Grupo de Neurociencias\Universidad de Antioquia

Robert Stempel College of Public Health & Social Work

INICIATIVA DE PREVENCIÓN DEL ALZHEIMER COLOMBIA

THE GENETIC AUTOSOMAL DOMINANT ALZHEIMERS´S DISEASE (ADAD)

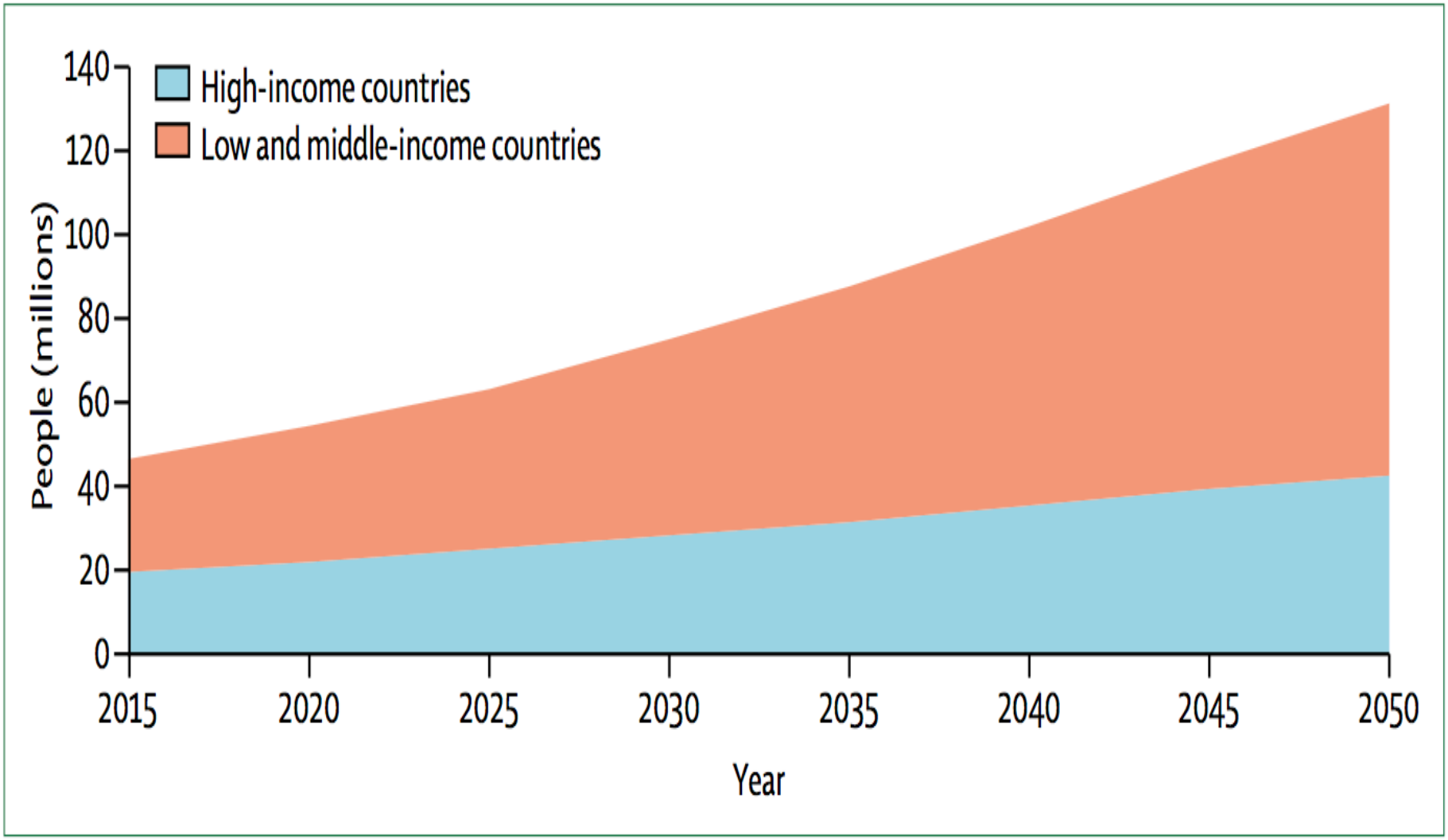
A WINDOW FOR PREVENTION

Florida International University
Miami May 9/2019

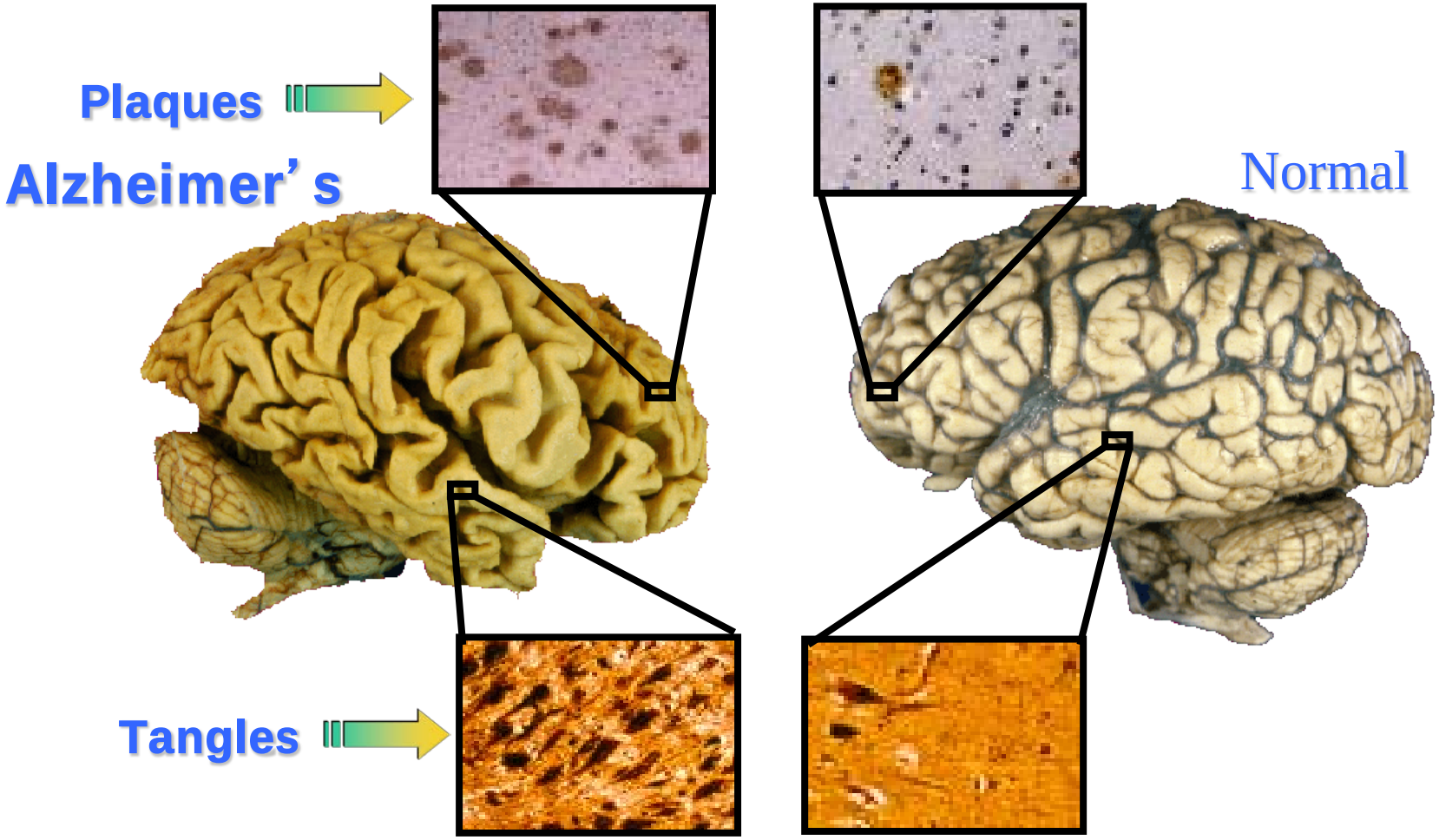
Francisco Lopera
francisco.lopera@gna.org.co
floperar@gmail.com

The growth of dementia in the world

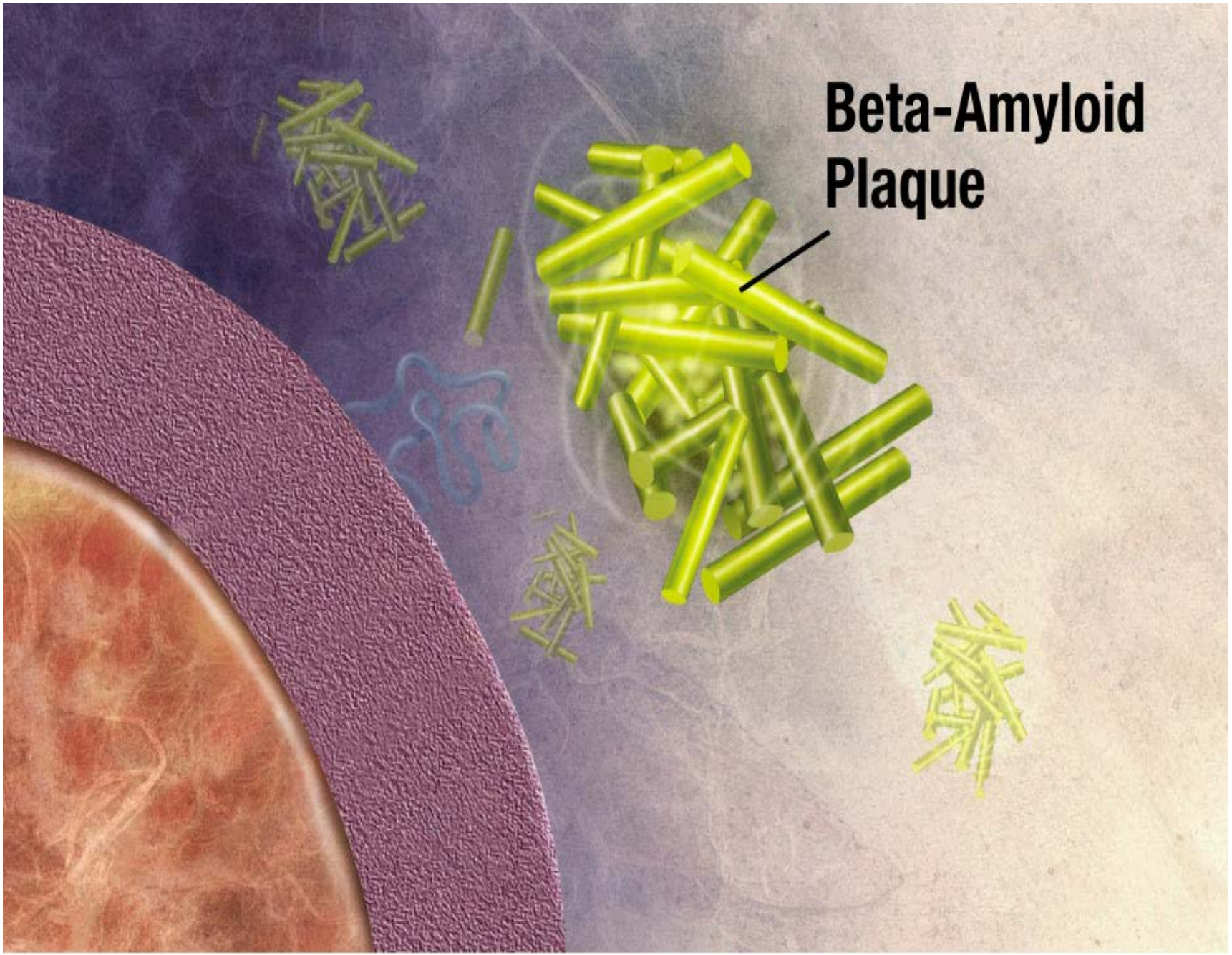
The Lancet Commissions (ADI)



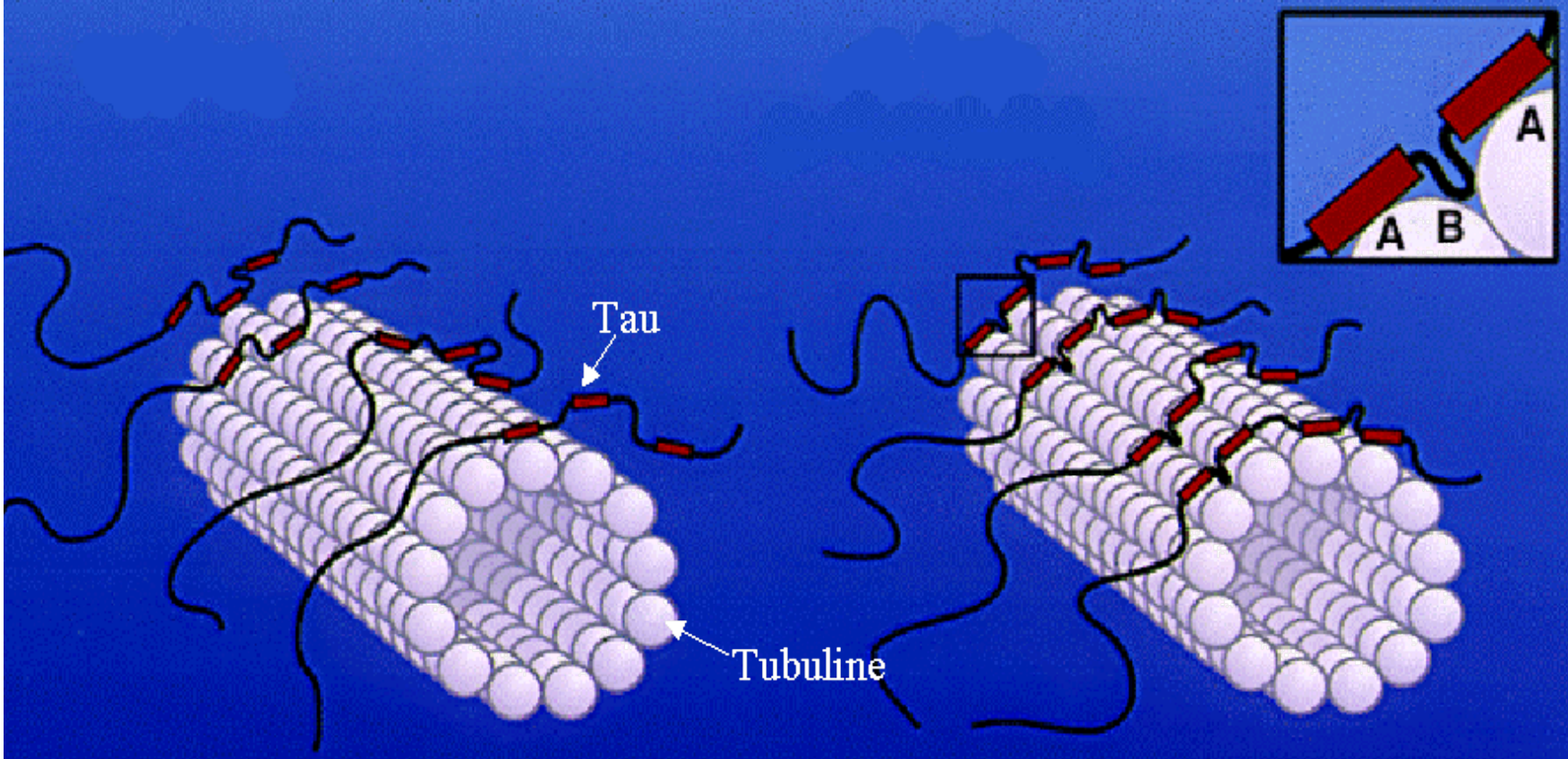
Amyloid Plaques and Neurofibrillary Tangles in Alzheimer's Disease and Normal Aging



Courtesy of Harry Vinters, MD.


Beta-Amyloid
Plaque

Stabilisation des microtubules

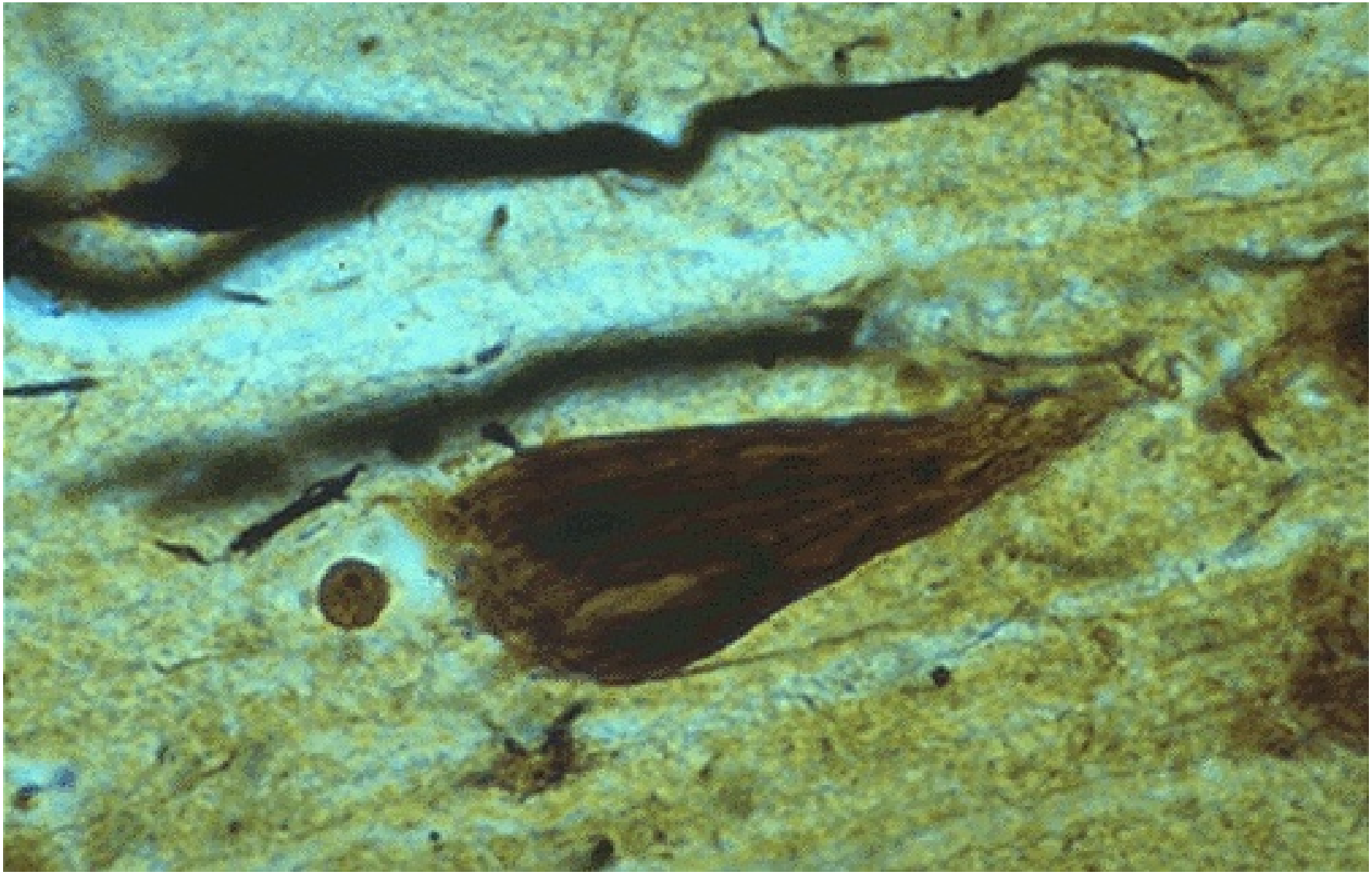


3 répétitions: exon 10 -

4 répétitions: exon 10 +

Interaction Tau <-> Tubuline augmentée 40 fois

Neurofibrillary degeneration



The Amyloid Cascade Hypothesis

AGE

30

40

50

60

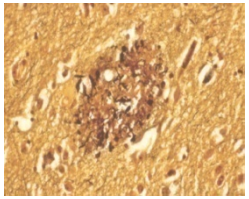
70

80

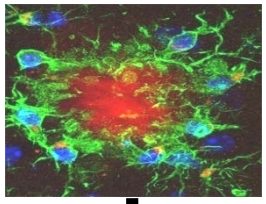
90

100

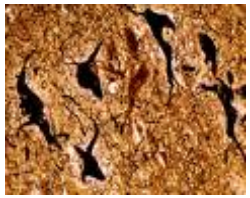
β-amyloid Deposits



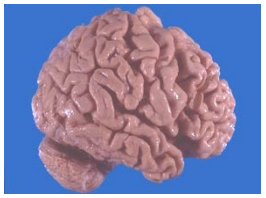
Activation of Microglia



Neurofibrillary tangles



Neuronal Loss Biochemical Changes



DEMENTIA

Tau Phosphorylation

Tangle formation

Synaptic loss
Neuronal death

Cognitive Impairment

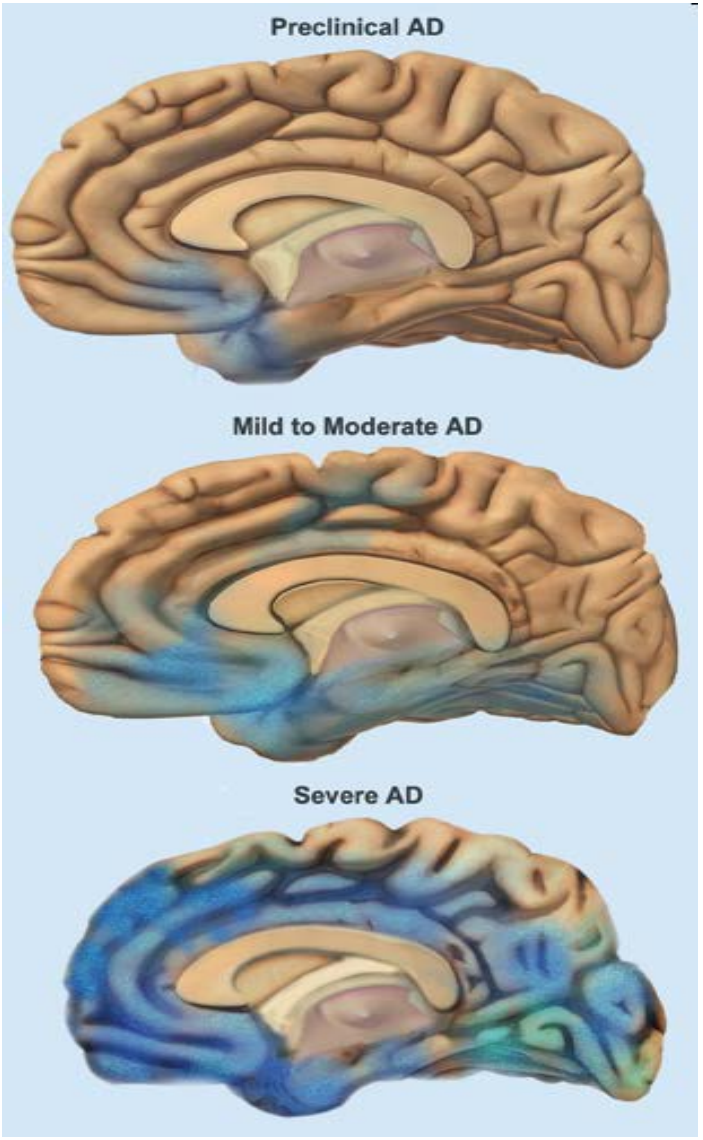
ALZHEIMER'S DISEASE: 3 STATES

2018 NIA-AA Guides

Preclinical Alzheimer's
(Asymptomatic +
Biomarker)

Prodromic Alzheimer's
MCI + Biomarker

Dementia for Alzheimer's



ATN

ATN

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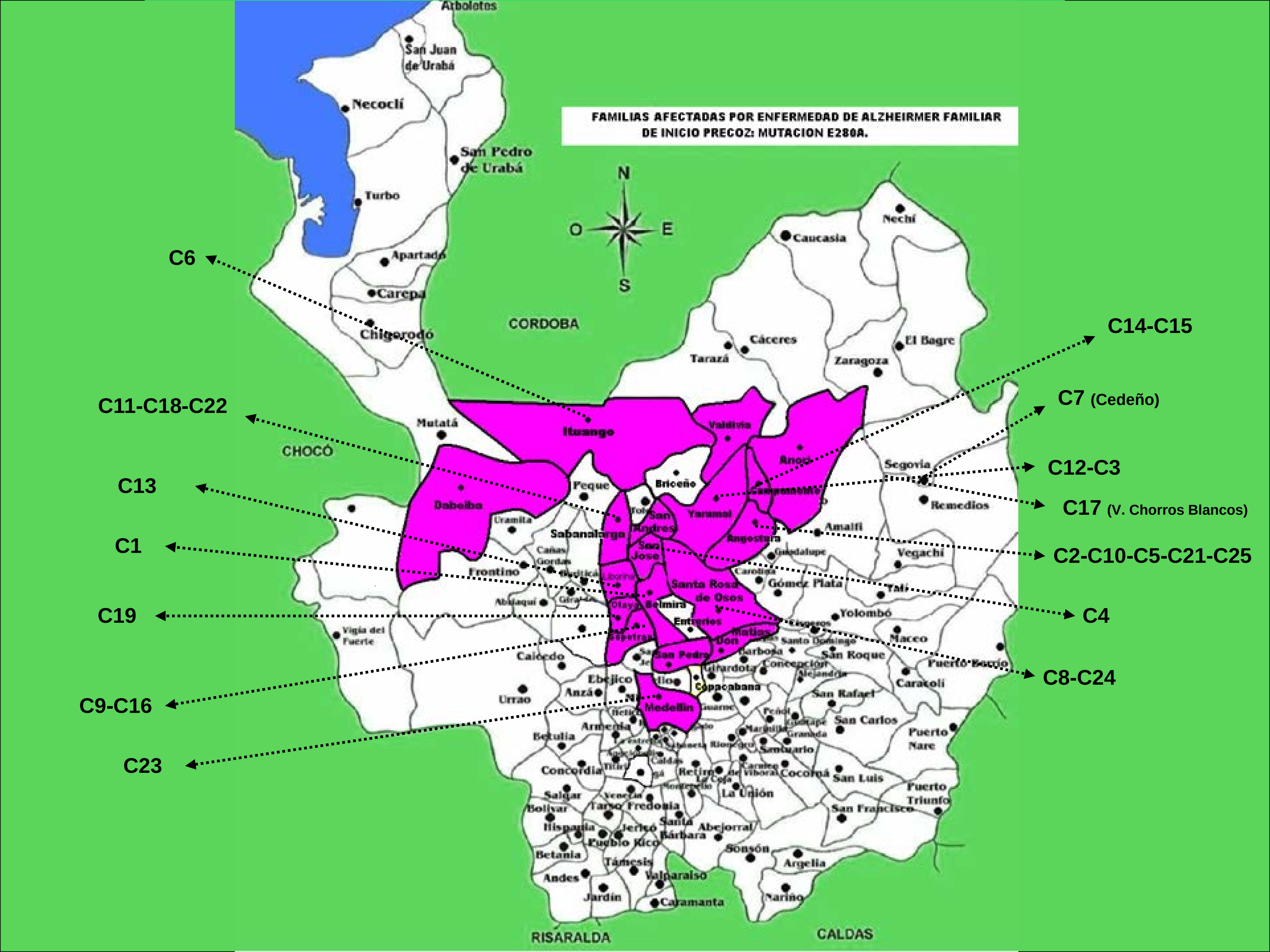
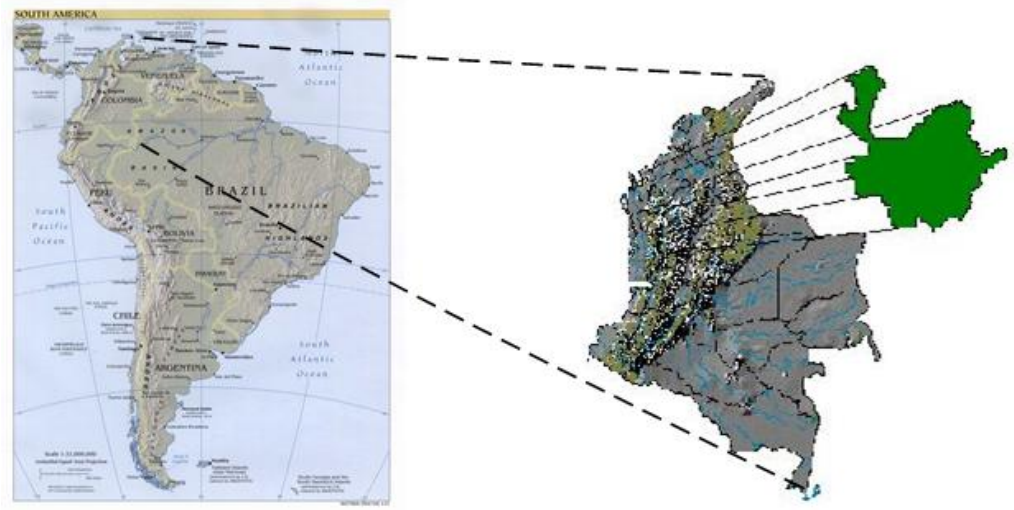
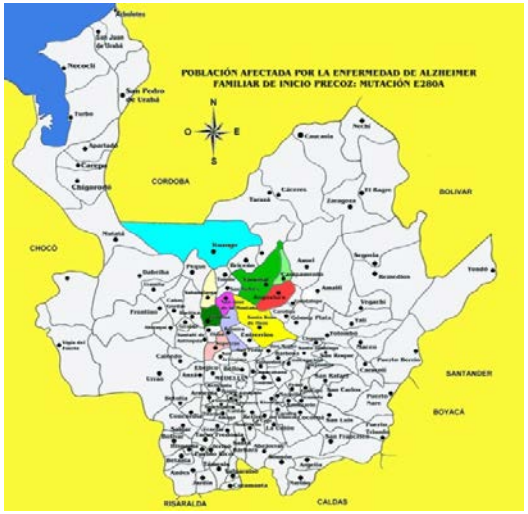


FAMILIAS AFECTADAS POR ENFERMEDAD DE ALZHEIRMER FAMILIAR
DE INICIO PRECOZ: MUTACION E280A.
N
S
O
E
C6
C11-C18-C22
C13
C1
C19
C9-C16
C23
C14-C15
C7 (Cedeño)
C12-C3
C17 (V. Chorros Blancos)
C2-C10-C5-C21-C25
C4
C8-C24
CORDOBA
CHOCÓ
RISARALDA
CALDAS
Arboletes
San Juan de Urabá
Necoclí
San Pedro de Urabá
Turbo
Apartadó
Carepa
Chigorodó
Mutatá
Ituango
Valdivia
Anorí
Dabeiba
Peque
Briceño
San Andrés
Yarumal
Sabanalarga
Uramita
Angostura
Campamento
San José
Santa Rosa de Osos
Frontino
Cañasgordas
Olaya
Belmira
Entrerrios
Don Matías
San Pedro
Sopetrán
Caicedo
Ebéjico
Anzá
Urrao
Medellín
Copacabana
Girardota
Barbosa
Concepción
Caucasia
Nechí
Cáceres
Tarazá
Zaragoza
El Bagre
Segovia
Remedios
Amalfi
Vegachí
Guadalupe
Carolina
Gómez Plata
Yalí
Yolombó
Santo Domingo
San Roque
Maceo
Puerto Berrío
Caracolí
San Rafael
San Carlos
Puerto Nare
Vigía del Fuerte
Abriaquí
Betulia
Armenia
Concordia
Salgar
Bolívar
Hispania
Betania
Andes
Jardín
Támesis
Valparaíso
Caramanta
Venecia
Tarso
Fredonia
Jericó
Pueblo Rico
Santa Bárbara
Abejorral
Sonsón
Argelia
Nariño
La Unión
Cocorná
San Luis
Puerto Triunfo
San Francisco
Santuario
Granada
Marinilla
Rionegro

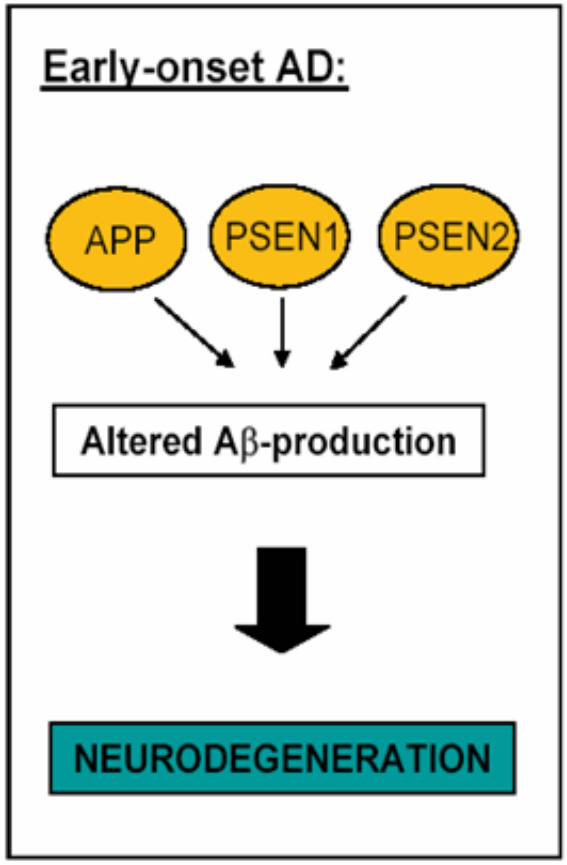
INICIATIVA DE PREVENCIÓN DEL ALZHEIMER COLOMBIA

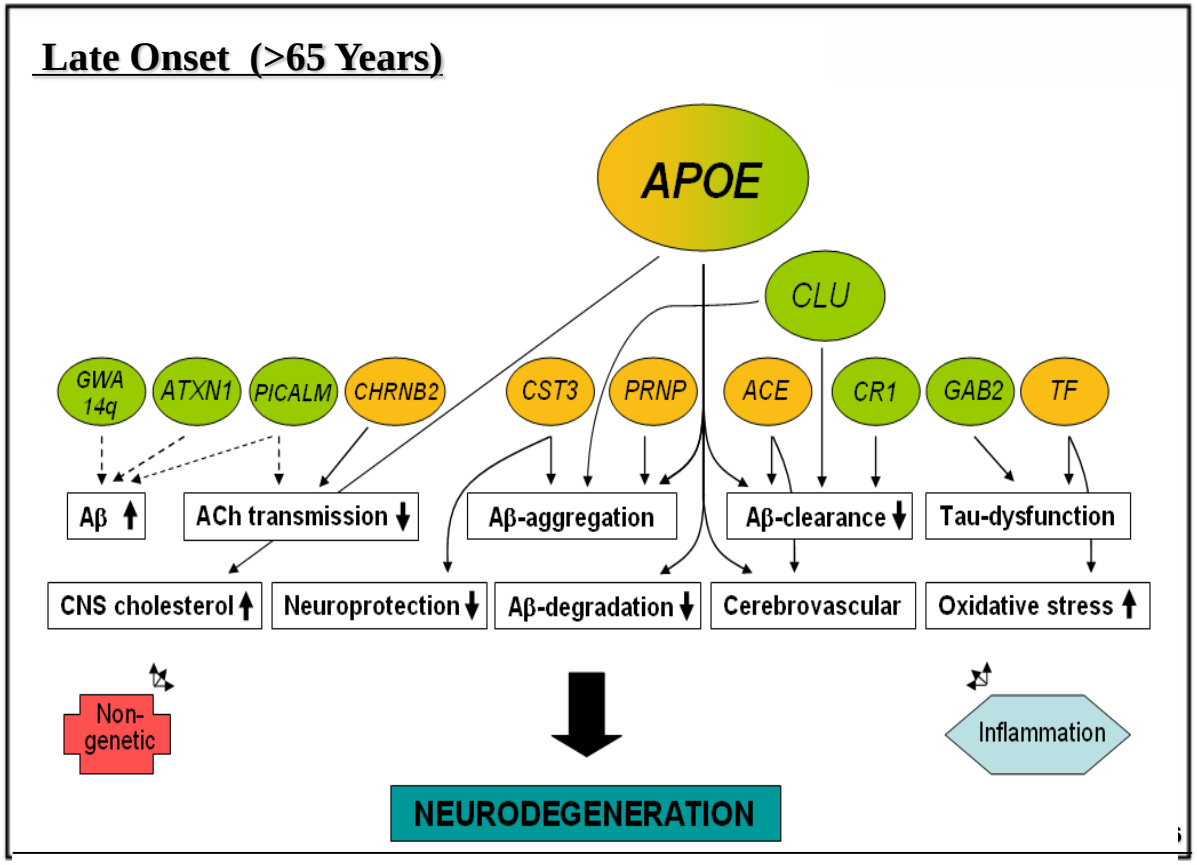
Antioquia, Colombia: A genetically isolated area with strong founder effect for an autosomal dominant mutation causing early onset AD





Genetics of Alzheimer´s Disease





" Simple Genetics " (<5%)

" Complex Genetics" (>95%)

Most of the mutations that produce FAD are in PSEN1

Gene	# Mutations	
APP	58	
PSEN1	253	E280A 25 Famillies Colombia >6000 members
PSEN2	48	
Total	359	

ALZFORUM

We began our first International colaboration with Ken Kosik, John Morris And Alison Goate in decade of 90’s

Paisa Mutation E280A a subtitution of ALANINE FOR GLUTAMIC ACID in CODON 280 OF THE PRESENILIN 1 GEN in CHROMOSOME 14.

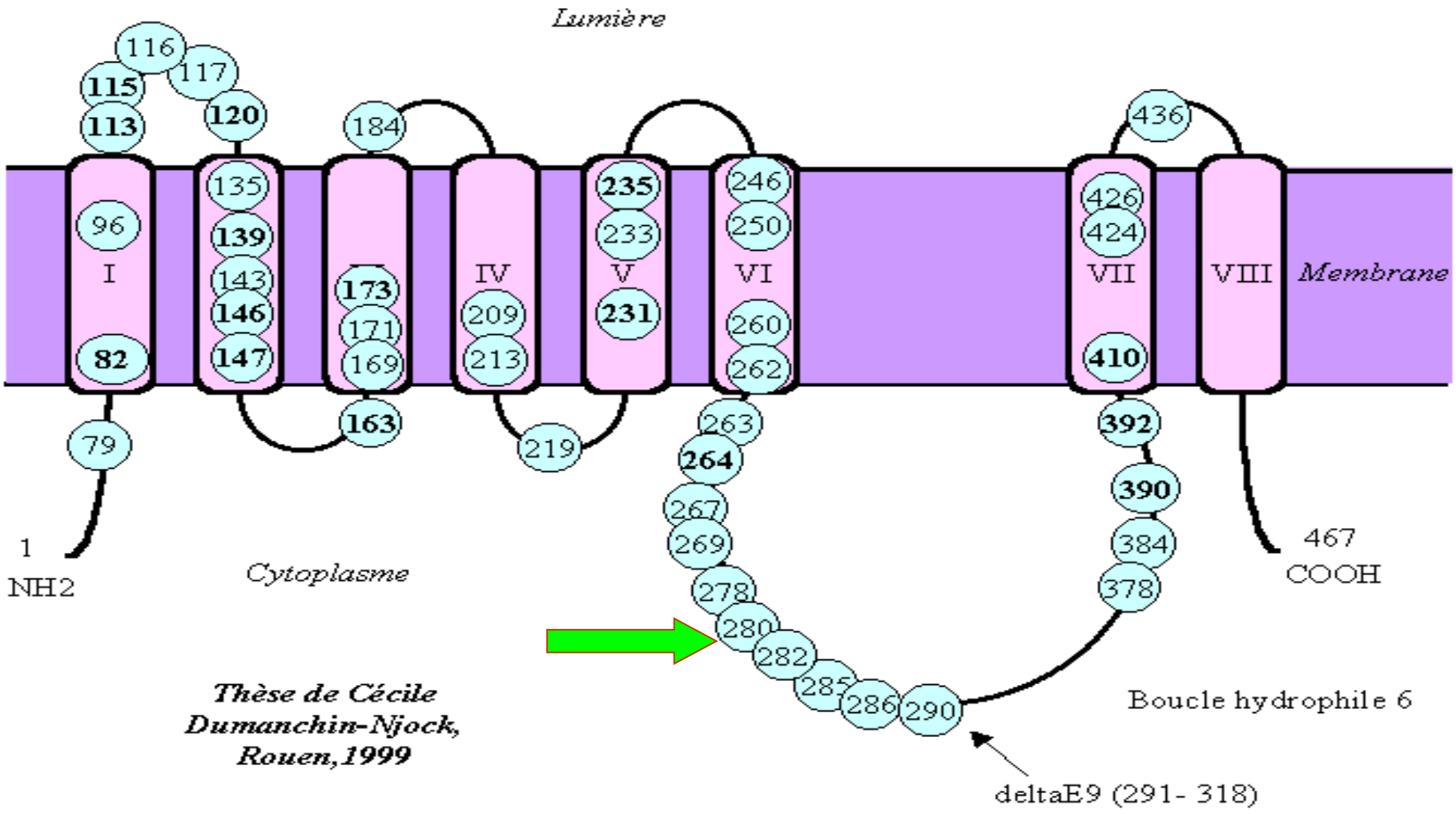


Figure 5. Structure de la préséniline 1 et distribution des mutations. Les mutations documentées dans les familles françaises sont en gras.


V-28-67

Nino

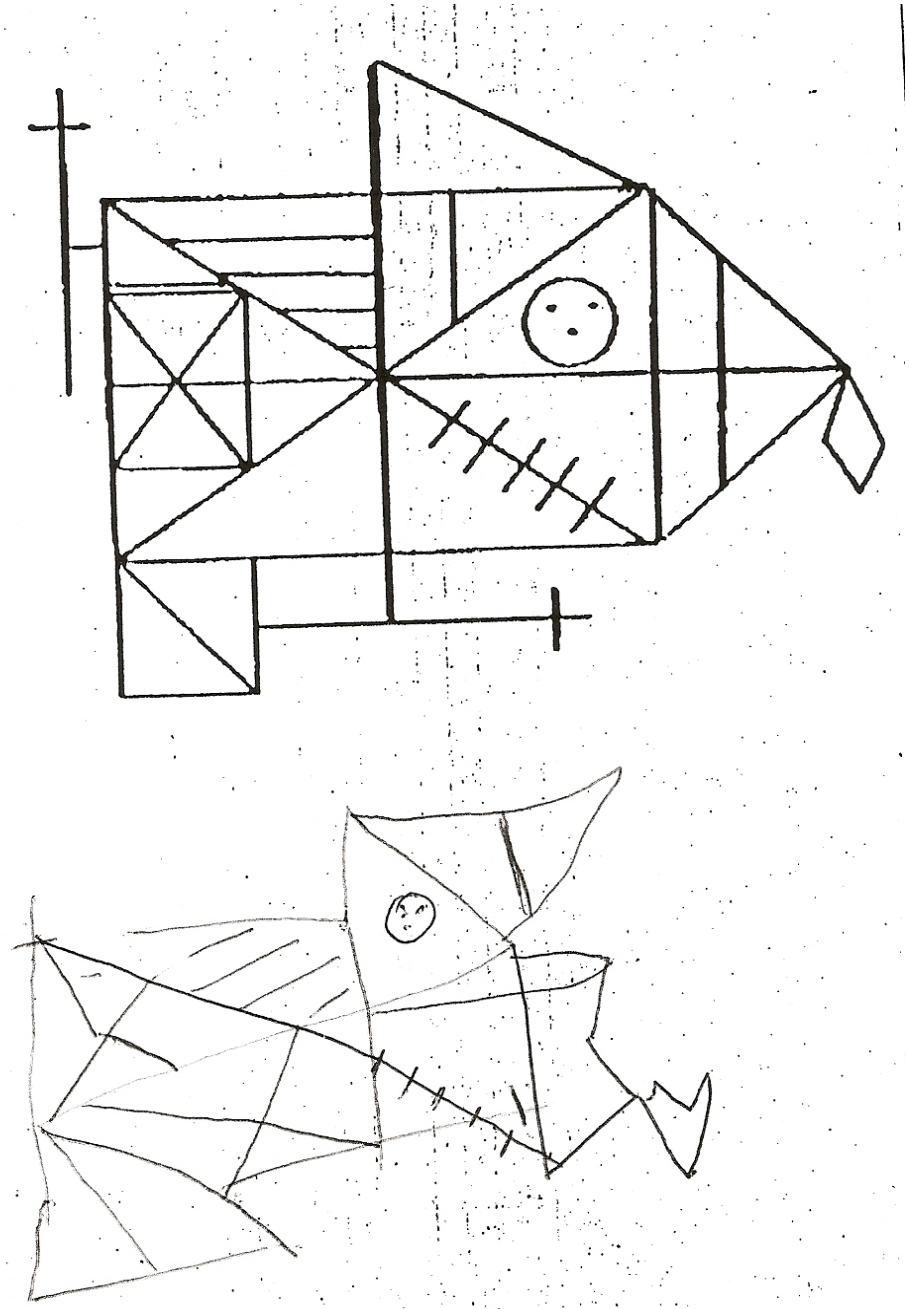
Antonio

Hi !

ott 29/91

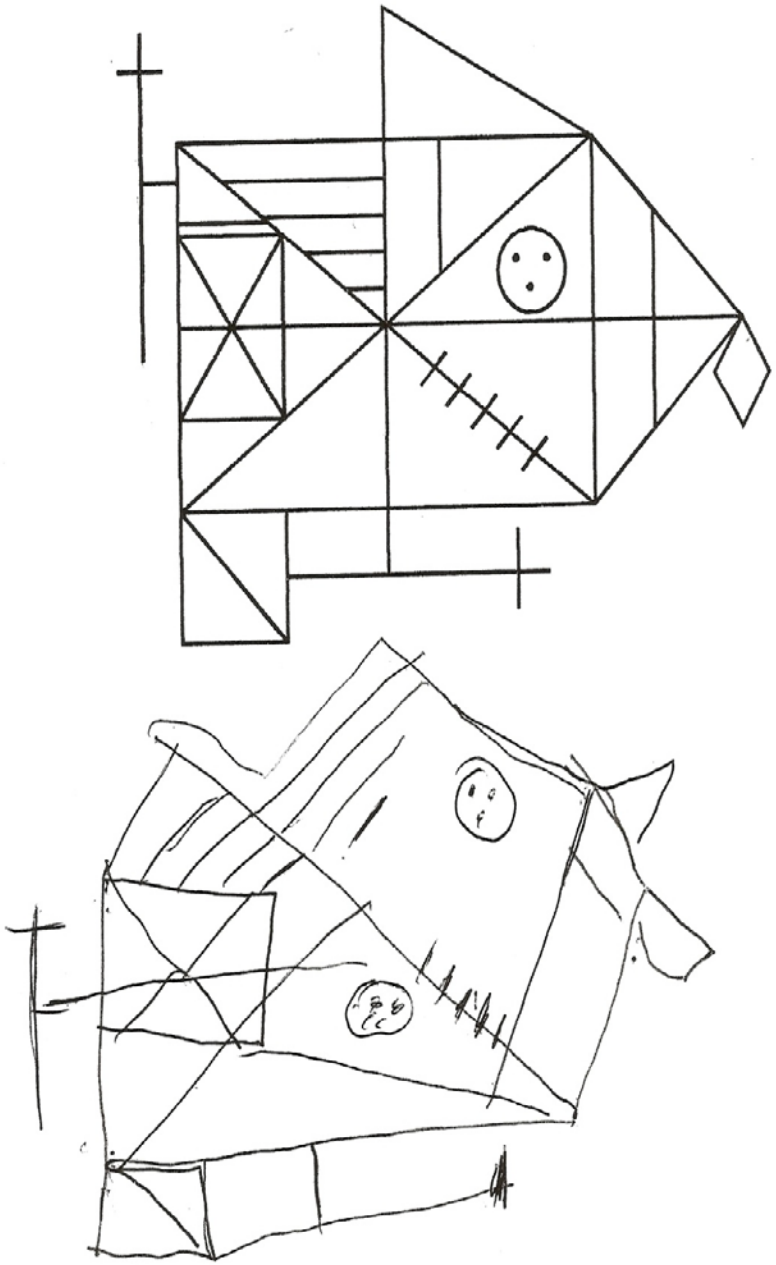
ott 29/91

Andrea Balbi



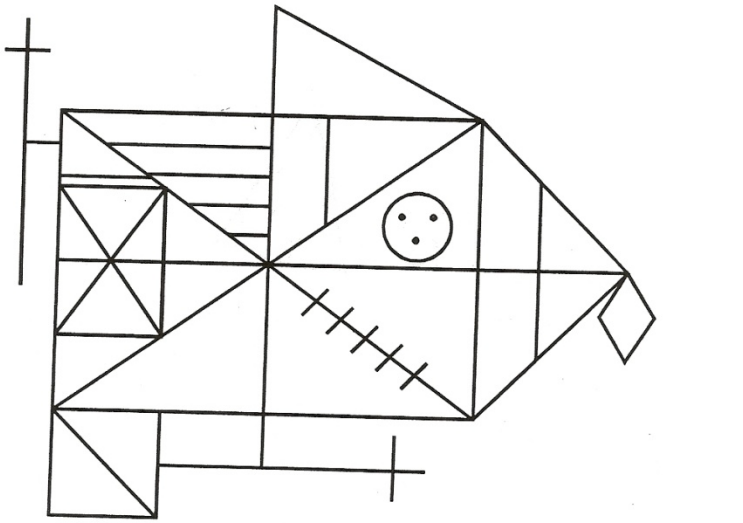
38 years

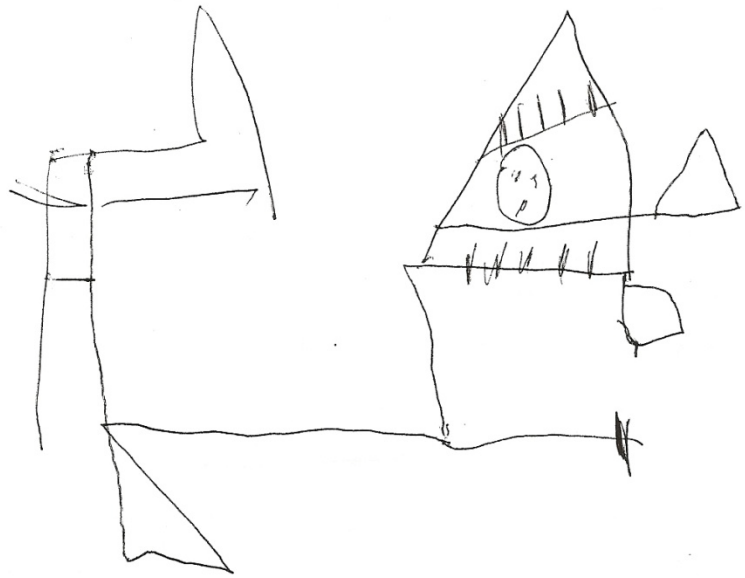
Figura COMPLEJA DE REY-OSTERRIETH



43 years

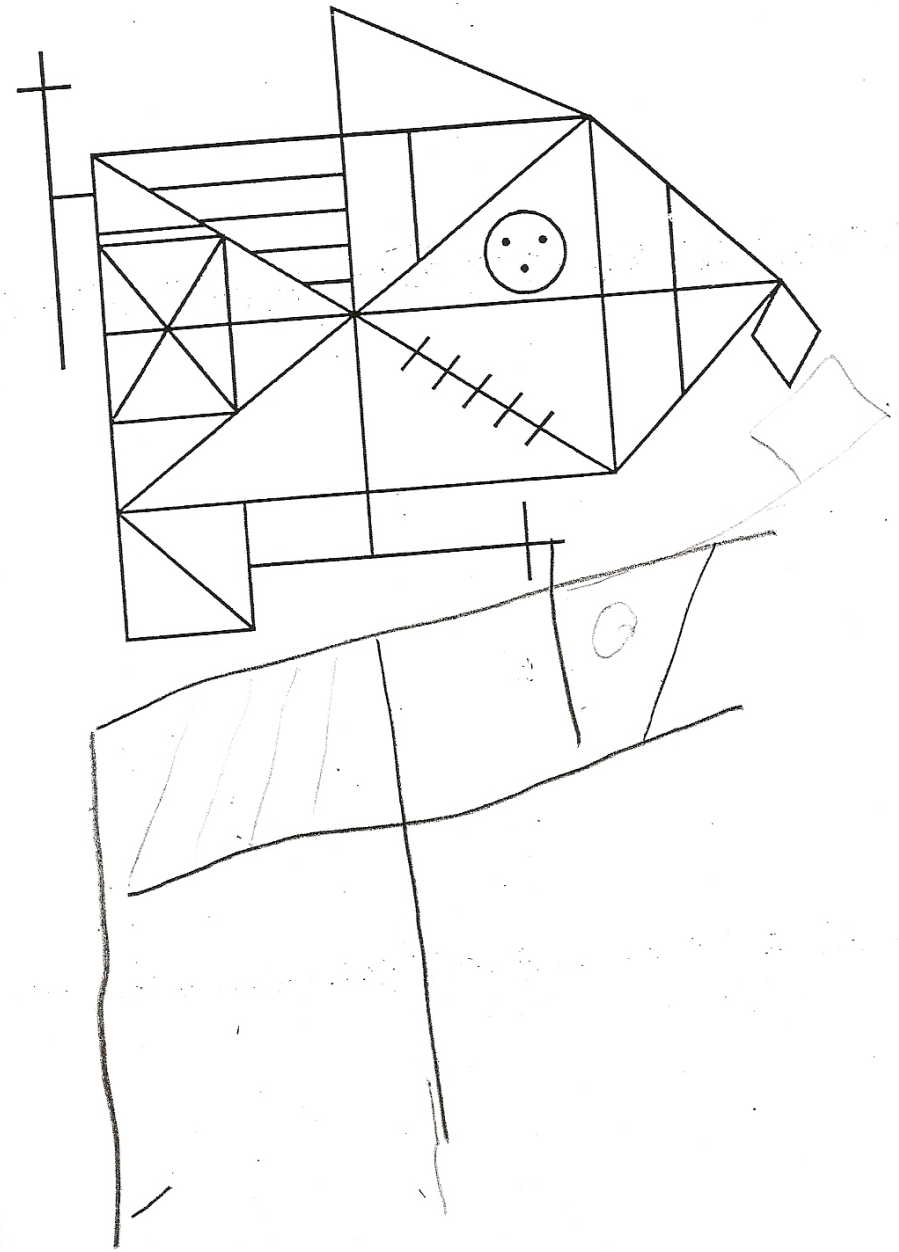
Figura COMPLEJA DE REY-OSTERRIETH





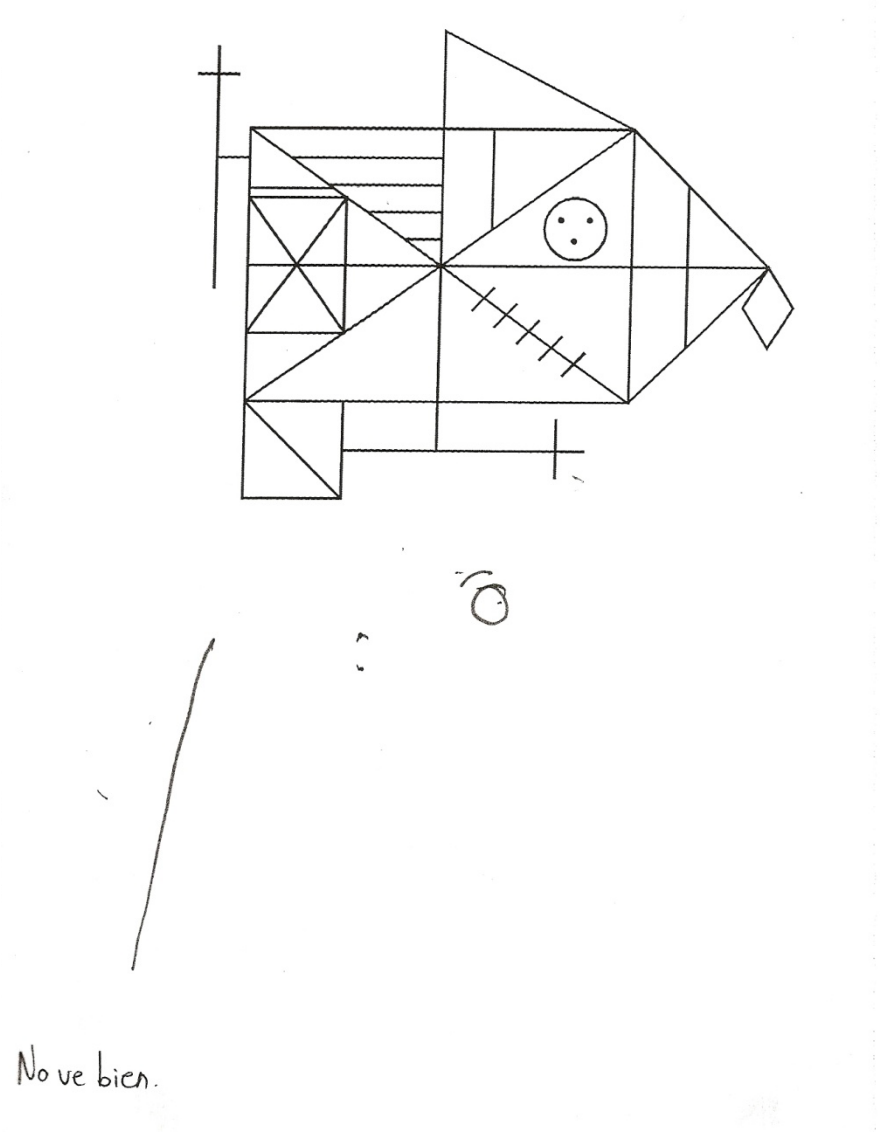
45 years

Figura COMPLEJA DE REY-OSTERRIETH



50 years

Figura COMPLEJA DE REY-OSTERRIETH

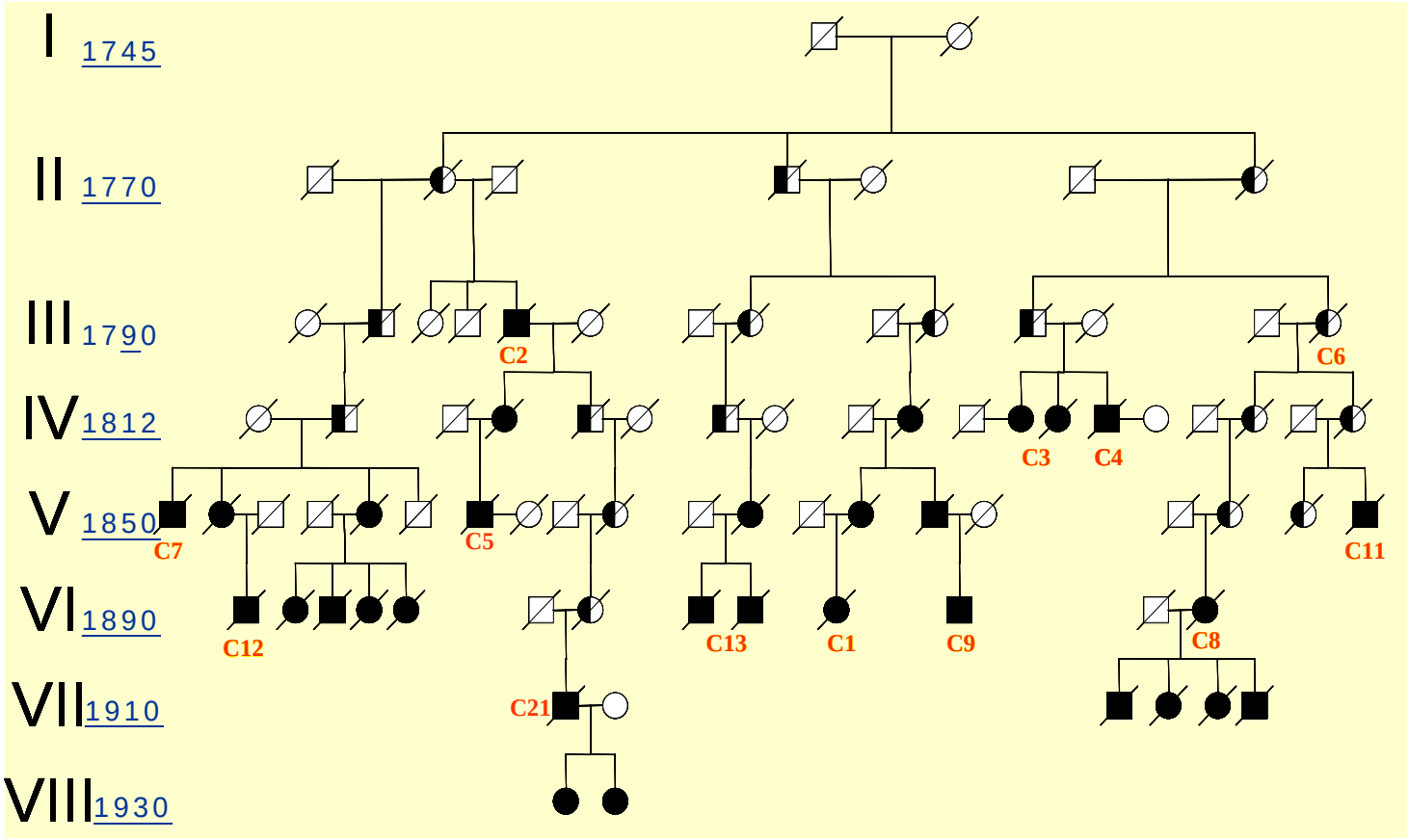


51 years

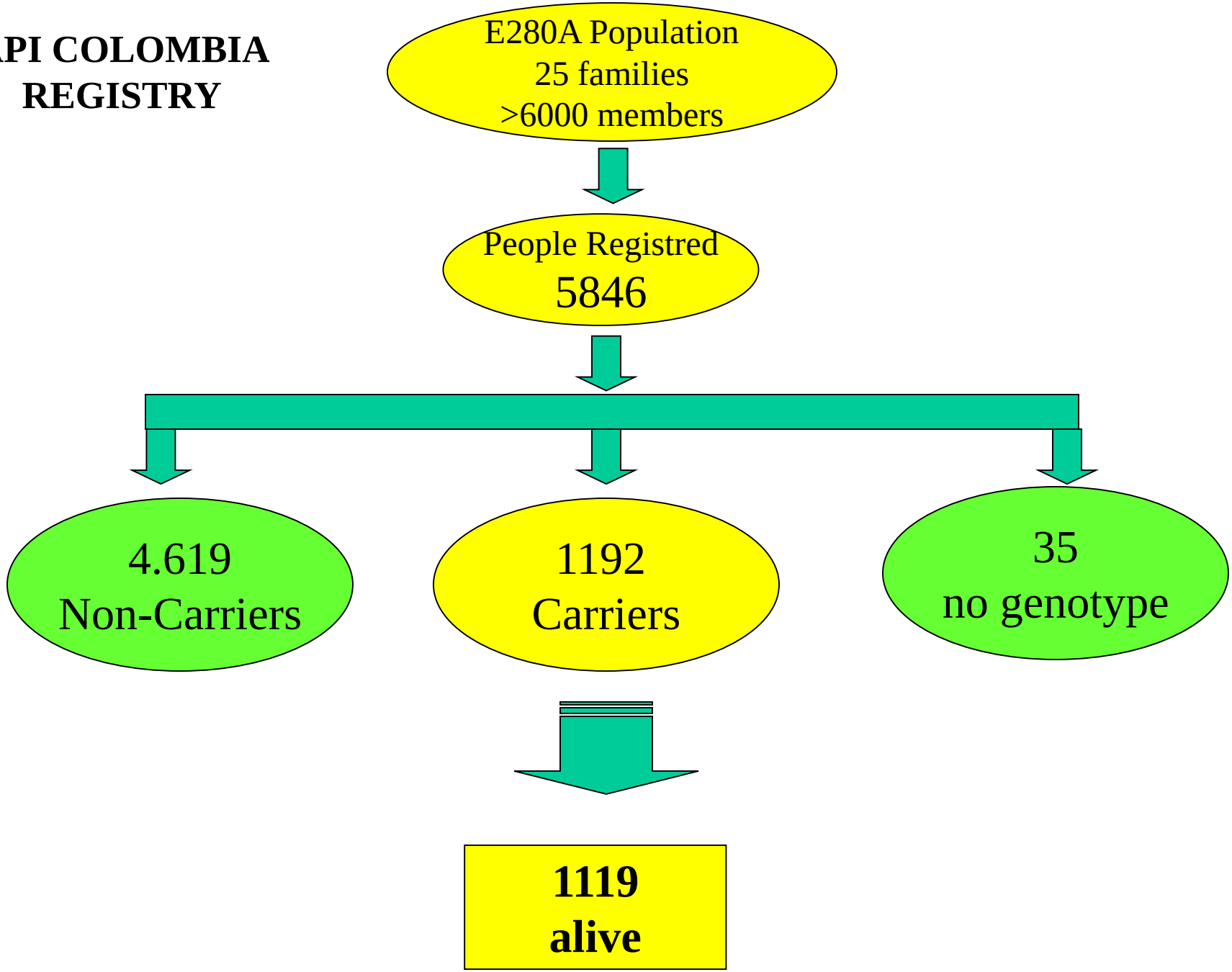
Figura COMPLEJA DE REY-OSTERRIETH

Common ancestry of 14 families with E280A associated AD

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



API COLOMBIA REGISTRY



Florbetapir PET analysis of amyloid-β deposition in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: a cross-sectional study

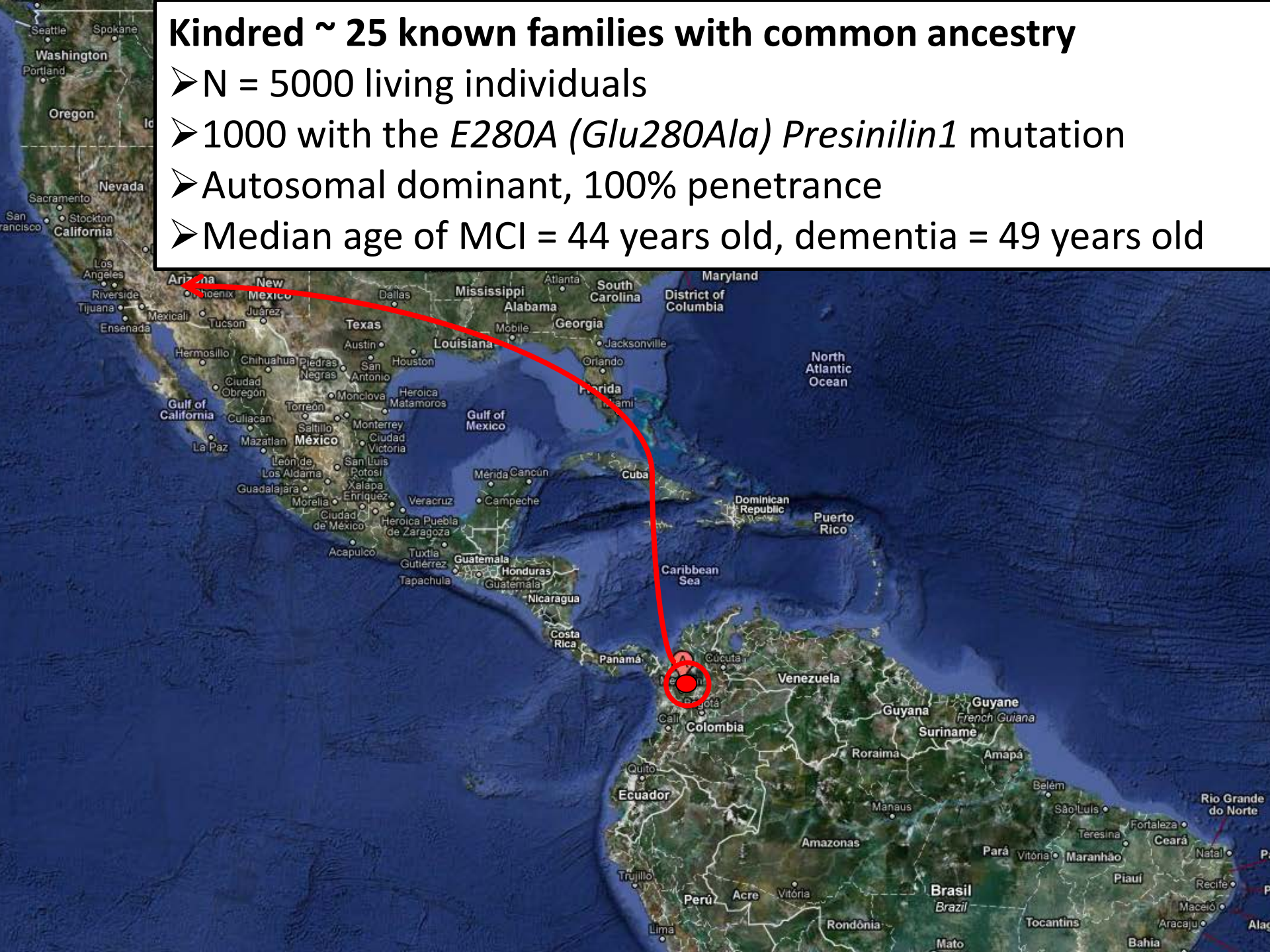
Adam S Fleisher, Kewei Chen, Yakeel T Quiroz, Laura J Jakimovich, Madelyn Gutierrez Gomez, Carolyn M Langois, Jessica B S Langbaum, Napatkamon Ayutyanont, Auttawut Roontiva, Pradeep Thiyyagura, Wendy Lee, Hua Mo, Liliana Lopez, Sonia Moreno, Natalia Acosta-Baena, Margarita Giraldo, Gloria Garcia, Rebecca A Reiman, Matthew J Huentelman, Kenneth S Kosik, Pierre N Tariot, Francisco Lopera, Eric M Reiman

Summary

Background Fibrillar amyloid-β (Aβ) is thought to begin accumulating in the brain many years before the onset of clinical impairment in patients with Alzheimer's disease. By assessing the accumulation of Aβ in people at risk of genetic forms of Alzheimer's disease, we can identify how early preclinical changes start in individuals certain to develop dementia later in life. We sought to characterise the age-related accumulation of Aβ deposition in presenilin 1 (PSEN1) E280A mutation carriers across the spectrum of preclinical disease.

Lancet Neurol 2012; 11: 1057–65
Published Online November 6, 2012
http://dx.doi.org/10.1016/S1474-4422(12)70227-2

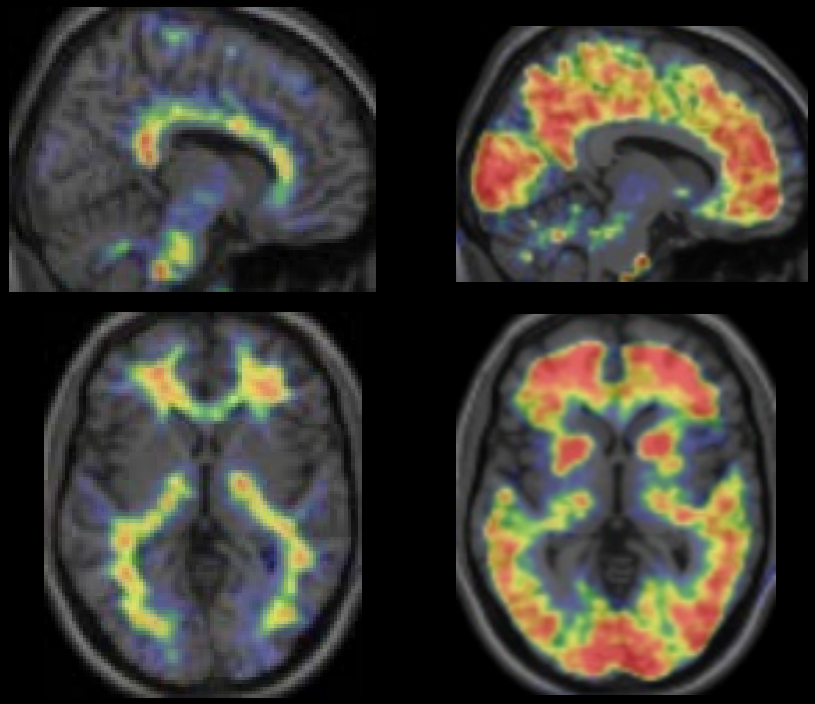
See Comment page 1018


Kindred ~ 25 known families with common ancestry
➢N = 5000 living individuals
➢1000 with the *E280A (Glu280Ala) Presinilin1* mutation
➢Autosomal dominant, 100% penetrance
➢Median age of MCI = 44 years old
Seattle
Spokane
Washington
Portland
Oregon
Nevada
Sacramento
San Francisco
Stockton
California
Los Angeles
Riverside
Tijuana
Mexicali
Ensenada
Arizona
Phoenix
New Mexico
Juárez
Tucson
Dallas
Texas
Austin
Houston
Hermosillo
Chihuahua
Piedras Negras
San Antonio
Ciudad Obregón
Monclova
Heroica Matamoros
Torreón
Culiacan
Saltillo
Monterrey
Mazatlan
México
Ciudad Victoria
La Paz
León de los Aldama
San Luis Potosí
Guadalajara
Xalapa Enríquez
Morelia
Veracruz
Ciudad de México
Heroica Puebla de Zaragoza
Acapulco
Tuxtla Gutiérrez
Tapachula
Guatemala
Honduras
Nicaragua
Costa Rica
Panamá
Gulf of California
Gulf of Mexico
Mississippi
Alabama
Atlanta
Georgia
Mobile
Louisiana
South Carolina
Maryland
District of Columbia
Jacksonville
Orlando
Florida
Miami
North Atlantic Ocean
Mérida
Cancún
Campeche
Cuba
Dominican Republic
Puerto Rico
Caribbean Sea
Cúcuta
Venezuela
Bogotá
Cali
Colombia
Guyane
Guyana
French Guiana
Suriname
Roraima
Amapá
Quito
Ecuador
Belém
Manaus
São Luís
Rio Grande do Norte
Fortaleza
Teresina
Ceará
Natal
Amazonas
Pará
Vitória
Maranhão
Piauí
Recife
Trujillo
Perú
Acre
Vitória
Brasil
Brazil
Maceió
Rondônia
Tocantins
Aracaju
Lima
Mato
Bahia

AMILOIDOSIS ATN

PS1 E280A
Non-Carrier

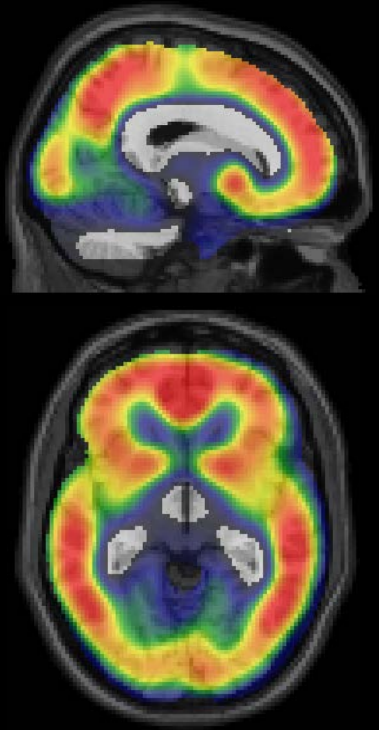
PS1 E280A
Dementia



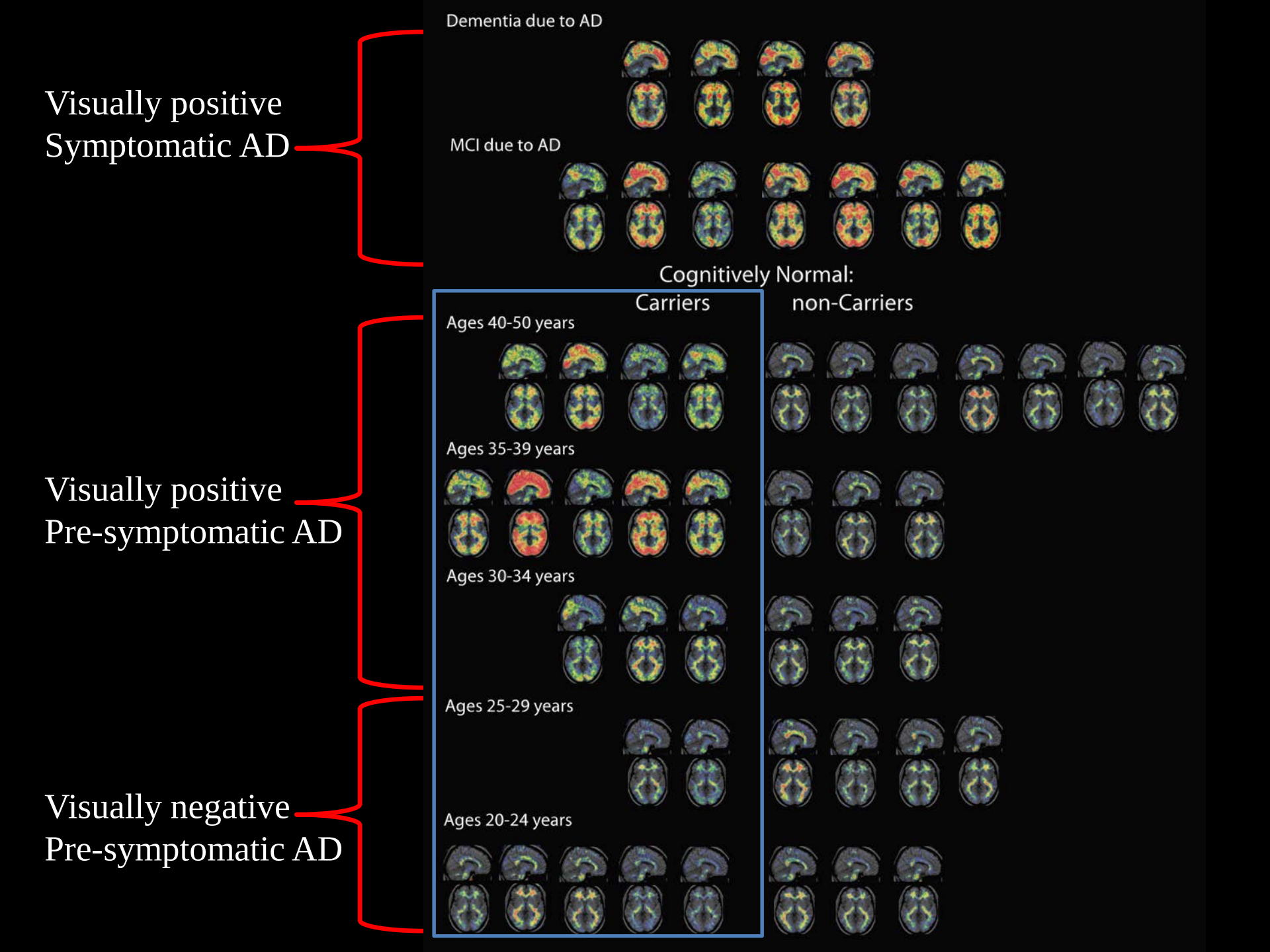
0.8
1.39

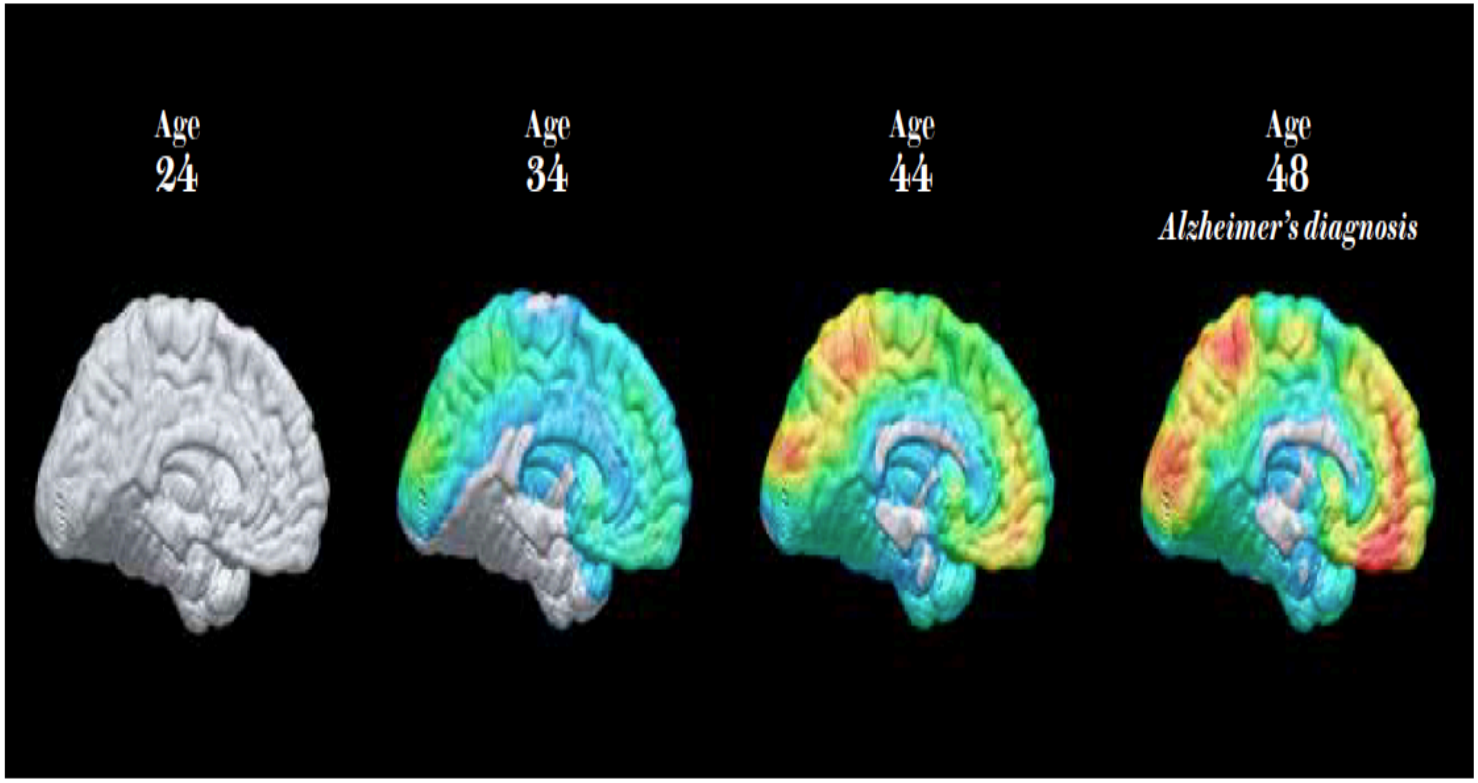
PET/CT scanner, 10 min scan, Pons ROIs, SUVR

LOAD Dementia
> HC



Adapted from Fleisher et al,
Arch Neurol 2011


Visually positive
Symptomatic AD
Visually positive
Pre-symptomatic AD
Visually negative
Pre-symptomatic AD
Dementia due to AD
MCI due to AD
Cognitively Normal:
Carriers
non-Carriers
Ages 40-50 years
Ages 35-39 years
Ages 30-34 years
Ages 25-29 years
Ages 20-24 years

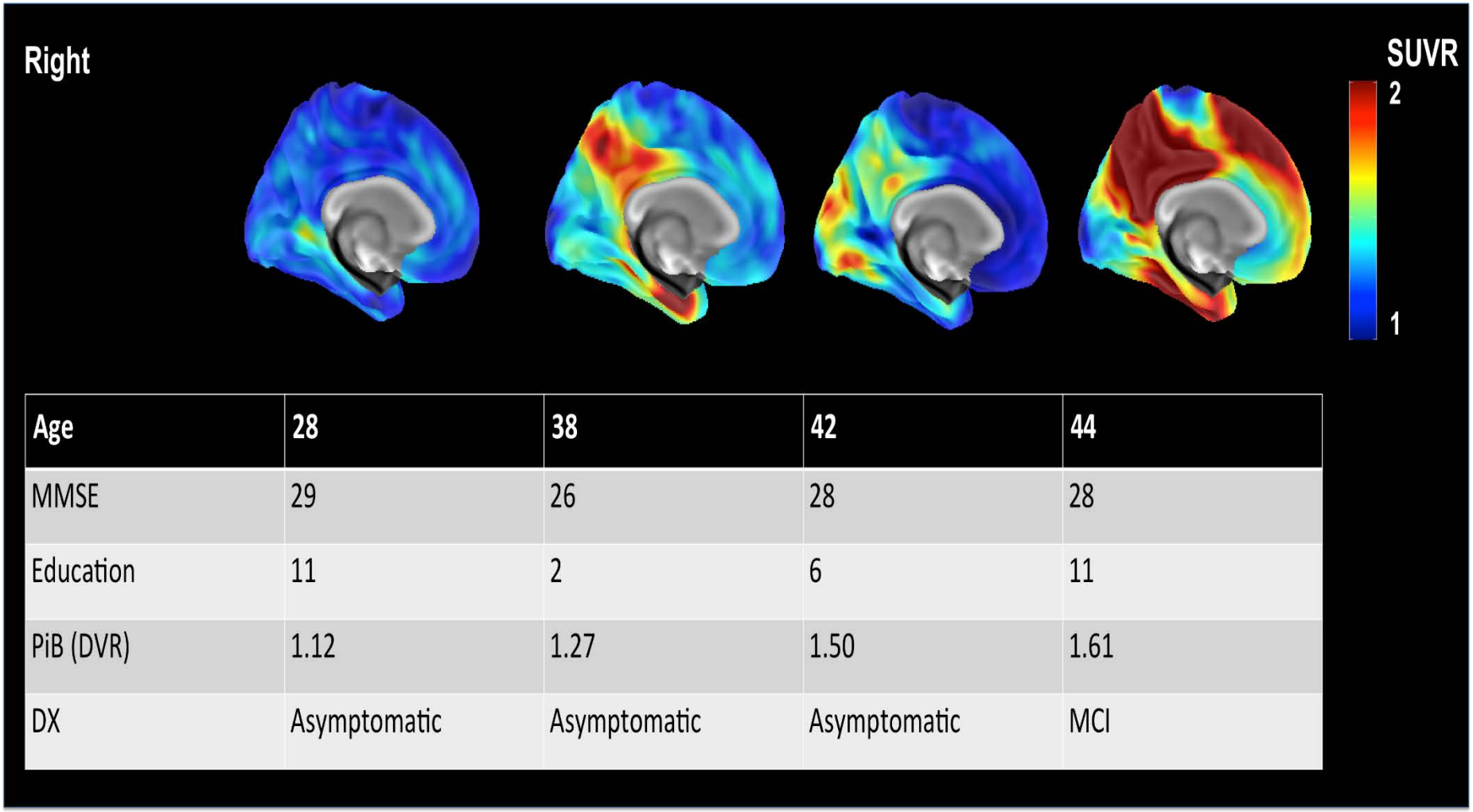


Watchful Waiting

Clinical trials to prevent Alzheimer's have become possible because of the arrival of technologies—brain scans, spinal taps and highly sensitive psychological tests—to determine if the disease is progressing before a patient becomes forgetful. A specialized form of positron-emission tomography shows typical buildup of harmful beta-amyloid in the brains of carriers of the Paisa mutation (*colored regions*) at various ages through the time of an Alzheimer's diagnosis. Beta-amyloid deposits are absent from the brains of members of these families at the same ages if they do not carry the mutation (*not shown*). Another technology used in the Colombian clinical trial, magnetic resonance imaging, reveals whether brain shrinkage has occurred as much as 10 years before a diagnosis is made (*below*).

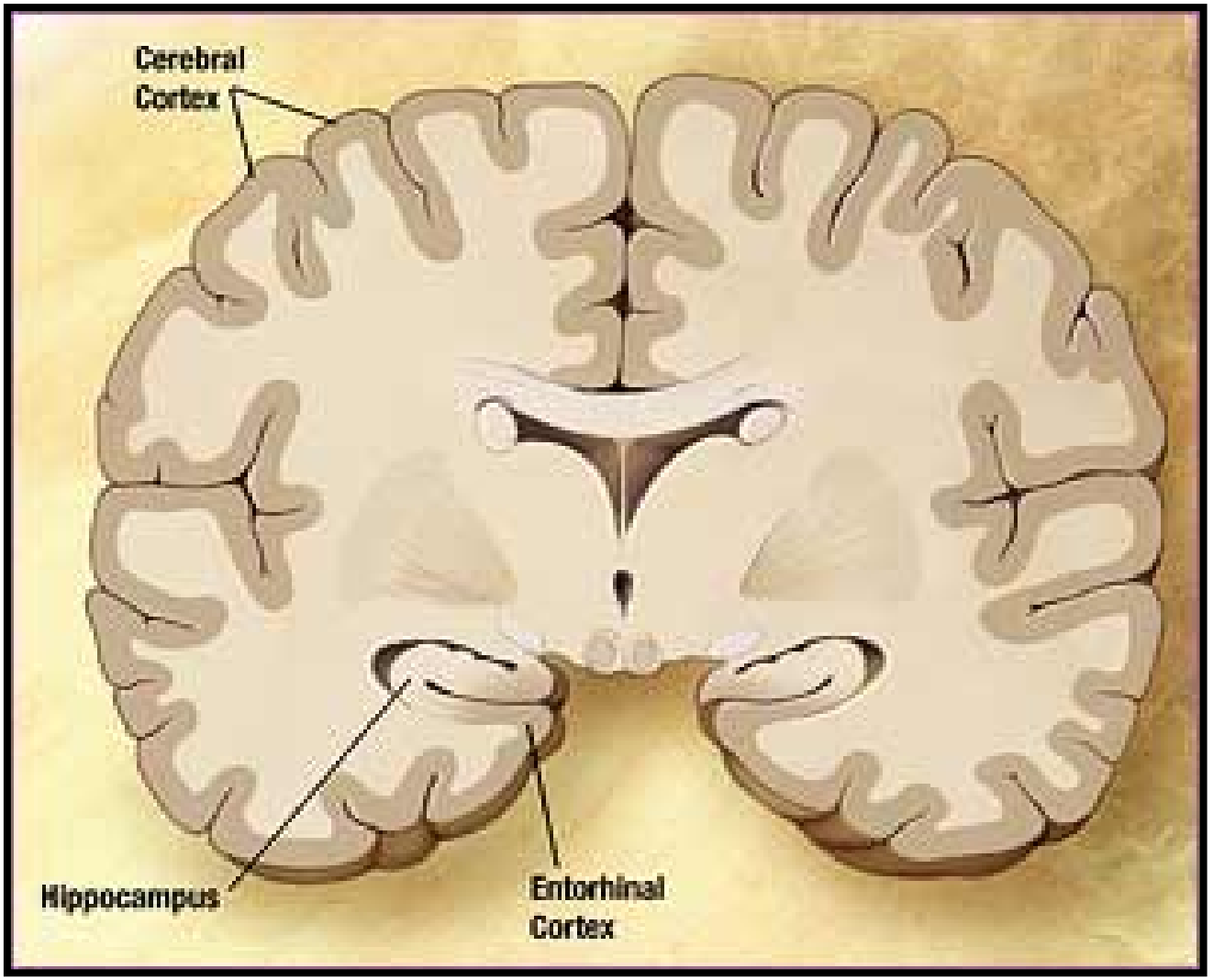
TAU (T) in carriers of the E280A Mutation

(Quiros et al, 2016)



Age	28	38	42	44
MMSE	29	26	28	28
Education	11	2	6	11
PiB (DVR)	1.12	1.27	1.50	1.61
DX	Asymptomatic	Asymptomatic	Asymptomatic	MCI

Entorrinal Cortex and Hippocampus

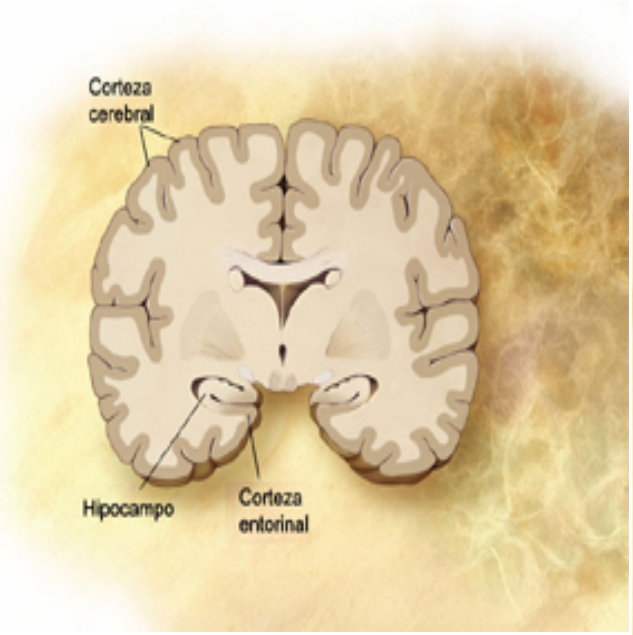


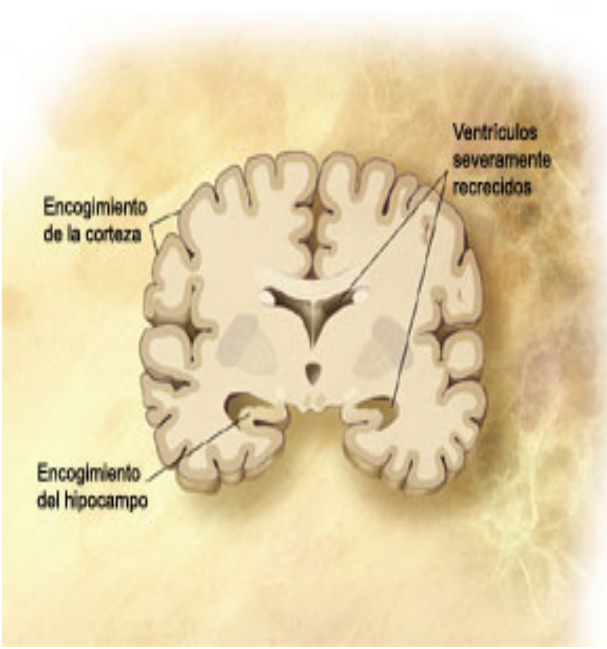
ATN

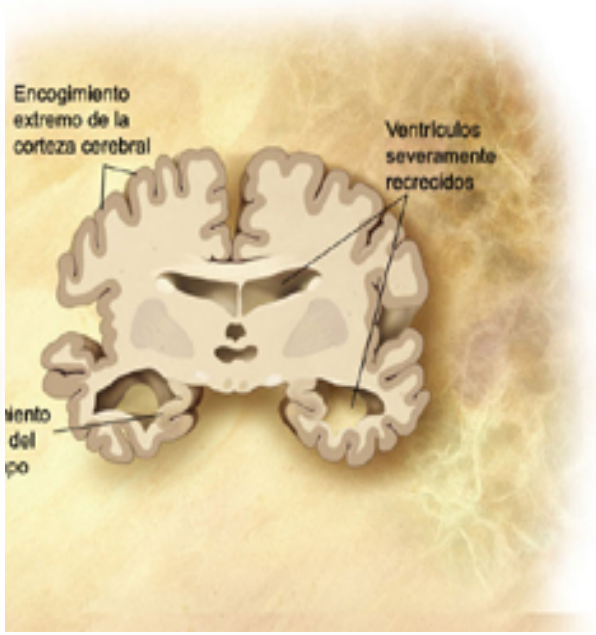
Pre DCL

Leve a Moderado

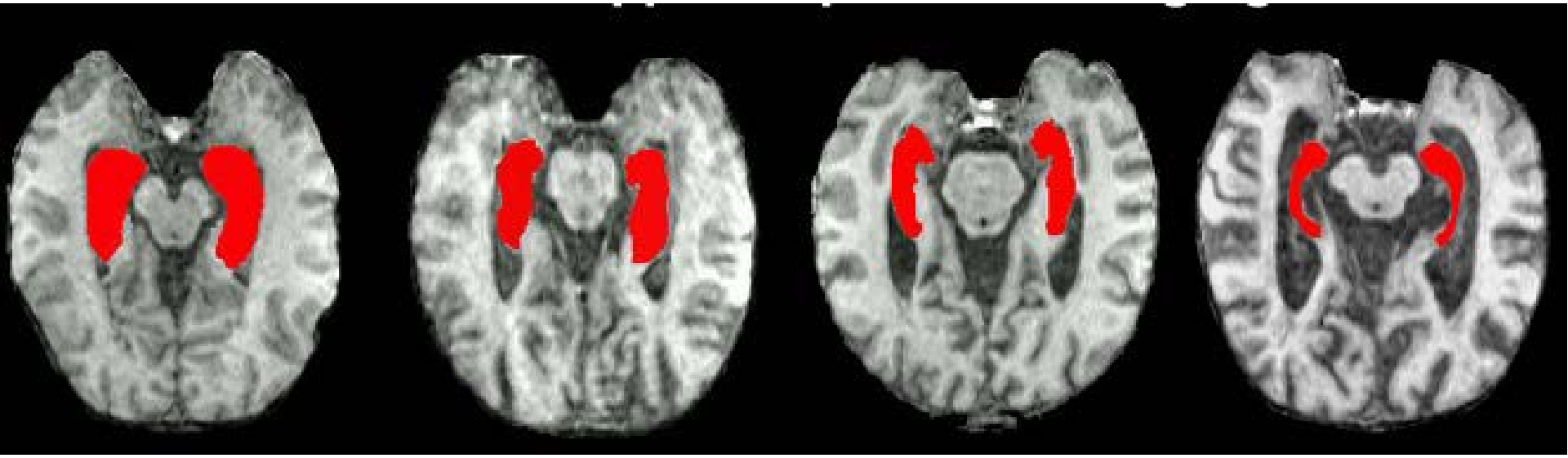
Severa







Biomarkers of Preclinical AD
Atrophy of the Hippocampus



Normal

Pre-MCI

MCI

Dementia

PET FDG ATN

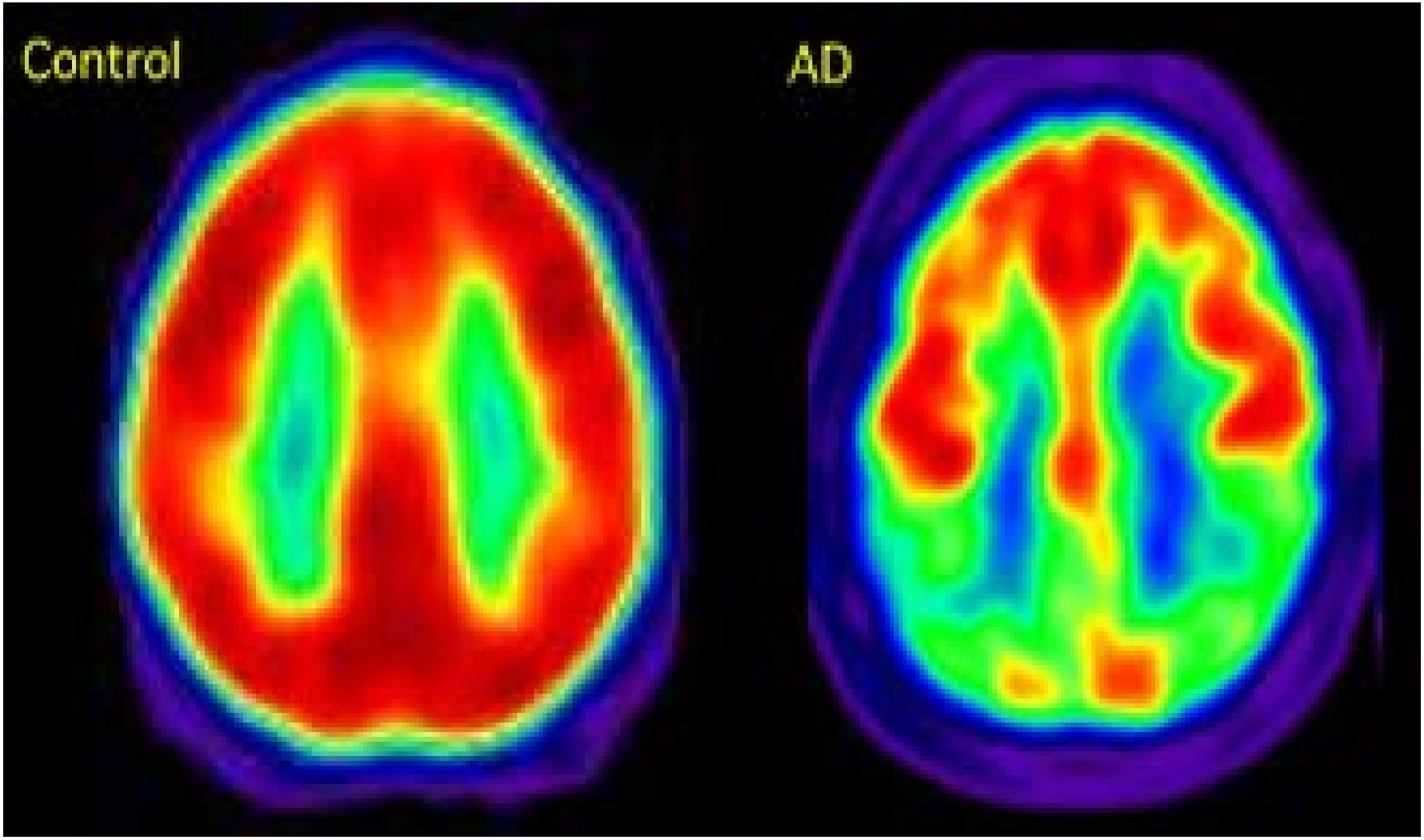
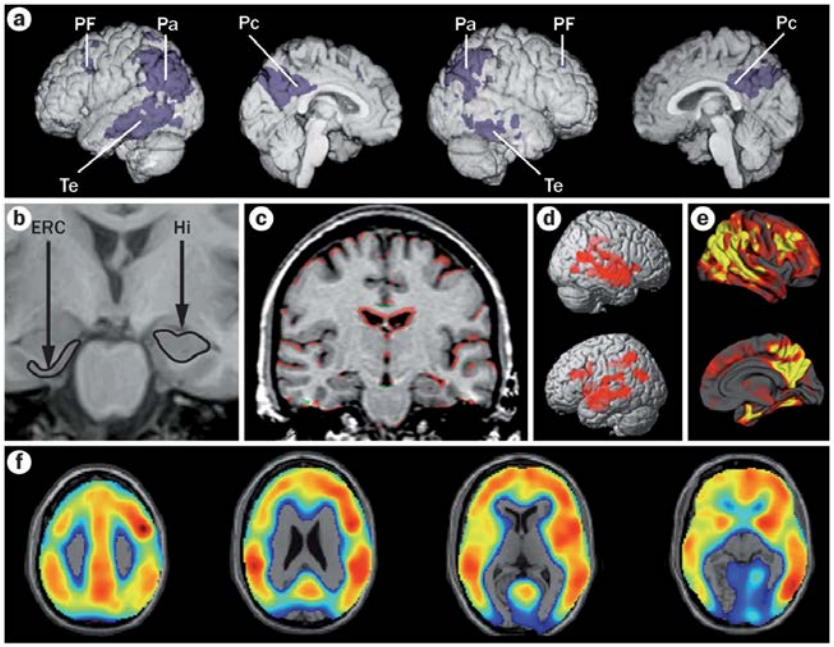


Figure 2 Selected brain imaging approaches for detection of AD



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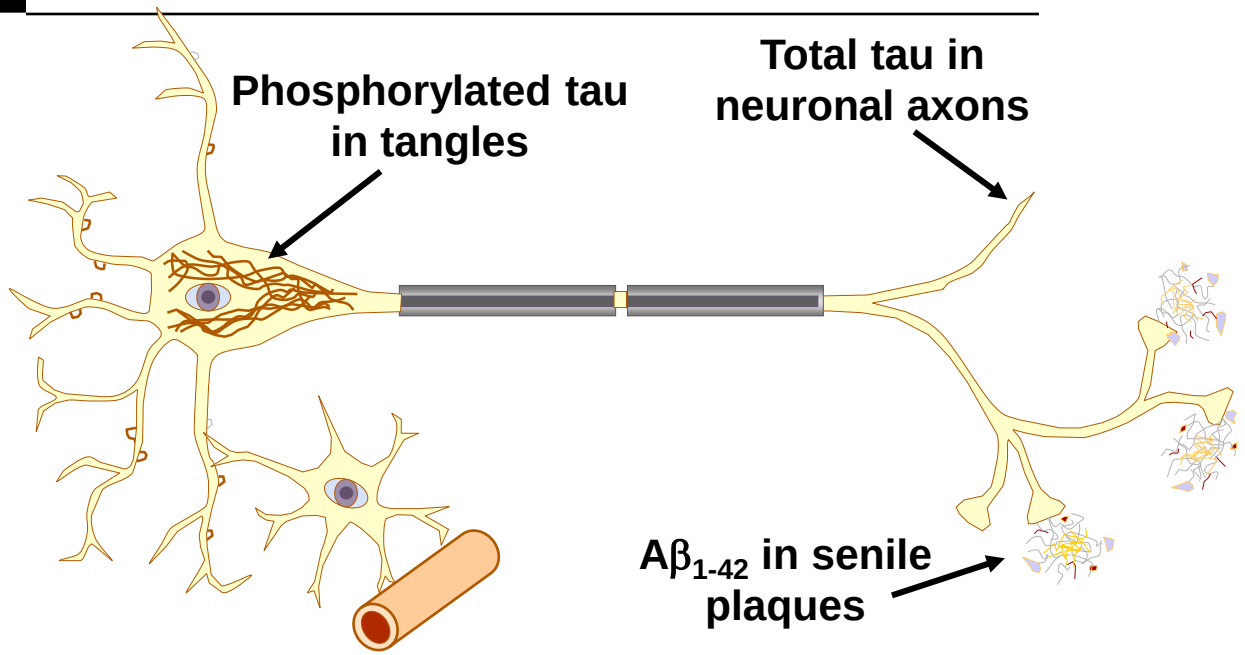
Langbaum, J. B. *et al.* (2013) Ushering in the study and treatment of preclinical Alzheimer disease *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2013.107

nature REVIEWS NEUROLOGY

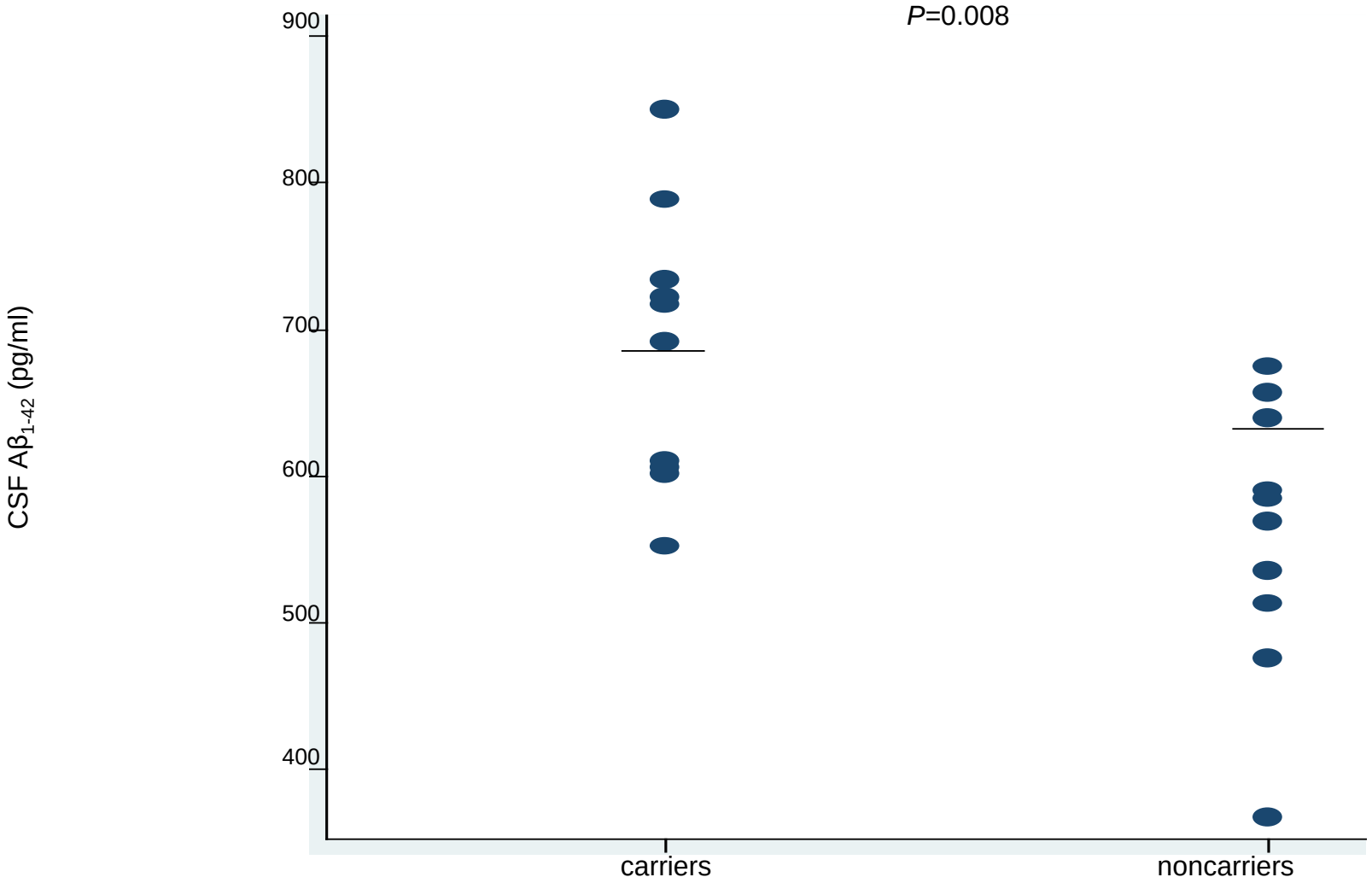
Biomarkers in CSF in AD

	Aβ42	Tau	Ptau
EA	↓↓	↑↑	↑↑
DCL	↓ or N	↑ or N	↑ or N
Control	N	N	N



Higher (not lower) CSF $A\beta_{1\text{-}42}$ Levels in E280A Population

(Fleisher, et al, 2015)



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The Lancet Neurology, Volume 10, Issue 3, Pages 213 - 220, March 2011
doi:10.1016/S1474-4422(10)70323-9 Cite or Link Using DOI
Published Online: 04 February 2011

< Previous Article | Next Article >

Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study

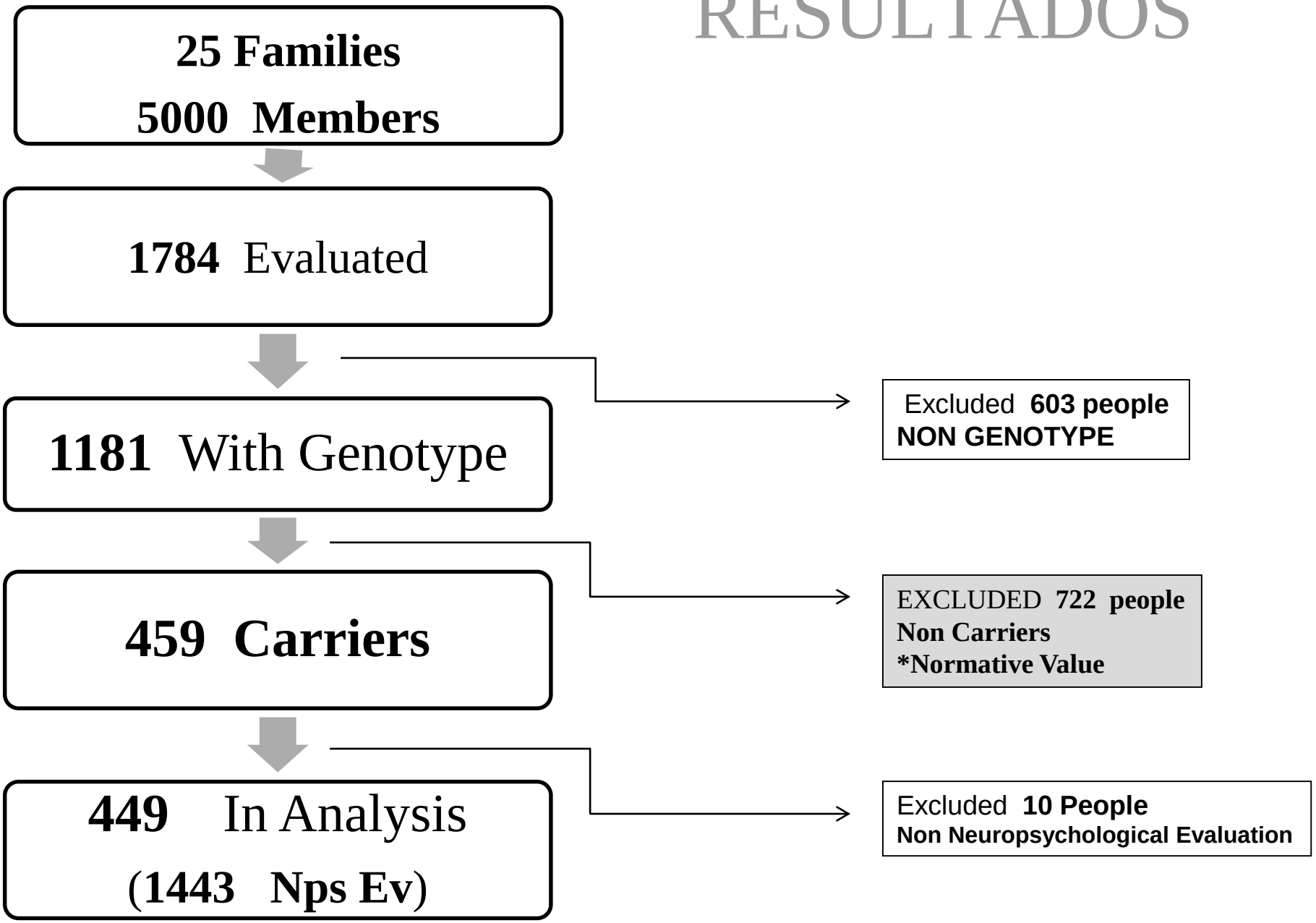
Natalia Acosta-Baena MD [a b c], Diego Sepulveda-Falla MD [a d], Carlos Mario Lopera-Gómez MSc [e], Mario César Jaramillo-Elorza MSc [e], Sonia Moreno MSc [a], Daniel Camilo Aguirre-Acevedo MSc [a b], Amanda Saldarriaga BSc [a], Prof Francisco Lopera MD [a]

Methods

Design:

We retrospectively assessed a Cohort of descendants of *PSEN1 E280A mutation carriers* *from 1995 to 2010*

RESULTADOS


25 Families
5000 Members
1784 Evaluated
1181 With Genotype
459 Carriers
449 In Analysis
(1443 Nps Ev)
Excluded 603 people
NON GENOTYPE
EXCLUDED 722 people
Non Carriers
*Normative Value
Excluded 10 People
Non Neuropsychological Evaluation

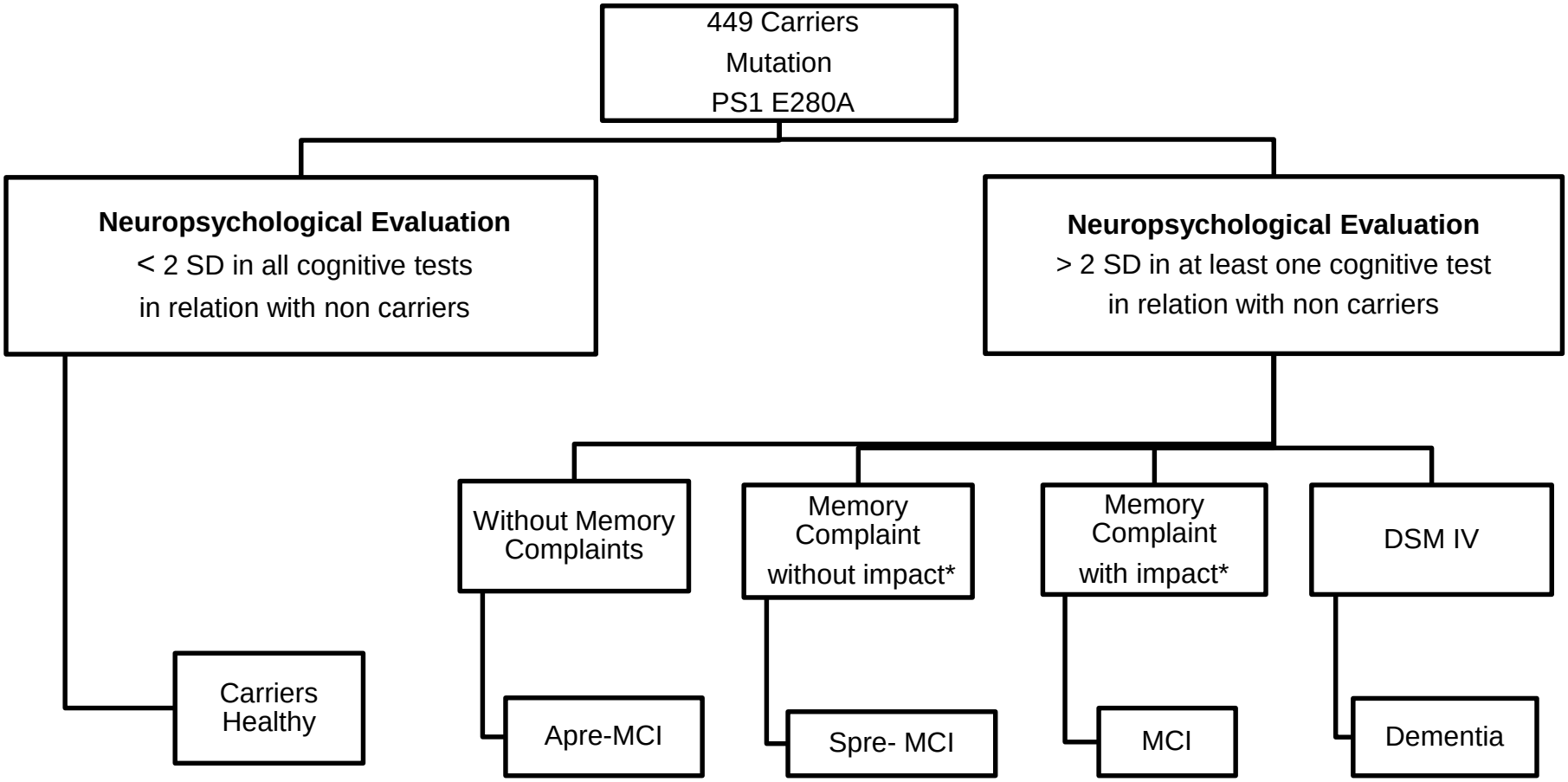
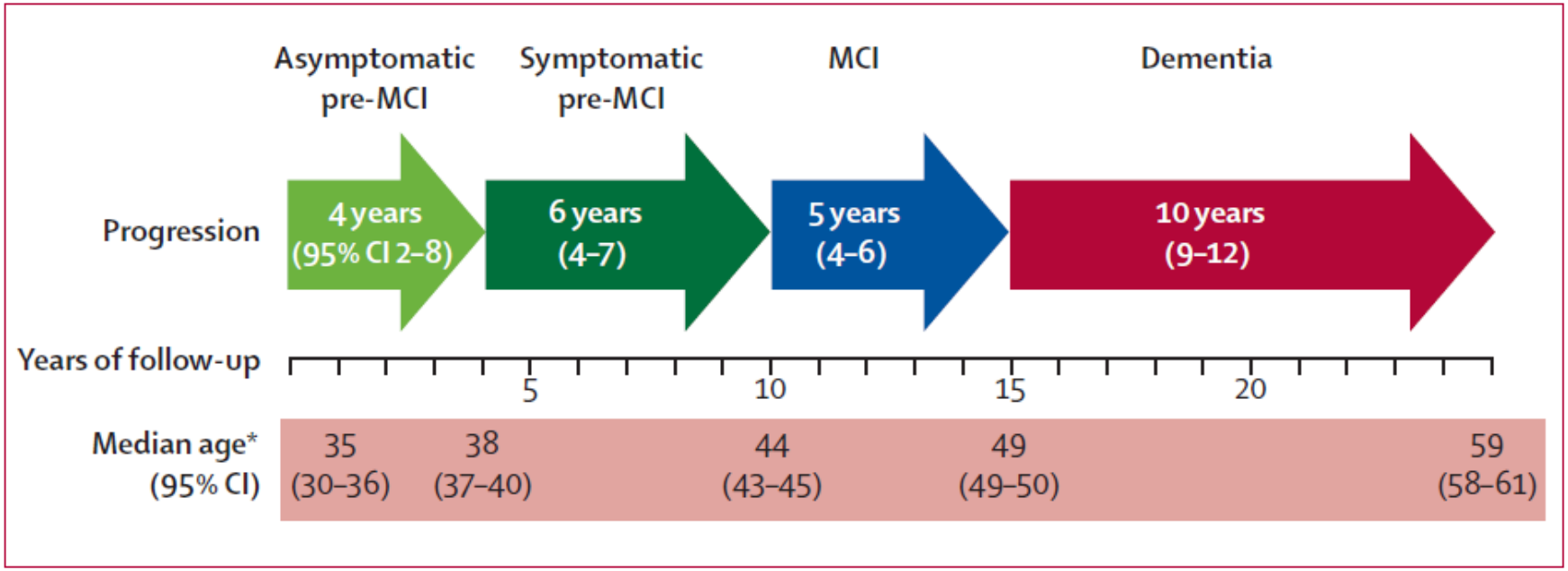


Figure 2: Clasifiación restrospectiva de los portadores E280A de acuerdo con los criterios de cada estado.
Portadores sanos: asintomáticos con puntajes en evaluación neuropsicológica menos de 2SD del promedio de acuerdo a la edad y educación.
*Impacto: Alto puntaje en la escala de quejas subjetivas de memoria con ninguna o mínima alteración en actividades instrumentales complejas y sin alteraciones en las actividades básicas de la vida cotidiana. .

Conclusions

Figure 2: **Survival analysis of disease progression in *PSEN1* E280A carriers**
MCI=mild cognitive impairment.



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JAMA Neurology

Original Investigation | February 22, 2016

Cognitive Decline in a Colombian Kindred With Autosomal Dominant Alzheimer Disease

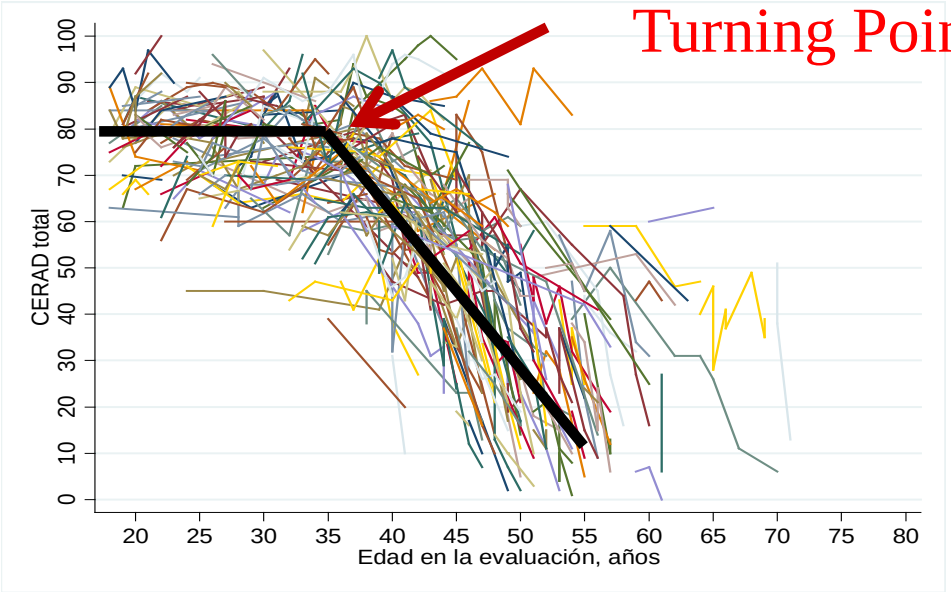
A Retrospective Cohort Study ONLINE FIRST

Daniel C. Aguirre-Acevedo, PhD[1,2]; Francisco Lopera, MD[1]; Eliana Henao, MS[1]; Victoria Tirado, MS[1]; Claudia Muñoz, MS[1]; Margarita Giraldo, MD[1]; Shrikant I. Bangdiwala, PhD[3]; Eric M. Reiman, MD[4]; Pierre N. Tariot, MD[4]; Jessica B. Langbaum, PhD[4]; Yakeel T. Quiroz, PhD[1,5]; Fabian Jaimes, PhD[2,6]

[+] Author Affiliations

JAMA Neurol. Published online February 22, 2016. doi:10.1001/jamaneurol.2015.4851

Estimate of the change point (CP) In CERAD



$$Y_{it} = \beta_{0i} + \beta_{1i}t + \beta_{02i} + \beta_{12i}t + \varepsilon_{it}$$

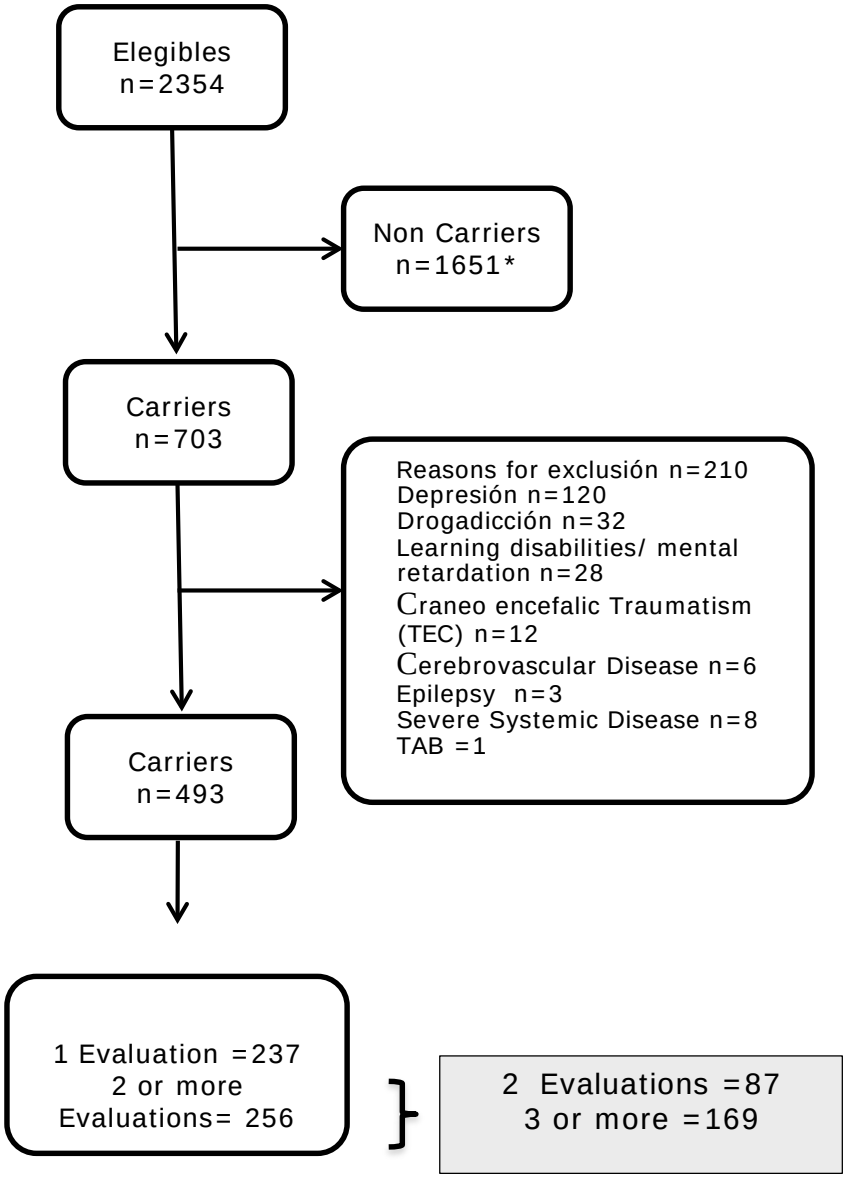
$$E(Y_{it}) = \begin{cases} \beta_{01i} + \beta_{11i}t & \text{If } t \le \tau \\ \beta_{02i} + \beta_{12i}t & \text{If } t > \tau \end{cases}$$

Función antes del punto de cambio

Función después del punto de cambio

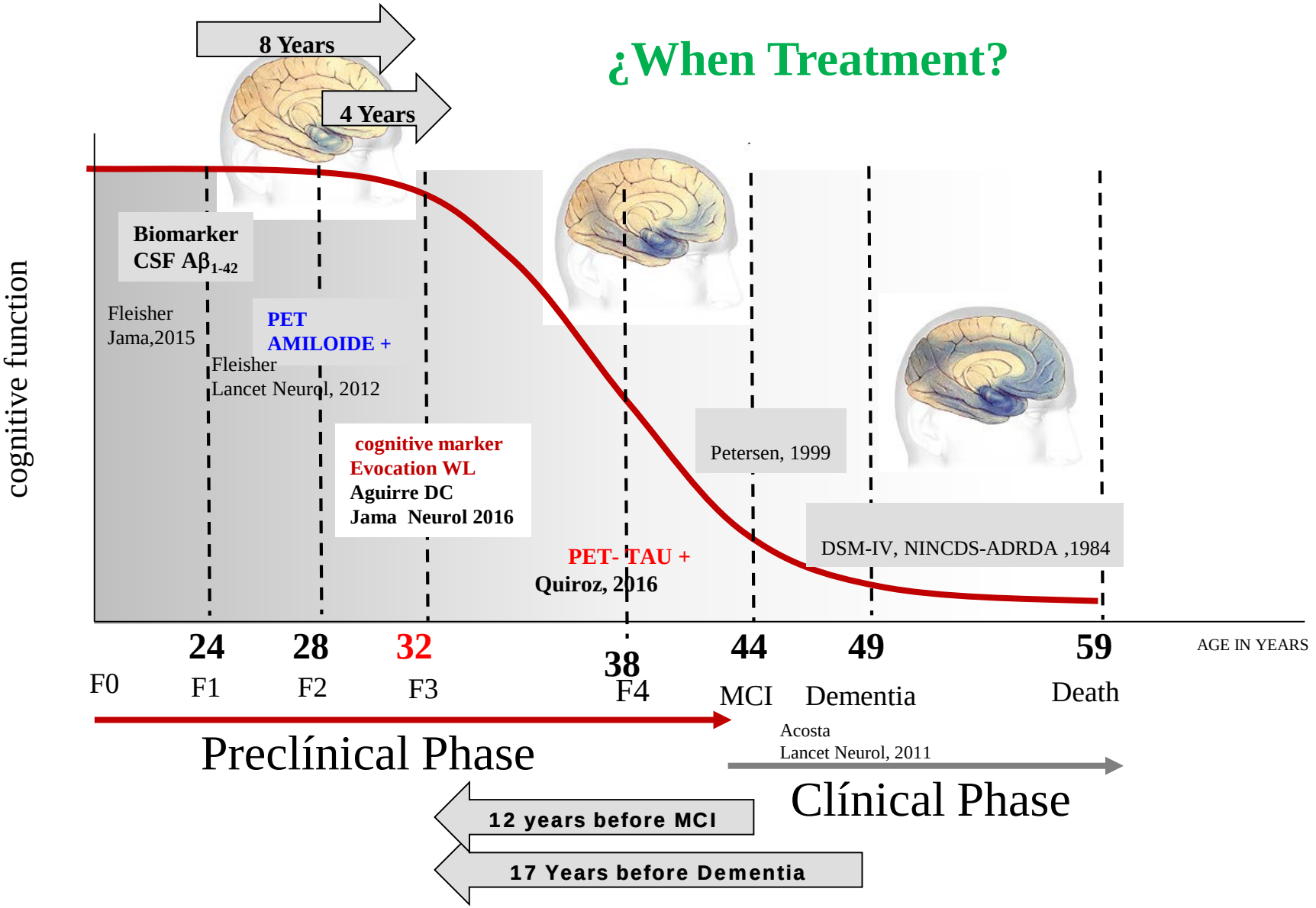
Hall CB, et al. Stat Med. 2000;19(11):1555-1566

Estimate of the change point (CP) In CERAD (Aguirre 2015)



*1287 Datos de los no portadores fueron utilizados para la comparación con los portadores. Distribución de exclusiones similar a la de los portadores.

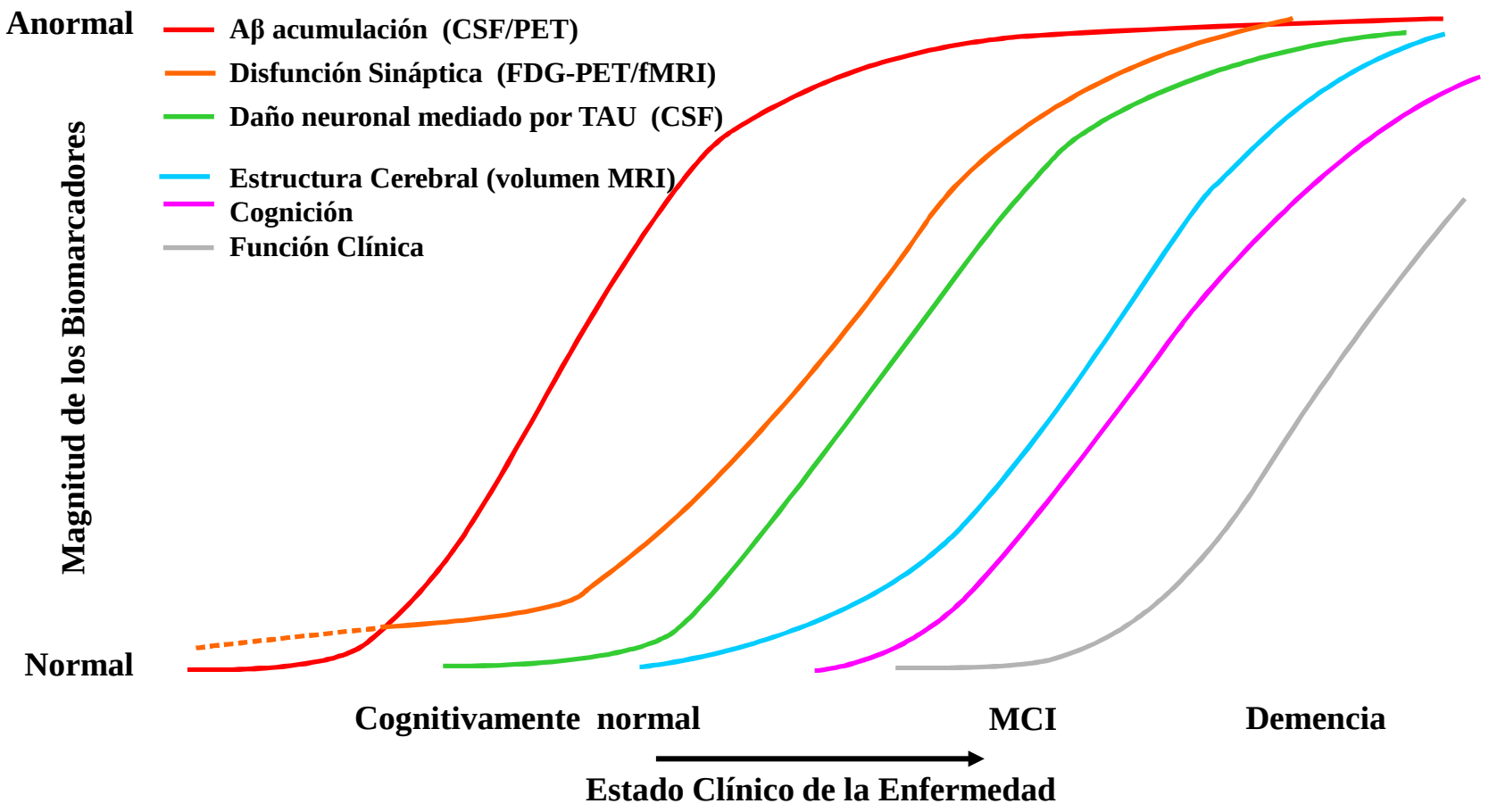
Clinical and Preclinical phases in FAD caused by E280A PS1 Mutation (Aguirre et al, 2015)



Sperling R, et al. Alzheimer's & Dementia, 2011; 7(3): 280-292

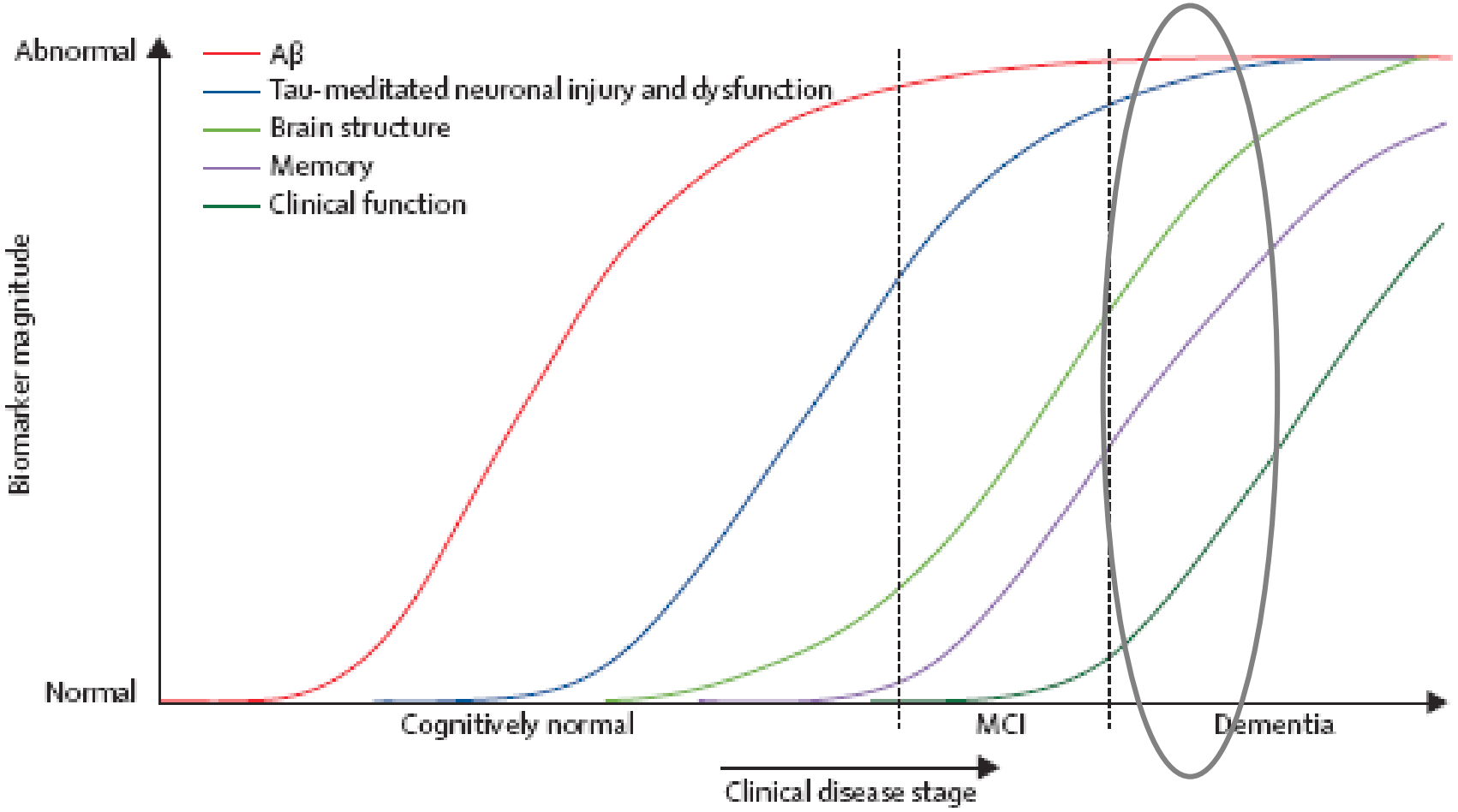
ALZHEIMER'S PREVENTION INITIATIVE

Alzheimer's disease is a continuum



Sperling, et al. *Alzheimers Dement.* 2011;7:280-292.

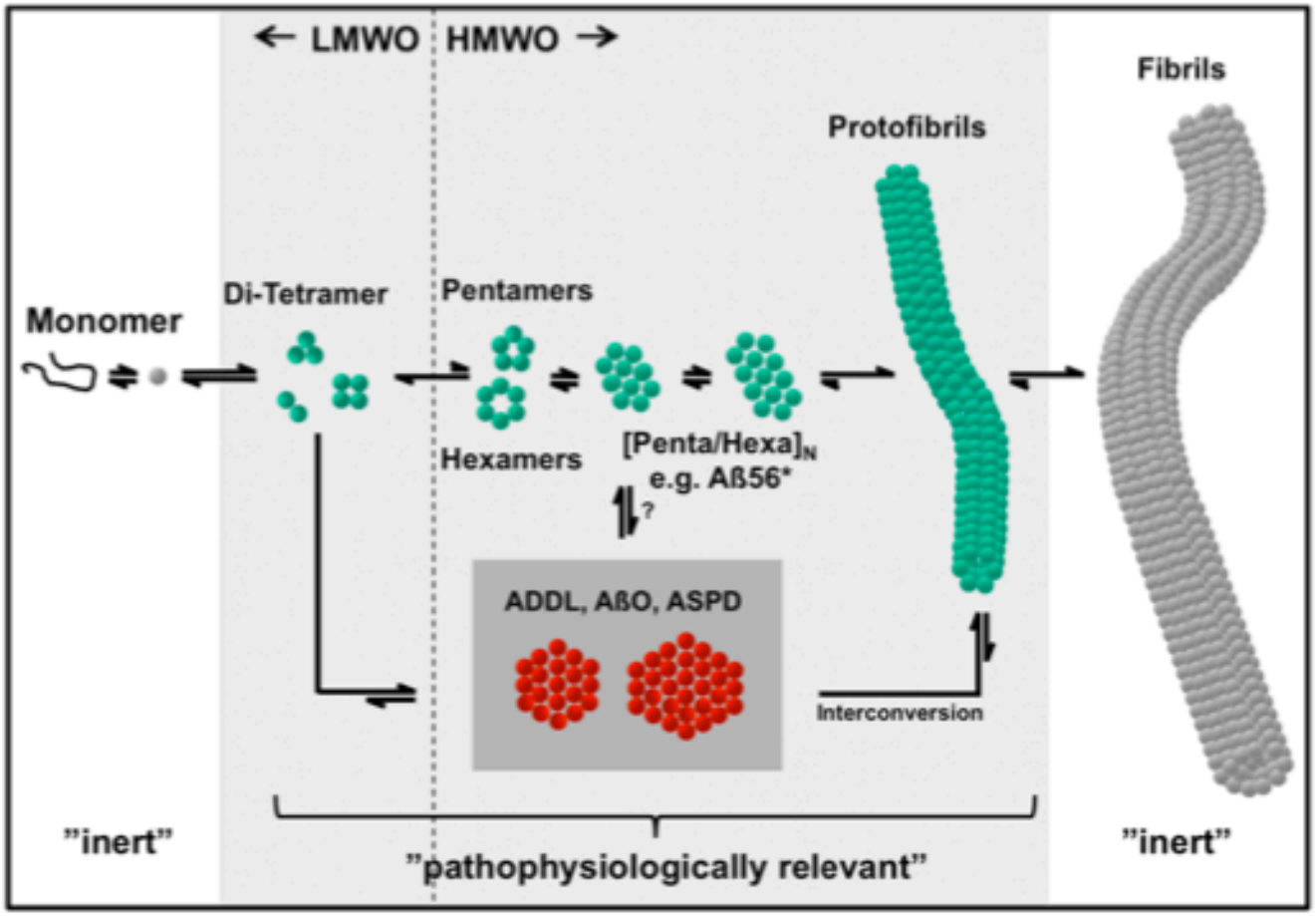
Pathological cascade implications for therapy: treatment and prevention



Jack et al, Lancet Neurol 2010; 9: 119-28

Ab Amyloid = CSF Ab42 or amyloid PET imaging; Tau Mediated Neuron Injury and Dysfunction = CSF tau or FDG PET; Brain Structure = structural MRI

Aβ Amyloid species (Therapeutic targets)



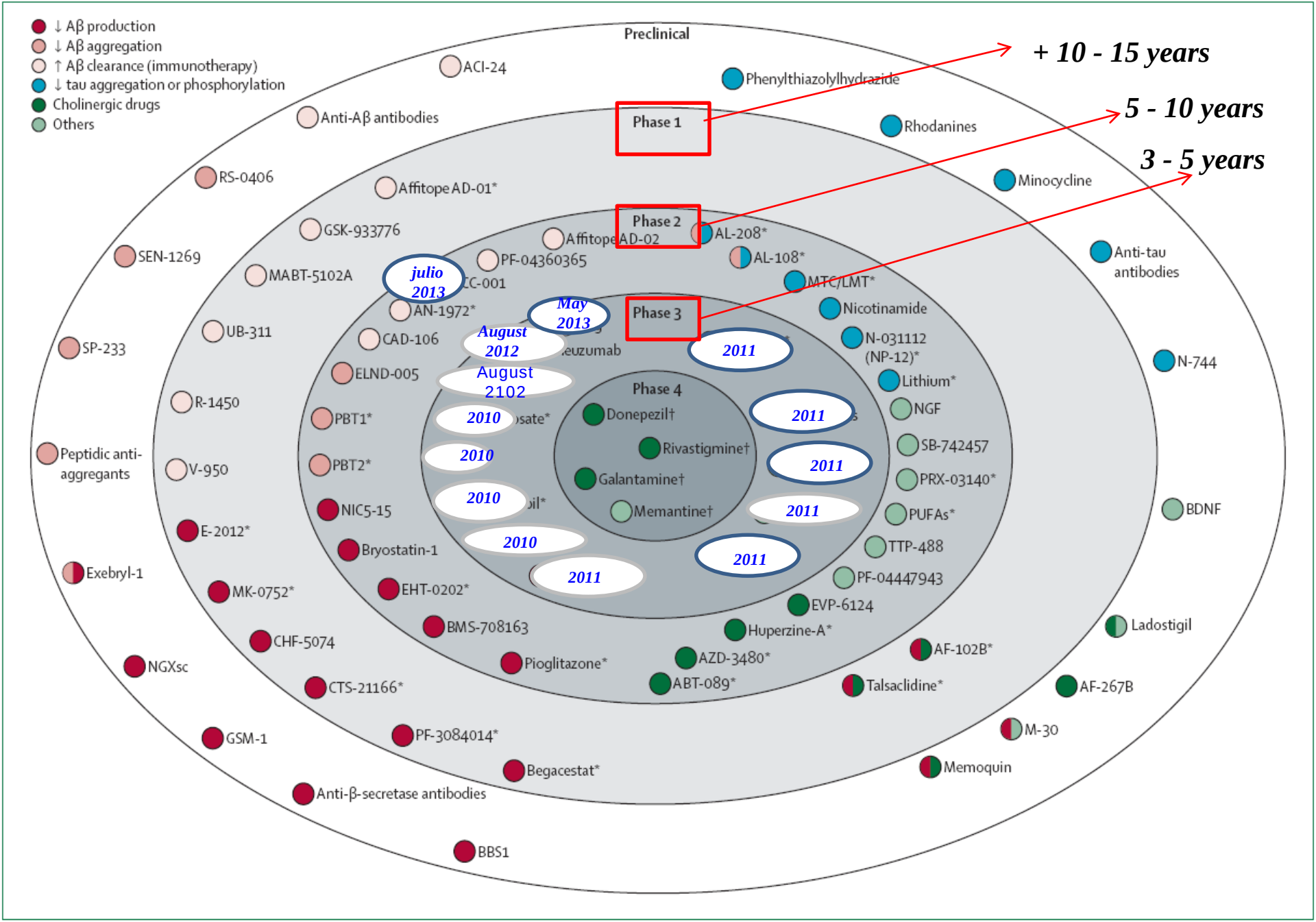
- Bace

Sola

Gante Adeca Crene

Gante
Adeca

Anti-tau



Mangialasche F et al. Lancet Neurol 2010; 9: 702–716

Anti-amyloid Medications in People with Symptomatic AD?

BAPINEZUMAB : suspended by cerebral Edema

SOLANEZUMAB: ineffective

ADECANUMAB: ineffective

CRENEZUMAB: ineffective

GANTENERUMAB: ineffective

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INICIATIVA DE PREVENCIÓN DEL ALZHEIMER COLOMBIA

Amyloid Inmunothrapy for AD

4 BACE INHIBITORS

DISCONTINUED in patients with mild-to-moderate or prodromal AD

Verubecestat
Atabecestat
Lanabecestat
LY3202626

Amyloid Inmunothrapy for AD

Two GAMA Secretasa inhibitors:

Detrimental effects on cognition in Prodromal and established AD patients

---

Semagacestat

Avagacestat

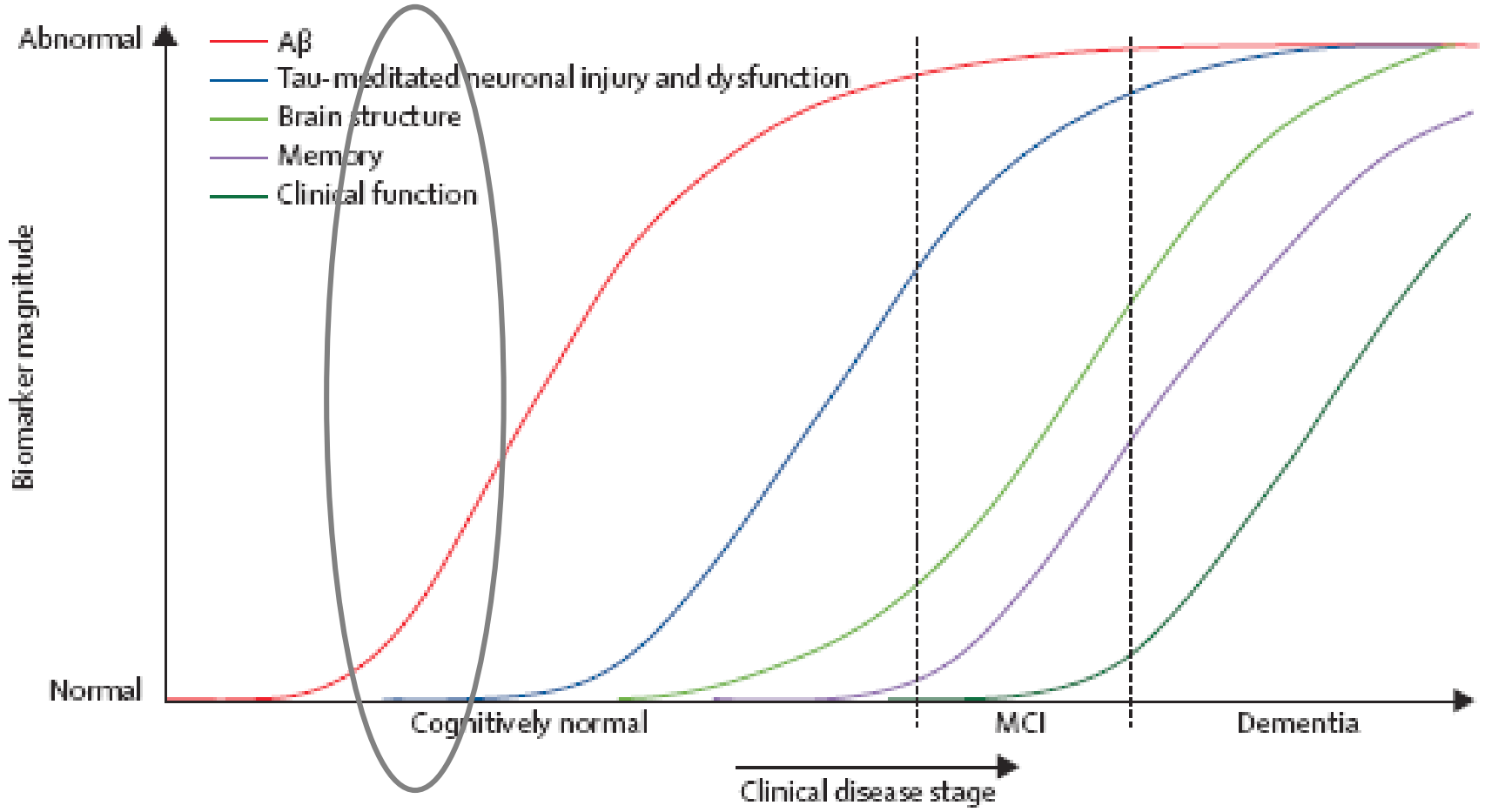
Physiological Role of AB

In AD **Aβ Amyloid** overproduction and accumulation may represent an adaptative response.

The real cause of the initial neuronal damage would not be **Aβ** accumulation but other possible insults like:

1. Chronic inflammation
2. Tau associated network disruption
3. Metabolic failure
4. Abnormal microglial activation
5. Oxidative stress
6. Cholesterol stress
7. Multiple causes

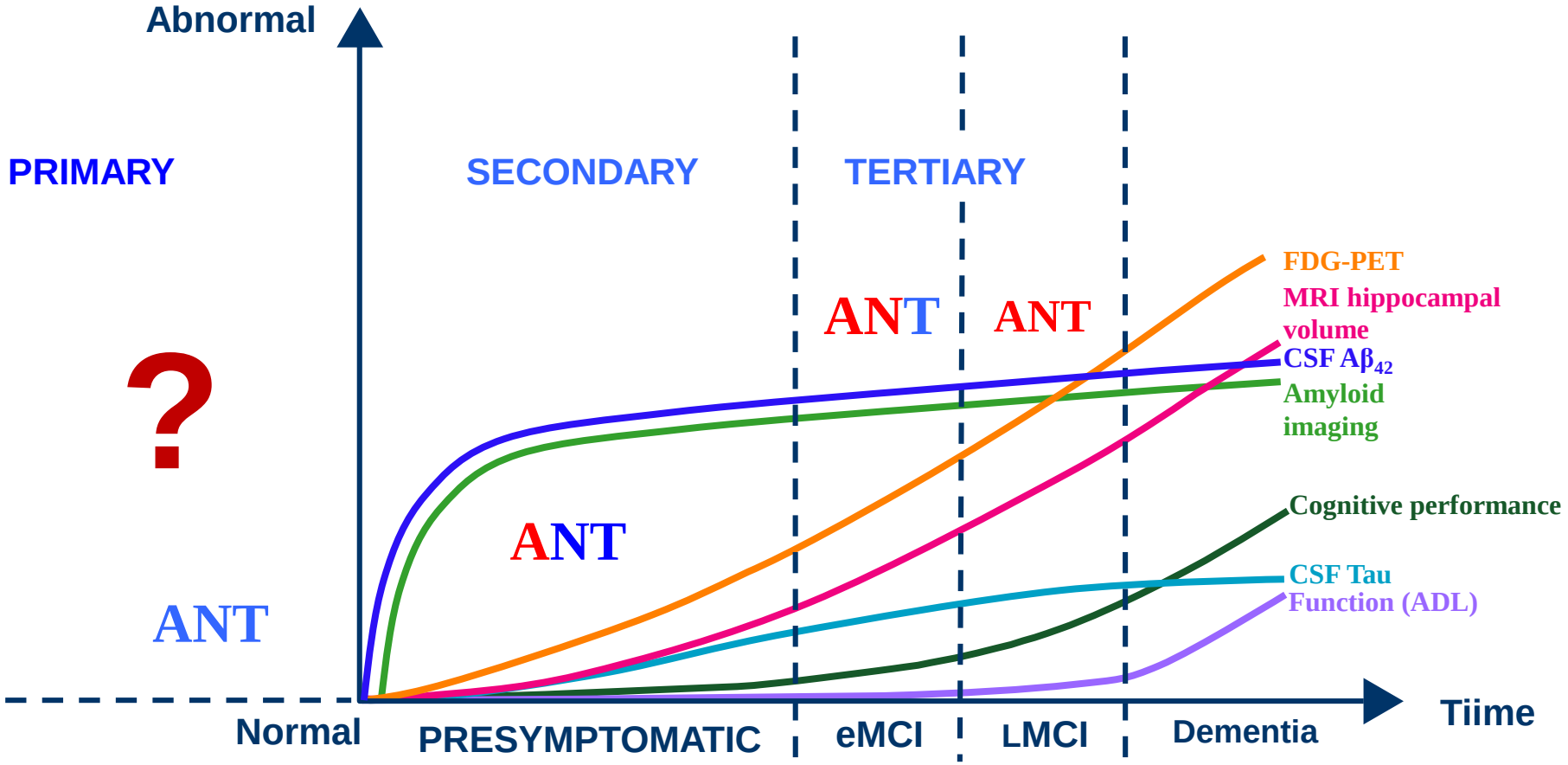
TIME FOR PREVENTION



Jack et al, Lancet Neurol 2010; 9: 119-28

Ab Amyloid = CSF Ab42 or amyloid PET imaging; Tau Mediated Neuron Injury and Dysfunction = CSF tau or FDG PET; Brain Structure = structural MRI

PREVENTION



Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

CLINICAL TRIAL
API COLOMBIA
GN28352
(CRENEZUMAB)

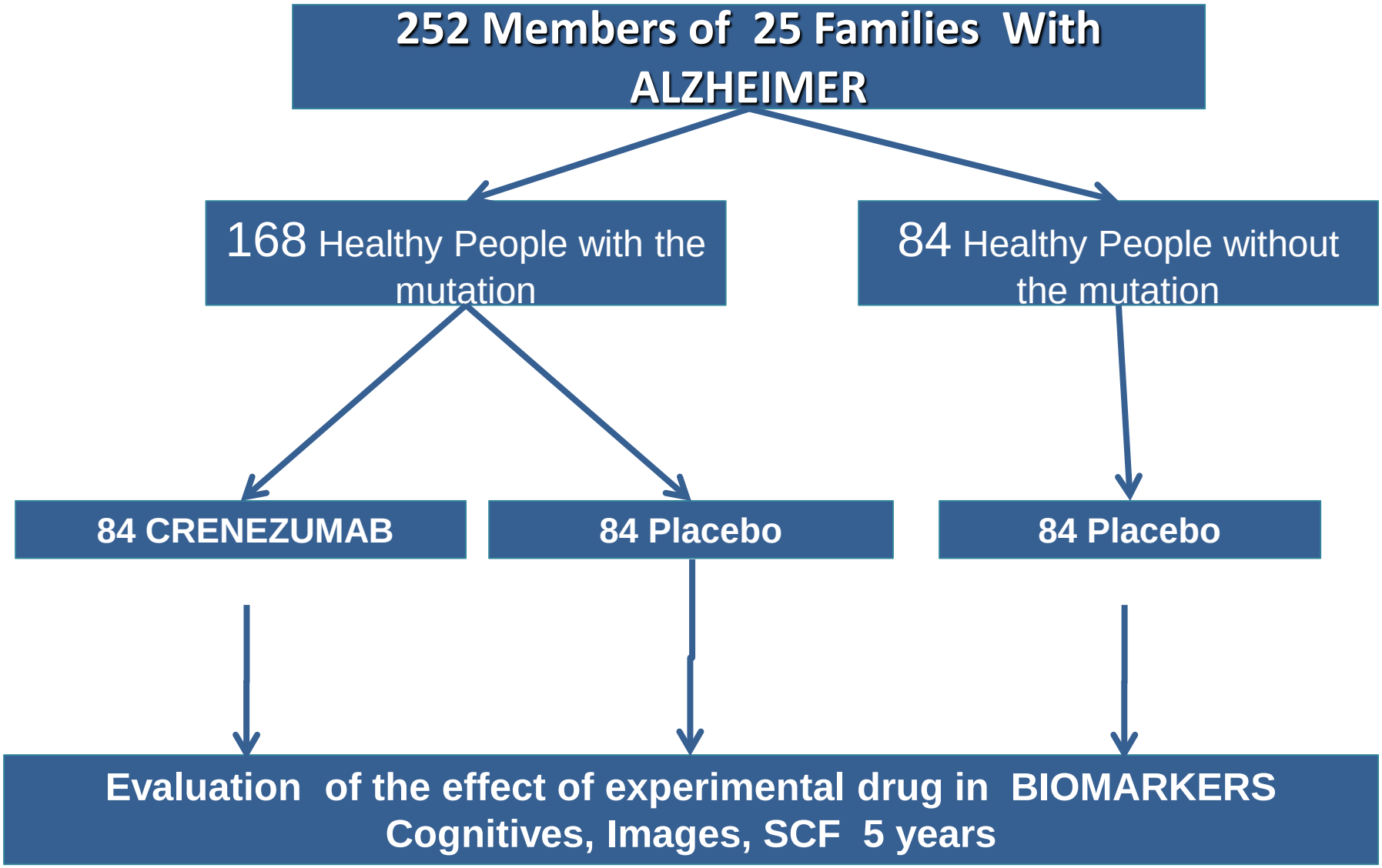
Conducted by Neurosciences Group of Antioquia:

supported by NIA, Banner, Genentech & Roche

Launched 2nd half 2013

INICIATIVA DE PREVENCIÓN DEL ALZHEIMER COLOMBIA

Clinical Trial for ALZHEIMER PREVENTION



Anti-amyloid Medications in Asymptomatic AD?

BAPINEZUMAB : suspended by cerebral Edema

SOLANEZUMAB: 2021

ADECANUMAB: Suspended plan to use it in asymptomatic

CRENEZUMAB: 2022

GANTENERUMAB: 2020

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INICIATIVA DE PREVENCIÓN DEL ALZHEIMER COLOMBIA

How to identify populations with a high risk of Alzheimer's disease

1. Population with a family history of Dementia and genetic risk factors for EA
2. Population with environmental Risk Factors for cognitive impairment and Dementia
3. Populations with amnesic MCI
4. Populations with Amyloidosis

Populations with enviromental and conductual Risk Factors for cognitive impairment and Dementia

CV factor risks

Diabetes

Hypertension

Obesity

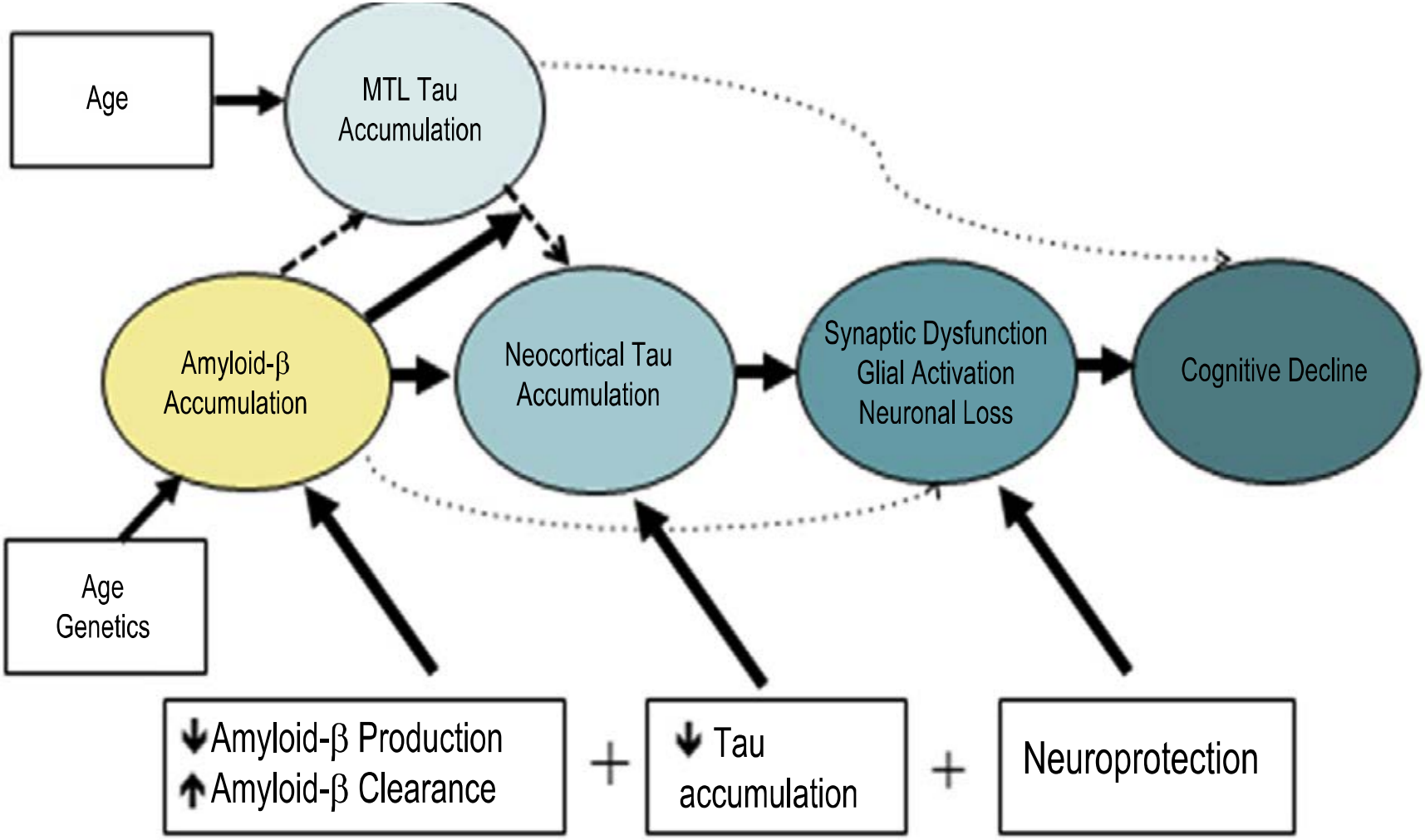
Dyslipidemia

Life-style Risks

1. Physical, intellectual, social and emotional inactivity
2. Smoking
3. Diet

Hypothetical interaction of amyloid and tau in preclinical AD

Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 64-75



Strategy for AD Prevention

STEP 1

Recommendations to General Population

Older than 50 years

1.Life-Style

2.CV risk factors

STEP 2

Multidomain Long-term Intervention to individuals with high risk for AD

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INICIATIVA DE PREVENCIÓN DEL ALZHEIMER COLOMBIA

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Can Alzheimer´s be Stopped?

Given that in Genetic Alzheimer's (ADFAD)
we know who will develop the disease
this is an exceptional window
to look for ways to prevent it

THE Neuroscience Group TEAM

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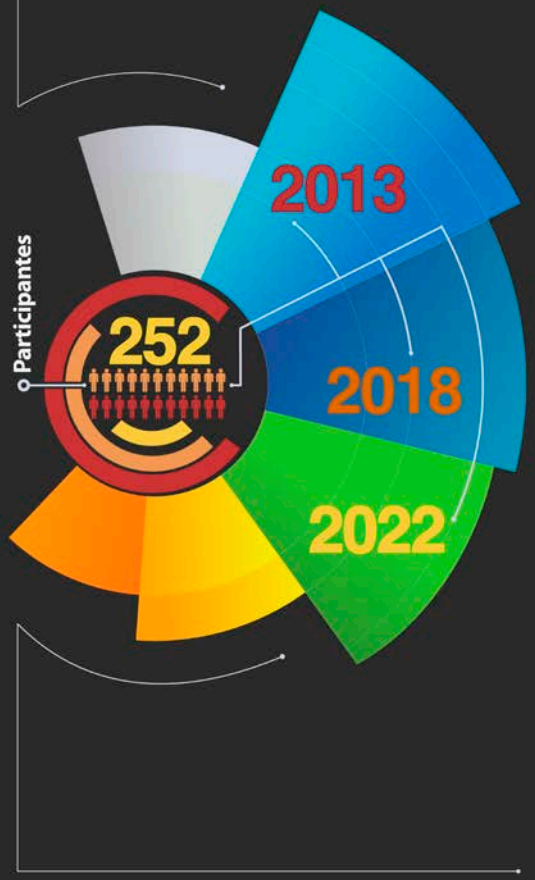
Alzheimer's Prevention Initiative

En colaboración con varias instituciones nacionales e internacionales, el GNA lleva a cabo el estudio de prevención API Colombia GN28352, que por primera vez se hace con personas cognitivamente sanas pero que están en alto riesgo de desarrollar la enfermedad de Alzheimer debido a su historia genética.

En este trabajo conjunto, participan las siguientes instituciones:



Sitios principales:
Universidad de Antioquia, SIU, GNA.

Sitios satélites:
Hospital San Juan de Dios – Yarumal
Servicios Médicos MS – Bogotá
Fundación Cardiomet – Armenia

Proveedores de Servicios
Disponibilidad e infraestructura física y técnica y prestación de servicios especializados indispensables en la ejecución del estudio.

Patrocinadores
Financiación y acompañamiento del estudio.

Roche
NIH
Banner Alzheimer's Institute
Fundación anónima

Administrador Financiero / CRO

Fundación Universidad de Atioquia
PRA Health Sciences
BIOCLINICA
MedAvante

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INTERNATIONAL COLABORATION

NIH (NIA): Support for API COLOMBIA

Banner and Genentech: Support to API Colombia Registry and CT

Sta Barbara California University	Kenneth Kosik
Banner institute Arizona	Eric Reiman, Pierre Tariot
Edinburgo University:	Sergio de la Salla. Mario Parra
University of Rosario	Mauricio Arcos-Burgos
Harvard University	Jhoseph Arboleda
Boston University	Yakeel Quiroz
Universidad de Oviedo	Fernando Cuetos
Washington University:	Alison Goate, Jhon Morris
Florida Atlantic University:	Mónica Roselli, A Ardila
Centro de Neurociencias de Cuba:	Maria A Bobes, M Valdés
Instituto Cajal Madrid España:	Javier de Felipe
University College of London:	Andrés Ruiz
Universidad de Hamburgo	Markus GLATZEL, Diego Sepulveda

NIH In EEUU: Max Muenke, Xavier Castellanos, Yudy Rapaport, Kate Berg