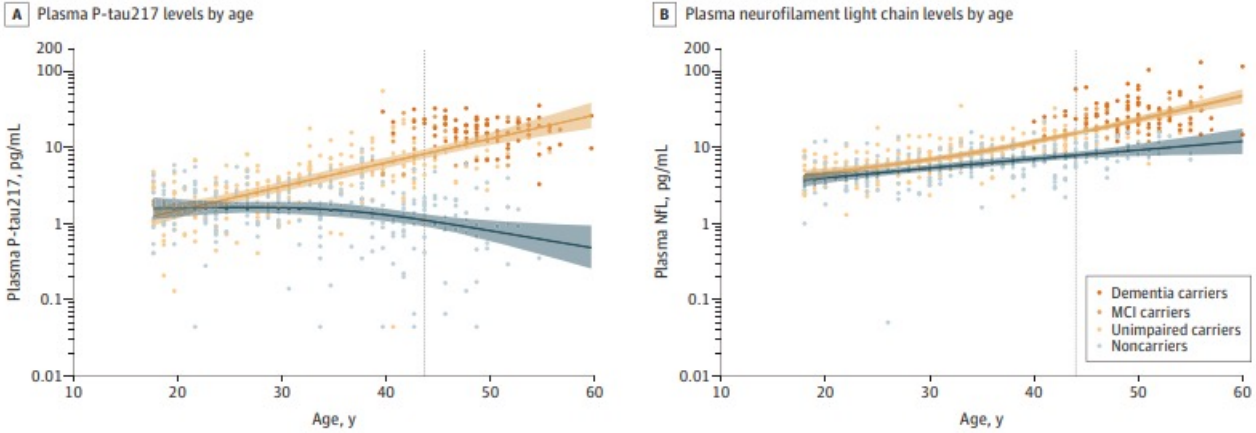
Brain Imaging and Fluid Biomarkers in ADAD Carriers





The threshold of significance was $P < .001$.



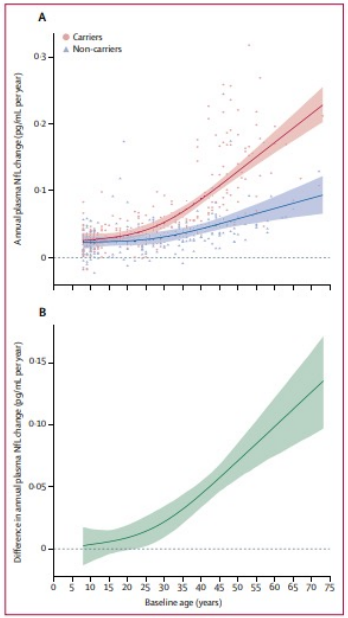


Figure 2: Longitudinal change rates of plasma NfL concentrations as a function of age in mutation carriers and non-carriers
Log-transformed longitudinal data. Shaded areas represent 99% credibility intervals. (A) Longitudinal change rates of plasma NfL as a function of age. (B) Change rate differences between carriers and non-carriers as a function of age (ie, the space between the carrier and non-carrier mean values at any given age). Non-carrier rates are set at 0. Log-transformed data were modelled using linear mixed effects models, a restricted cubic spline, and Hamiltonian Markov chain Monte Carlo analyses. The underlying modelling procedures used in the generation of these representations of the longitudinal change rates of plasma NfL are very similar to those used to generate the representations in figure 1 (cross-sectional plasma NfL between mutation carriers and non-carriers) but the dependent variable (ie, the rate of change in plasma NfL concentrations) of the models was different between the analyses. NfL=neurofilament light chain.

Quiroz et al, 2018 *JAMA Neurology;* Arbloleda-Velasquez et al., *Nat Med* 2019, Palmqvist et al *JAMA* 2020; Quiroz et al, 2020 *Lancet Neurol*

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