Grupo de Neurociencias\Universidad de Antioquia

UNIVERSIDAD DE ANTIOQUIA
1803

THE PAISA MUTATION FOR ALZHEIMER'S DISEASE: Cognitive and Clinical Biomarkers

MCI Symposium

Worshop- Miami January 15, 2017

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CONFLICT OF INTERESTS

Proyect: API COLOMBIA (IP)

Financed by:

NIH, Banner and Genentech

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OVERVIEW:

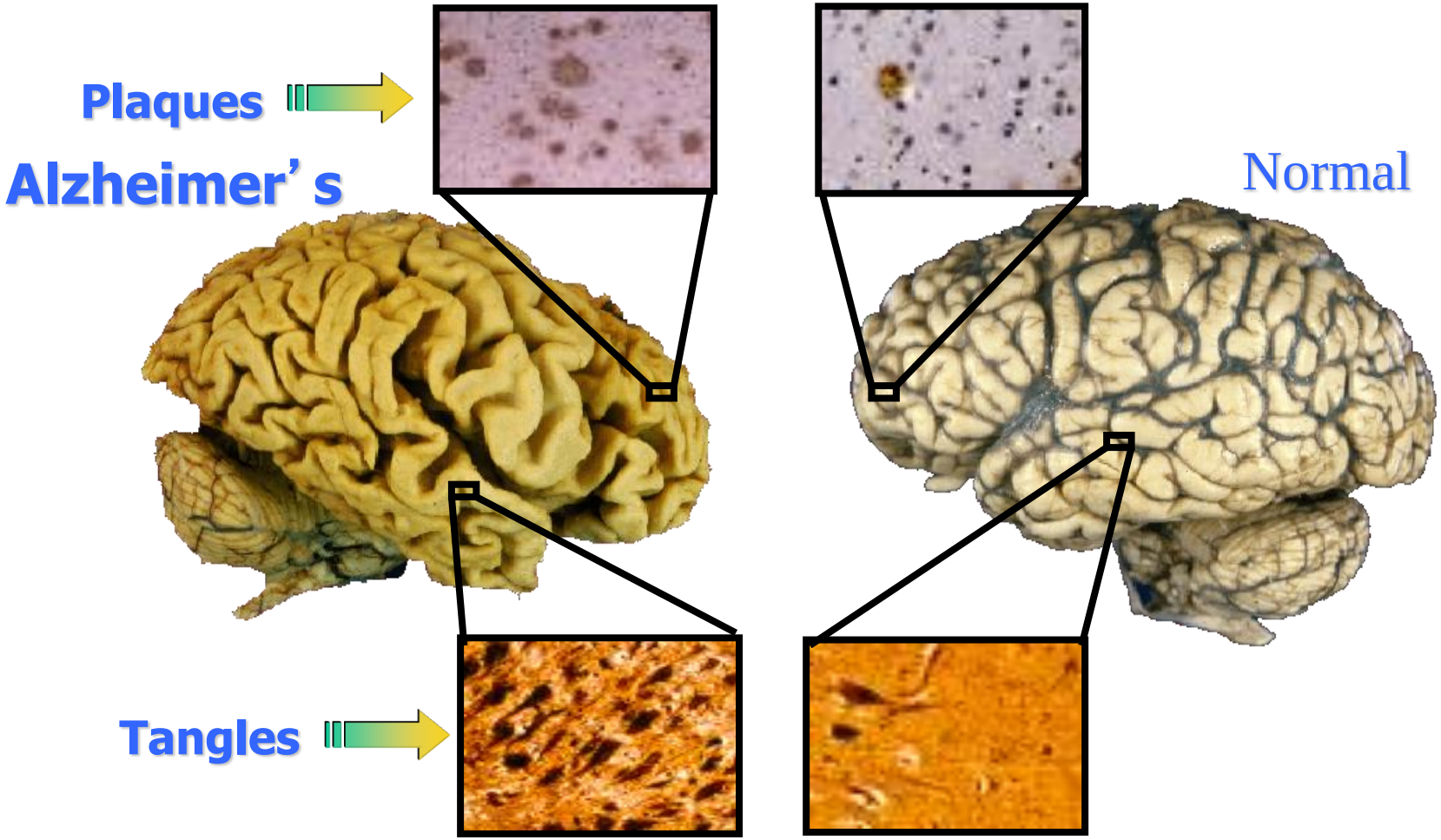
Description of the Presenilin-1 (PSEN1) E280ACohort

1. Cognitive and other Biomarkers

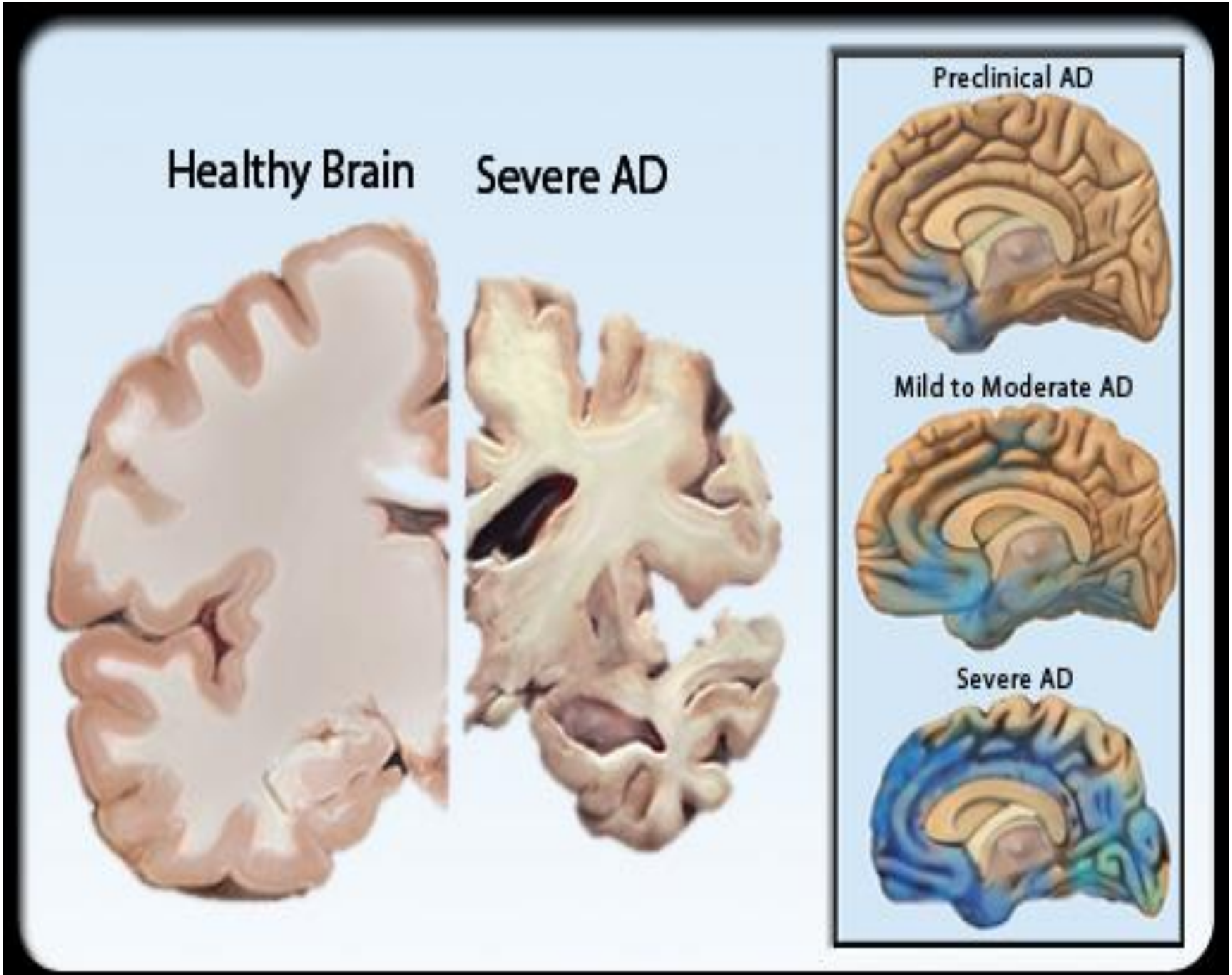
2. Predementia Clinical Stages

1. API Colombia- Research Study

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

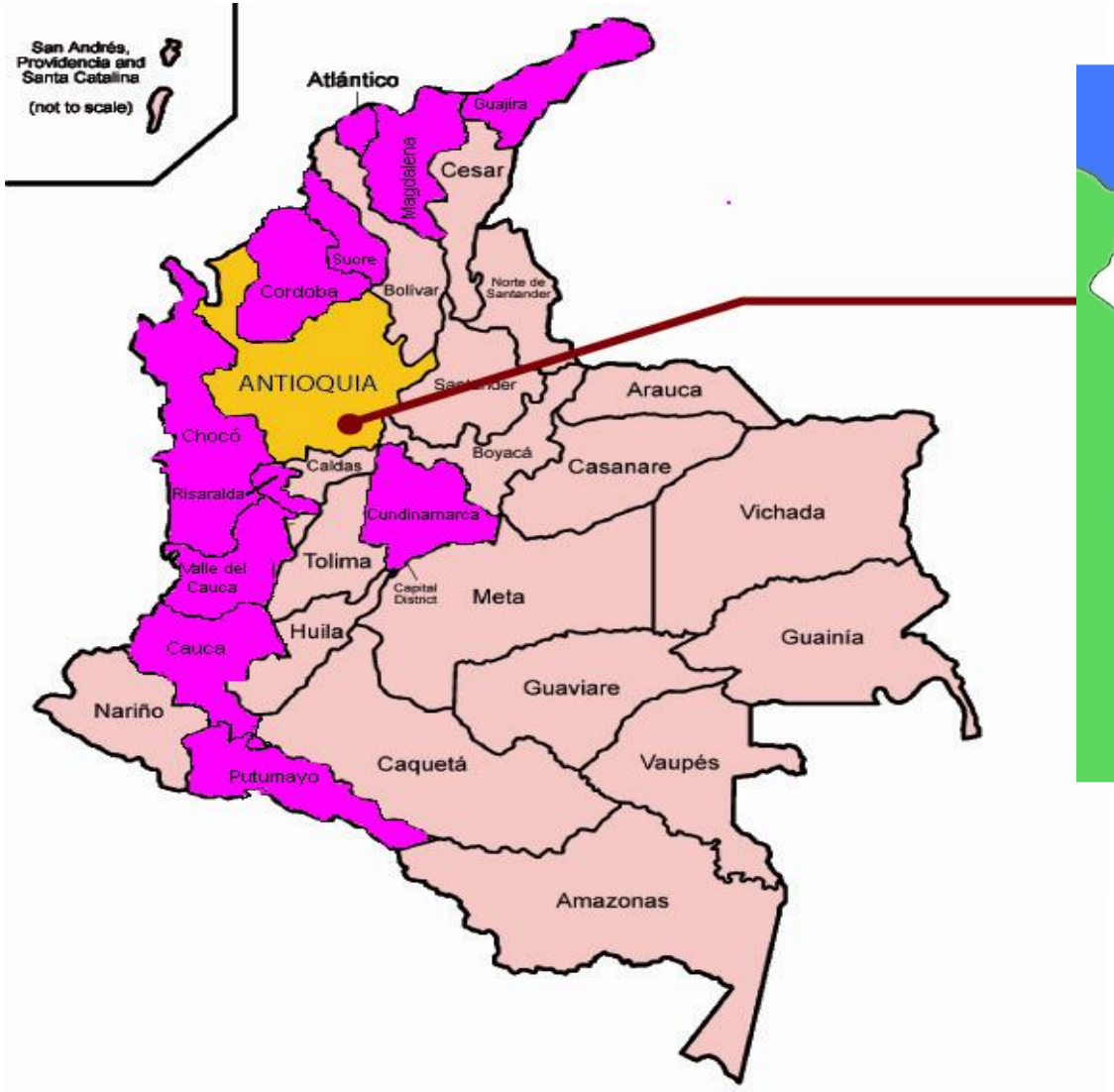


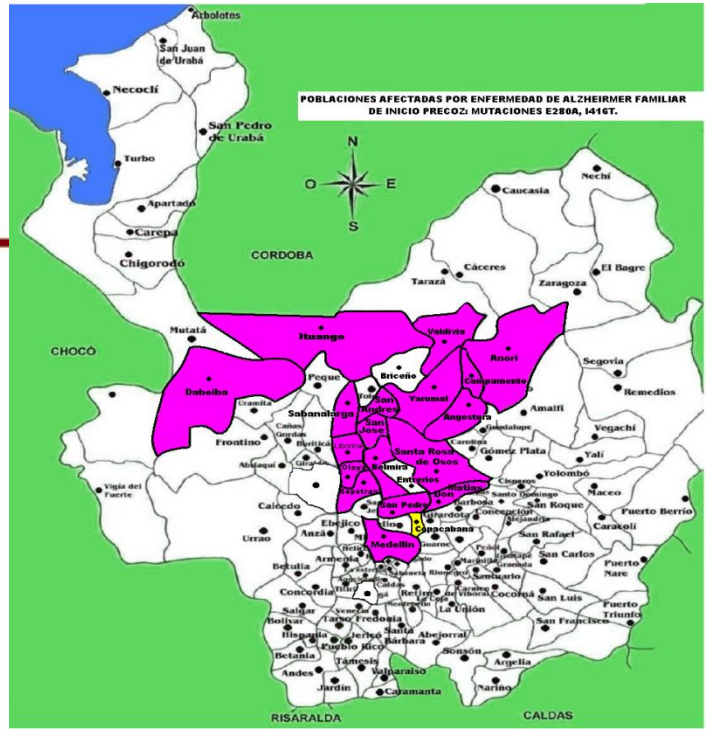
Courtesy of Harry Vinters, MD.

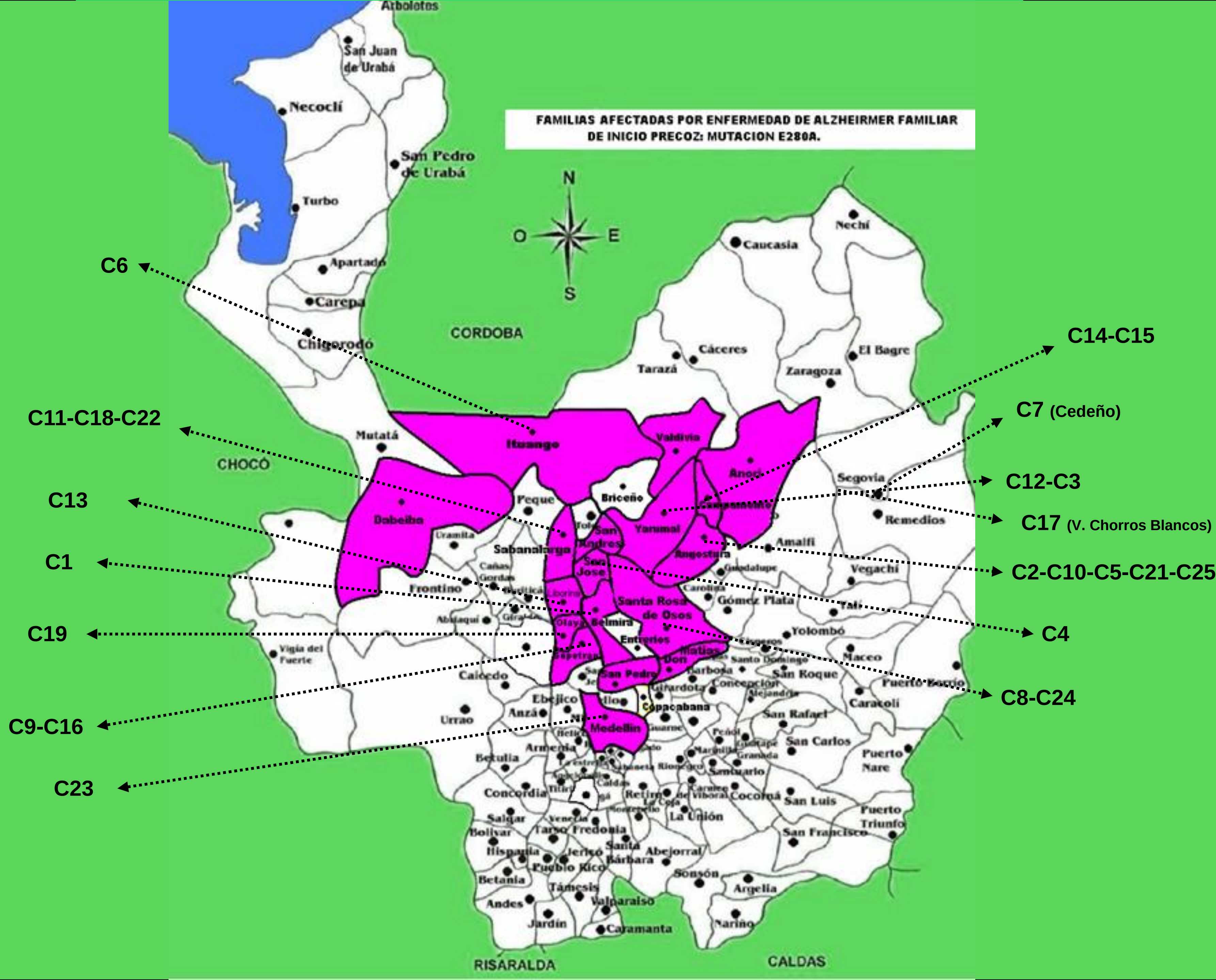

Healthy Brain
Severe AD
Preclinical AD
Mild to Moderate AD
Severe AD

Location of the affected population with EOFAD PSEN1 E280A mutation

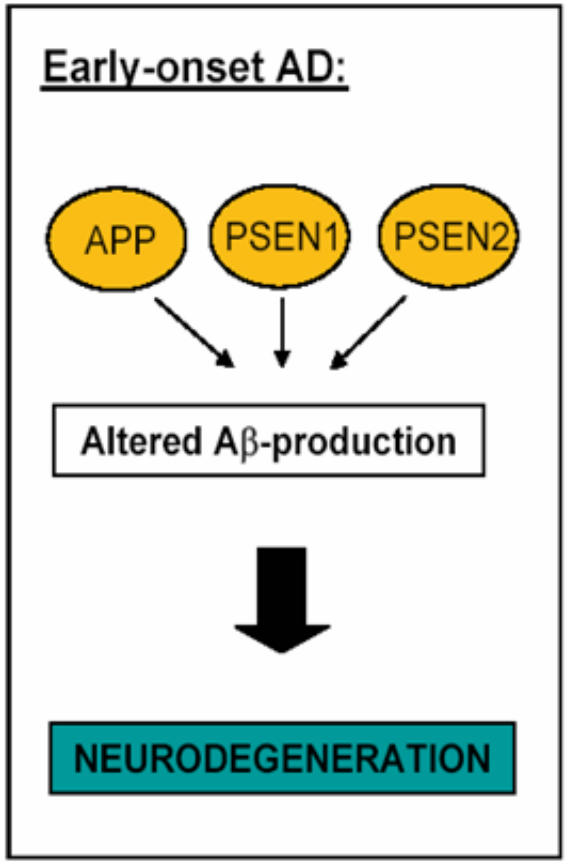
(Some members are living in Caracas, Sidney, USA)

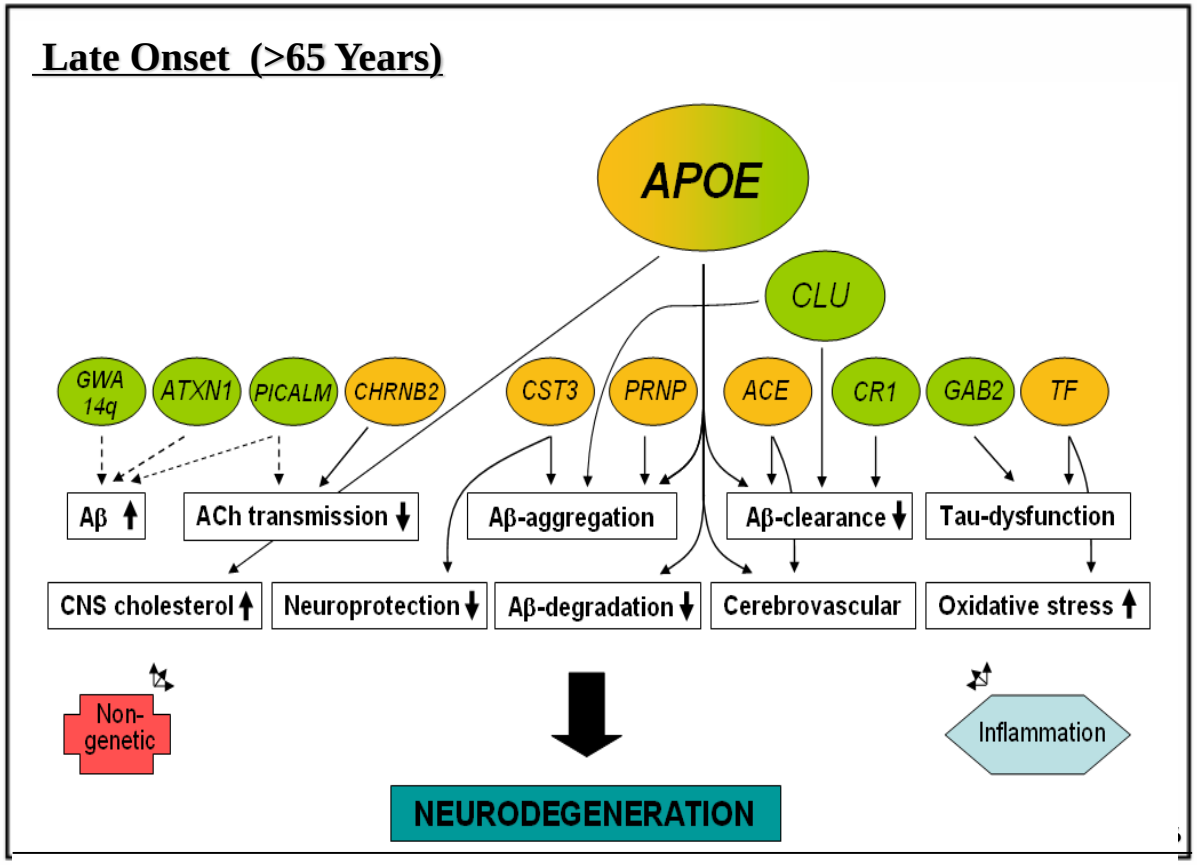





FAMILIAS AFECTADAS POR ENFERMEDAD DE ALZHEIRMER FAMILIAR DE INICIO PRECOZ: MUTACION E280A.
N
O
E
S
CORDOBA
CHOCÓ
RISARALDA
CALDAS
C6
C11-C18-C22
C13
C1
C19
C9-C16
C23
C14-C15
C7 (Cedeño)
C12-C3
C17 (V. Chorros Blancos)
C2-C10-C5-C21-C25
C4
C8-C24
Arboletes
San Juan de Urabá
Necoclí
San Pedro de Urabá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

Genetics of Alzheimer´s Disease





" Simple Genetics " (<5%)

" Complex Genetics" (>95%)

Most of the mutations that cause FAD are in the PSEN1 gene

Gene	# Mutations		# Familes	
APP	32	(14.3%)	86	(17.2%)
PSEN1	177	(78.4%)	392	(78.2%)
PSEN2	14	(6.3%)	23	(4.6 %)
Total	223		501	

AD mutation database:
http://molgen-www.uia.ac.be/ADMutations/

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

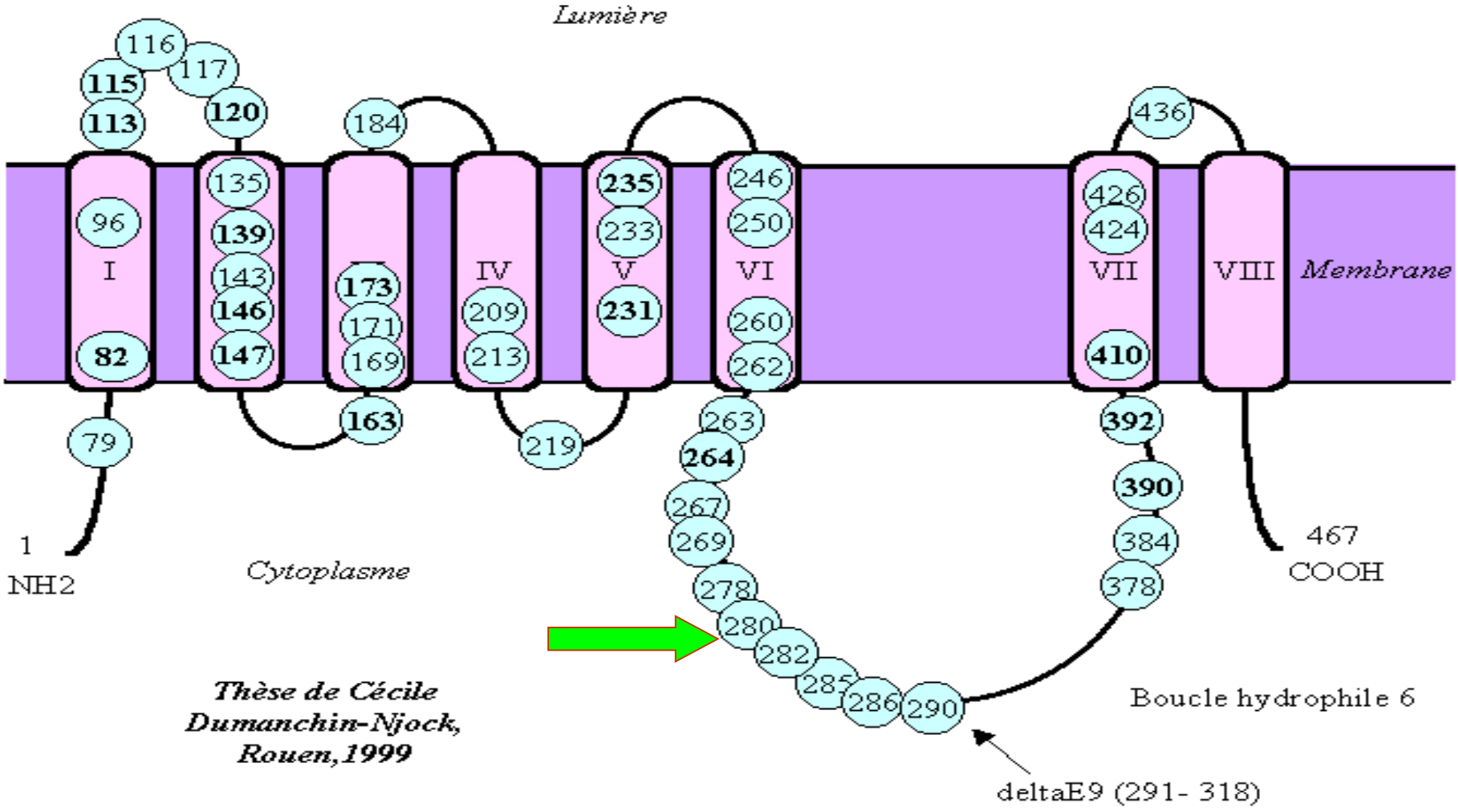


Figure 5. Structure de la préséniline 1 et distribution des mutations. Les mutations documentées dans les familles françaises sont en gras.

Decade of the 90's

Reprinted from JAMA ® The Journal of the American Medical Association March 12, 1997 Volume 277

Original Contributions

Clinical Features of Early-Onset Alzheimer Disease in a Large Kindred With an E280A Presenilin-1 Mutation

Francisco Lopera, MD; Alfredo Ardilla, PhD; Alonso Martínez; Lucia Madrigal; Juan Carlos Arango-Viana, MD; Cynthia A. Lemere, PhD; Juan Carlos Arango-Lasprilla; Liliana Hincapié; Mauricio Arcos-Burgos, MD; Jorge E. Ossa, DVM, PhD; Isabella M. Behrens, MD; Joanne Norton; Corrine Lendon, PhD; Alison M. Goate, PhD; Andres Ruiz-Linares, MD; Monica Rosselli, PhD; Kenneth S. Kosik, MD

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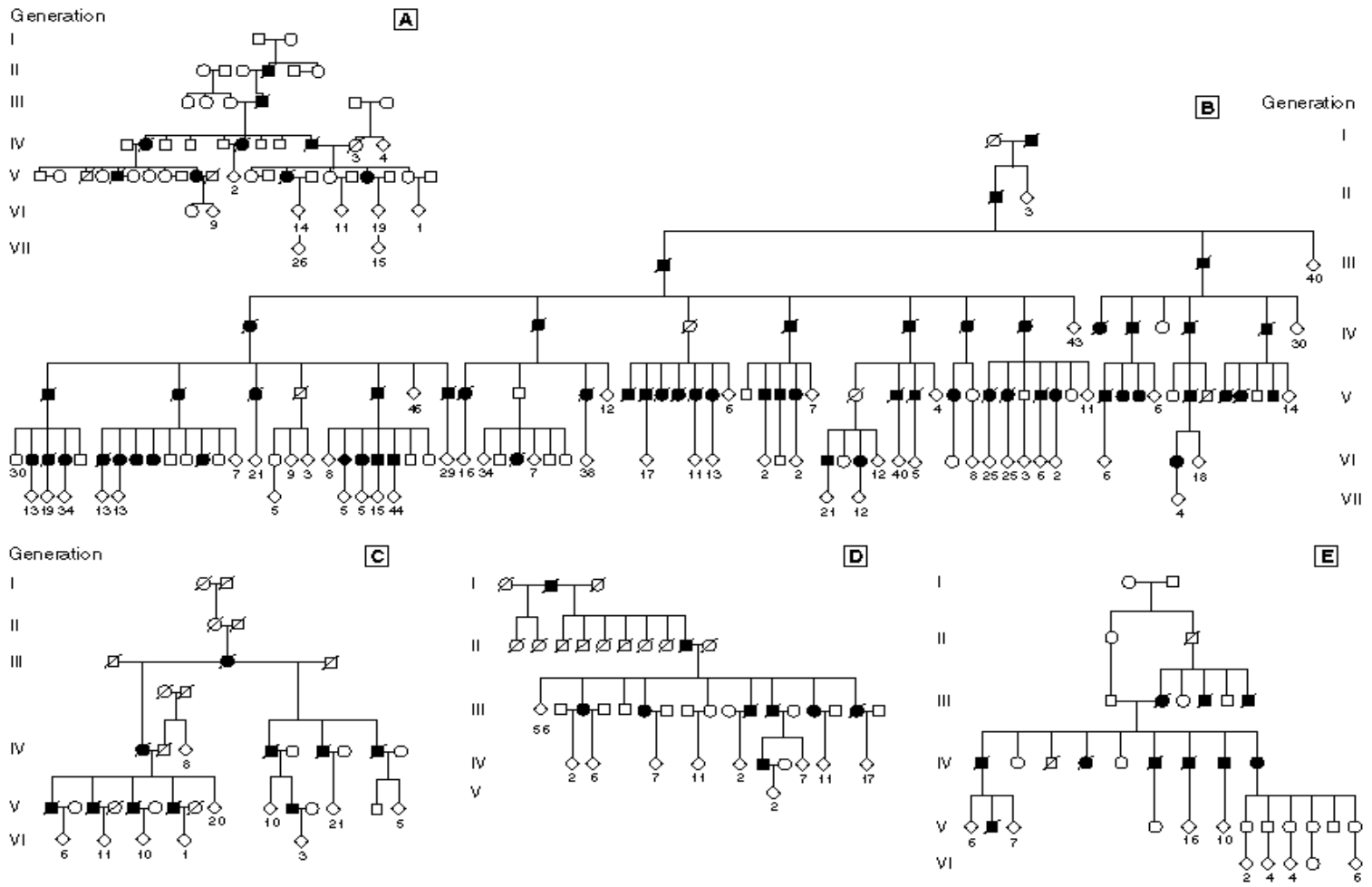
SYMPTONS AND CLINICAL SIGNS IN PSEN1 E280A

Lopera et al, Jama 1997

Symptom	No. (%)
Memory disturbance	118 (100)
Personality and behavioral changes	111 (94)
Language difficulty	96 (81)
Symptoms of depression	93 (79)
Headache	86 (73)
Gait difficulty	77 (65)
Aggressiveness	77 (65)
Wandering	74 (63)
Convulsions and myoclonus	53 (45)
Suck reflex	49 (42)
Babinski reflex	15 (13)
Grasp reflex	4 (3)
Cerebellar signs	22 (19)
Parkinsonism	22 (19)


V-28-67

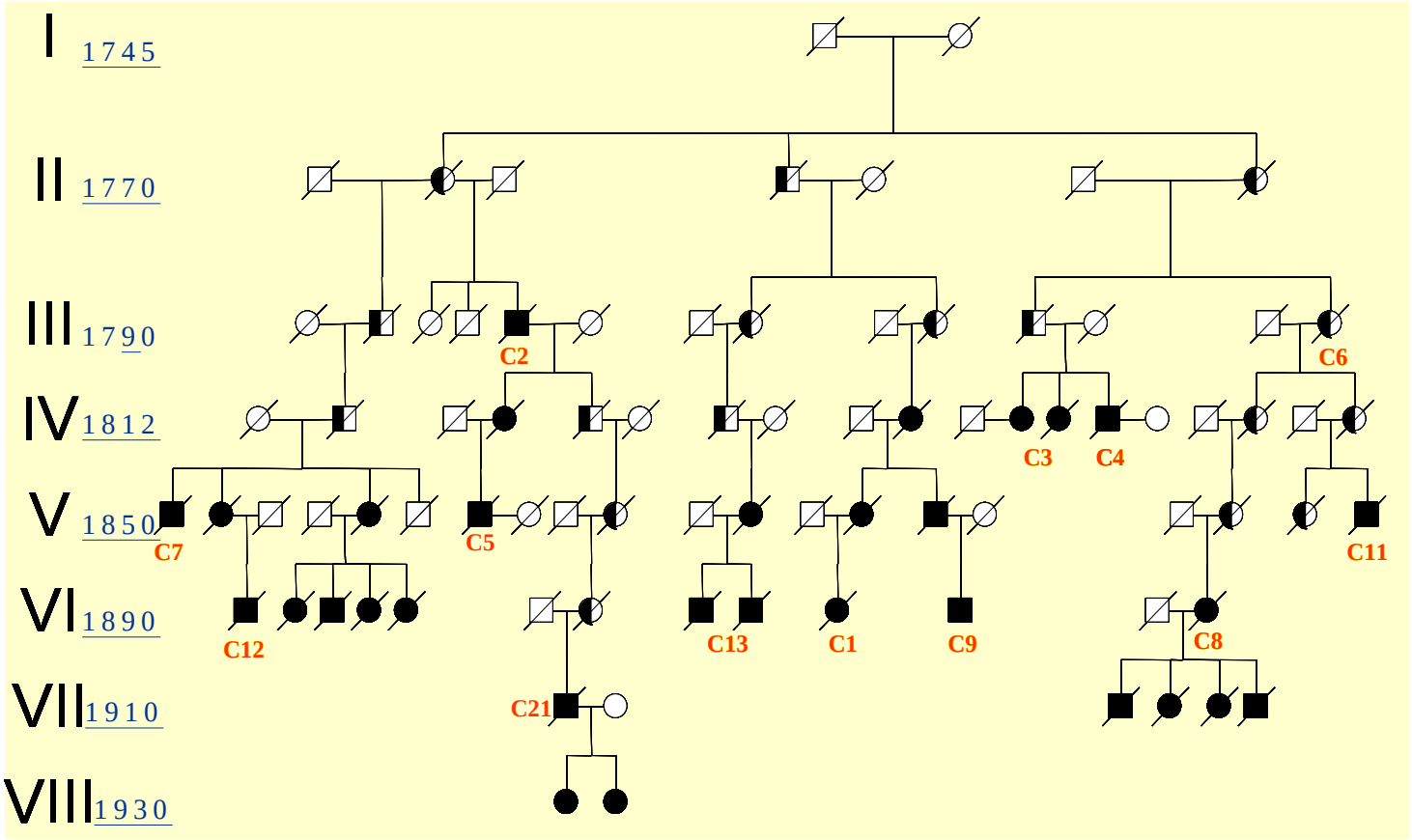
Family Trees with Alzheimer's disease associated with PSEN1 E280A mutation

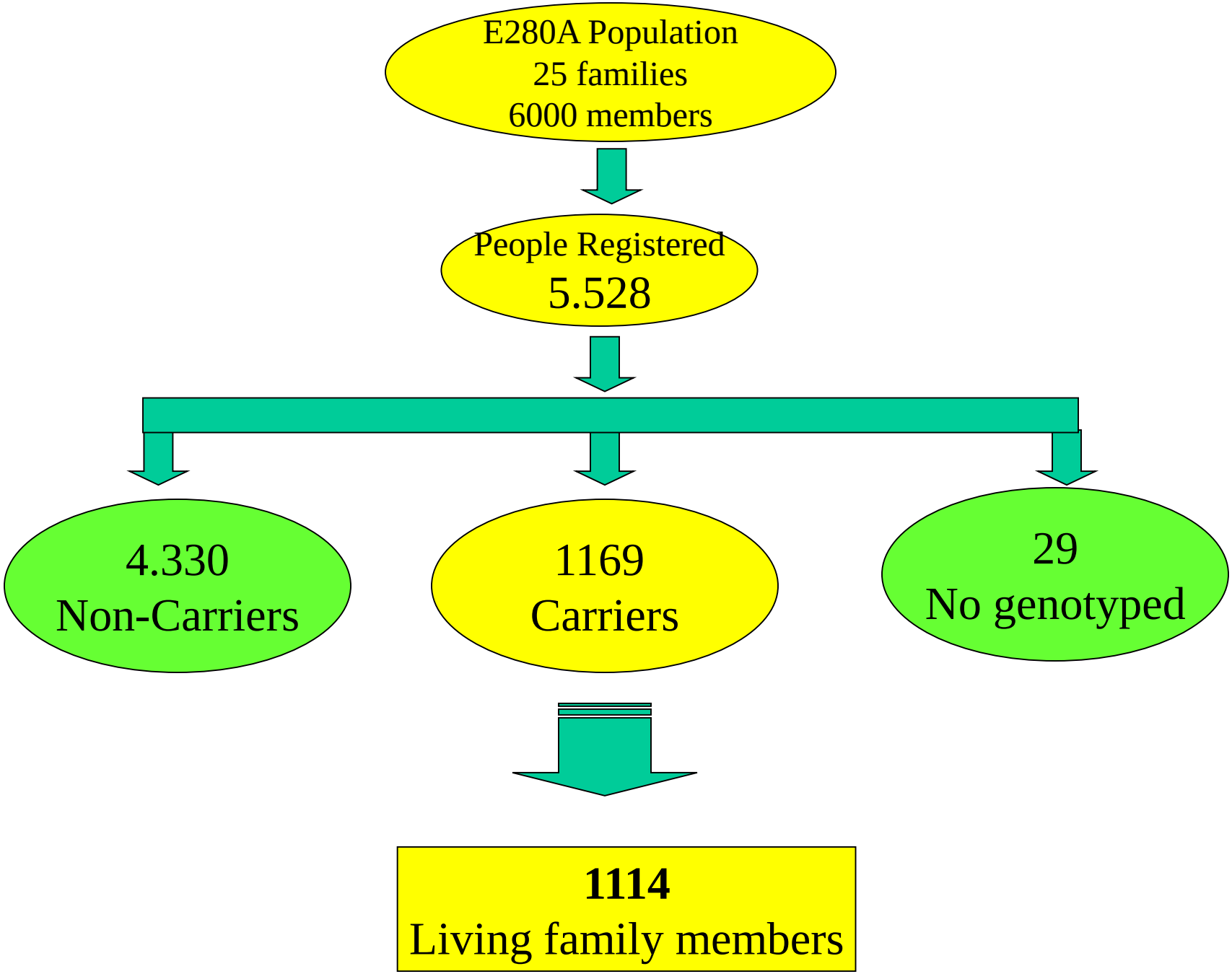


Source: Lopera *et al*, JAMA 1997

Common ancestry of 13 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




E280A Population
25 families
6000 members
People Registered
5.528
4.330
Non-Carriers
1169
Carriers
29
No genotyped
1114
Living family members

Preclinical Alzheimer Disease

BIOMARKERS

- COGNITIVES

1.Intrusions

2. Naming of famous people

3. Description of semantic Units

4. Visual Binding memory

Pergamon

Archives of Clinical Neuropsychology, Vol. 15, No. 6, pp. 515–528, 2000

0887-6177/00 $–see front matter

PII S0887-6177(99)00041-4

Neuropsychological Profile of a Large Kindred with Familial Alzheimer's Disease Caused by the E280A Single Presenilin-1 Mutation

Alfredo Ardila

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Francisco Lopera

University of Antioquia

Mónica Rosselli

Florida Atlantic University

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University of Antioquia

Alison Goate

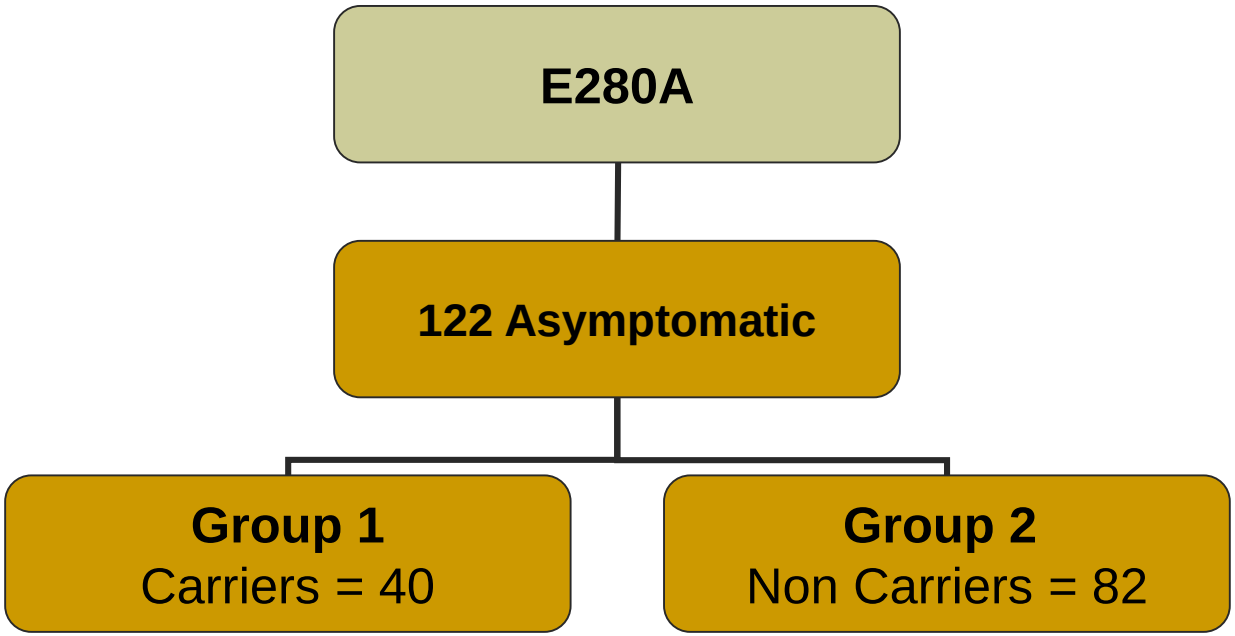
Washington University

Kenneth S. Kosik

Harvard Medical School

Preclinical Cognitive markers

Study Design



COGNITIVE MEASURES

CERAD (Morris et al; 1989)

- *Verbal Fluency*
- *Naming*
- *Mini-Mental State Exam (MMSE)*
- *Word List Learning*
- *Constructional Praxis*
- *Word List Recall*
- *Word List Recognition*
- *Recall of Line Drawings*

OTHER MEASURES

- RAVEN Test (Part A)
- WECHSLER MEMORY
- The Rey-Osterrieth Complex Figure
- Phonological Verbal Fluency (FAS)
- Boston Namig Test
- Categories Naming Test
- Boston Test for Aphasia
- Memory of Three Phrases
- Knopman Test
- DIGIT-SÍMBOL from WMS
- Visual “A” Cancellation Test (Ardila)
- Memory Complaints Scale (Matallana y Montañez).

Intrusions: A Preclinical Cognitive Marker

TEST (CERAD)	**E280A (-)** **N = 82**	**E280A (+)** **N = 40**	**t**	**p**
INTRUSIONS trial 2	0.12 (0.32)	0.30 (0.56)	2.19	.030
INTRUSIONS Total	0.67 (1.12)	1.48 (1.72)	3.09	.002
INTRUSIONS Remembering Words	0.36 (0.69)	1.05 (1.58)	3.32	.001

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2007, 29 (8), 892–900

Psychology Press
Taylor & Francis Group

Cognitive changes in the preclinical phase of familial Alzheimer's disease

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Few studies have examined the presence of linguistic deficits in the preclinical phase of Alzheimer's disease (AD). A total of 19 healthy carriers of the E280A presenilin-1 gene mutation in chromosome 14 and 21 noncarrier family members from Antioquia, Colombia, were administered a neurolinguistic evaluation of lexical-semantic processes. Both groups were similar in age, educational level, and gender. Carriers scored significantly lower than noncarriers on naming of famous faces. Cognitive changes in lexical-semantic tasks can be detected before the clinical diagnosis of probable familial AD, and a neurolinguistic evaluation may be a useful tool in the early clinical diagnosis of sporadic AD as well.

COGNITIVE MEASURES

- **Naming of famous people** (Uribe, C., Valencia, C. & Lopera, F., 2003).

- **Neuropsychological assessment of language. EPLA** (F. Cuetos, 2003).

Naming of famous people

- 30 photographs of famous people.
- 20 famous national and 10 international.
- Celebrities with high level of recognition.

Figure 1. Colombian version of the naming of famous faces test. Left: Fernando Botero, Colombian painter. Center: Shakira, pop singer. Right: Alvaro Uribe, president of Colombia.

Demographic characteristics of E280A mutation carriers and non-carrier controls

	Non-carriers (n = 21)	Carriers (n = 19)	U	*p*
Age in years	45.29 (3.68)	43.16 (3.00)	-1.9	0.061
Years of education	5.57 (3.82)	5.05 (3.05)	-0.3	0.768

Carrier vs. non-carrier scores on lexical and semantic tasks

	Non-Carriers (n=21)	Carriers (n=19)	U	*p*	Effect size (Cohen's *d*)
Semantic association	23.90 (3.88)	22.26 (4.00)	-1.1	0.282	0.42
Word-drawing matching	28.81 (1.47)	27.74 (2.02)	-1.9	0.069	0.61
Semantic verbal fluency	17.45 (3.49)	15.08 (2.95)	-2.3	0.023	0.73
Phonological verbal fluency	1429 (4.75)	12.61 (4.36)	-1.0	0.333	0.37
Naming drawings of objects	25.38 (3.04)	24.11 (3.30)	-1.3	0.215	0.40
Naming drawings of actions	28.19 (2.02)	26.84 (3.04)	-1.5	0.161	0.53
Naming drawings of famous people*	19.62 (6.78)	12.47 (8.16)	-2.8	0.004	0.96
Repetition of pseudo-words	29.81 (0.51)	29.79 (0.42)	-0.5	0.768	0.04
Reading of words	21.95 (5.21)	20.26 (4.54)	-1.1	0.258	0.34
Dictation of words	15.10 (5.01)	13.26 (4.43)	-1.8	0.083	0.39
Definitions	18.38 (8.04)	13.11 (6.47)	-2.1	0.036	0.72

Journal of the International Neuropsychological Society (2007), 13, 433–439.

DOI: 10.1017/S1355617707070609

Linguistic changes in verbal expression: A preclinical marker of Alzheimer's disease

FERNANDO CUETOS,[1] JUAN CARLOS ARANGO-LASPRILLA,[2] CLARAMÓNIKA URIBE,[2] CLAUDIA VALENCIA,[2,3] AND FRANCISCO LOPERA[2]

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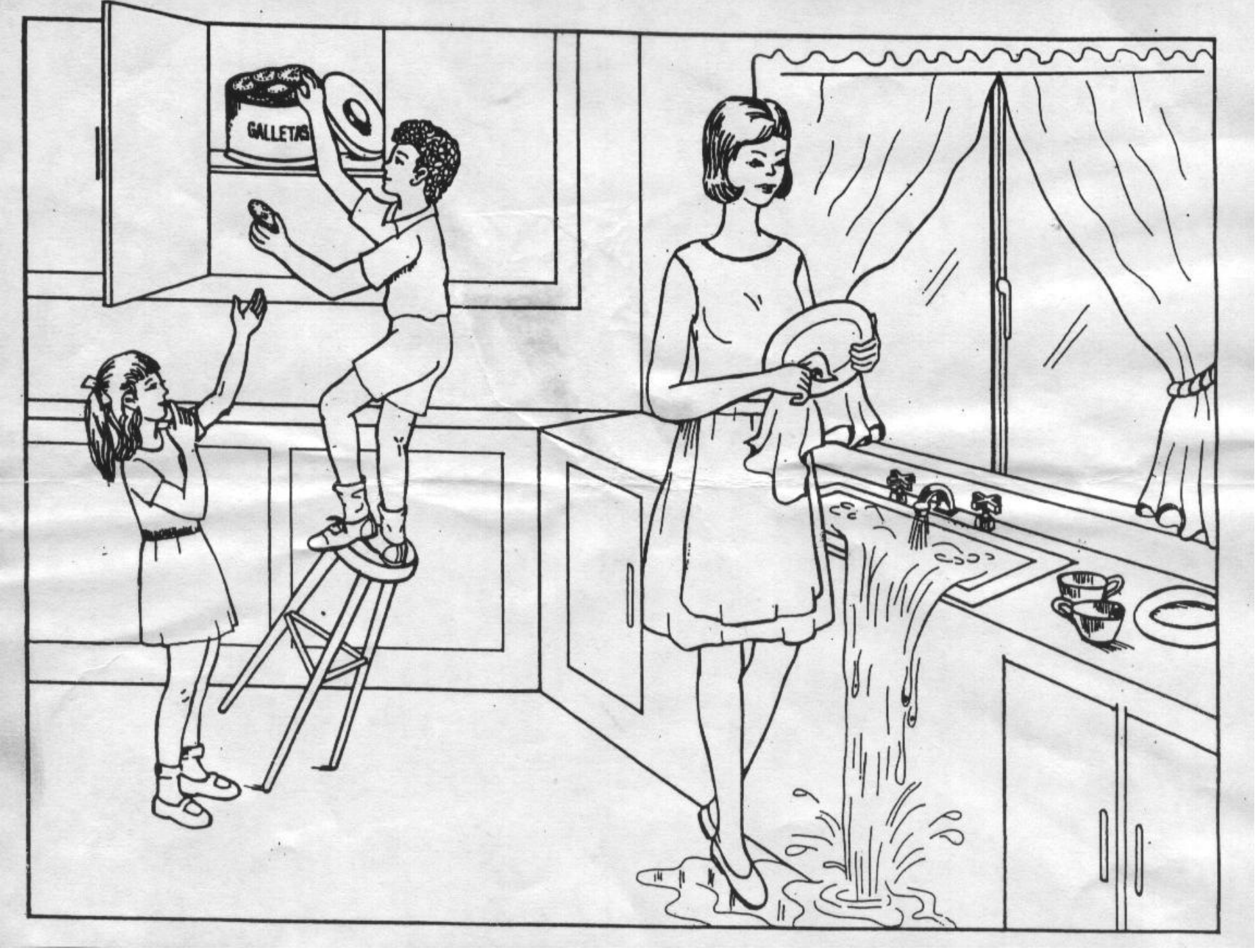
GALLETAS

Table 1. Performance of carriers and noncarriers on variables from the Boston Cookie Theft Picture Card

Variable	Group		*F* value	*p* value
	Carriers	Noncarriers		
Semantic units	4.26 (2.10)	6.14 (1.24)	12.15	.001*
Objective situations	5.68 (2.73)	8.29 (1.82)	12.80	.001*
Inferences	0.05 (0.23)	0.38 (0.67)	4.13	.049
Total number of sentences	12.10 (4.03)	11.09 (3.08)	0.80	.376
Average sentence length	9.61 (2.67)	10.12 (2.90)	0.34	.565
Open-class/closed-class words ratio	0.89 (0.17)	1.07 (0.23)	8.06	.007
Total number of simple verbs	14.11 (8.20)	8.38 (3.77)	8.31	.006
Total number of compound verbs	6.68 (3.76)	9.95 (3.97)	7.11	.011

*Significant *p* value (Bonferroni corrected $\alpha = .0035$).

OXFORD JOURNALS

BRAIN
A JOURNAL OF NEUROLOGY

http://brain.oxfordjournals.org/

doi:10.1093/brain/awq148 Brain 2010: Page 1 of 12 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Visual short-term memory binding deficits in familial Alzheimer's disease

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Short-term memory binding is a memory function that underpins the temporary retention of complex objects (e.g. shapes with colours). In the verbal domain, this function has been found to be impaired in sporadic Alzheimer's disease. Whether short-term memory binding is also impaired in familial Alzheimer's disease, whether this impairment extends to the visual domain and whether it could be detected earlier than other cognitive deficits are issues yet to be investigated. Twenty two patients with familial Alzheimer's disease caused by the E280A single *presenilin-1* mutation, thirty carriers of the mutation who did not meet Alzheimer's disease criteria (asymptomatic carriers) and 30 healthy relatives (non-carrier healthy controls) were assessed with a visual short-term memory task and a neuropsychological battery. The short-term memory task assessed the recognition of shapes, colours or shape-colour bindings presented in two consecutive arrays (i.e. study and test). Changes, which always occurred in the test array, consisted of new features replacing studied features (single feature conditions) or of features swapping across items (the binding condition). The neuropsychological battery comprised tests of associative and non-associative memory, attention, language, visuospatial and executive functions. Patients with Alzheimer's disease and asymptomatic carriers performed significantly worse than healthy controls in the feature binding condition only. Group comparisons between asymptomatic carriers and healthy controls on standard neuropsychological tasks revealed no significant differences. Classification and area under the curve analyses confirmed that the binding task combines more sensitivity and specificity for patients with Alzheimer's disease and most notably for asymptomatic carriers of the mutation than other traditional neuropsychological measures. This suggests that visual short-term memory binding deficits may be a preclinical marker for familial Alzheimer's disease.

COLOR-BINDING MEMORY TASK

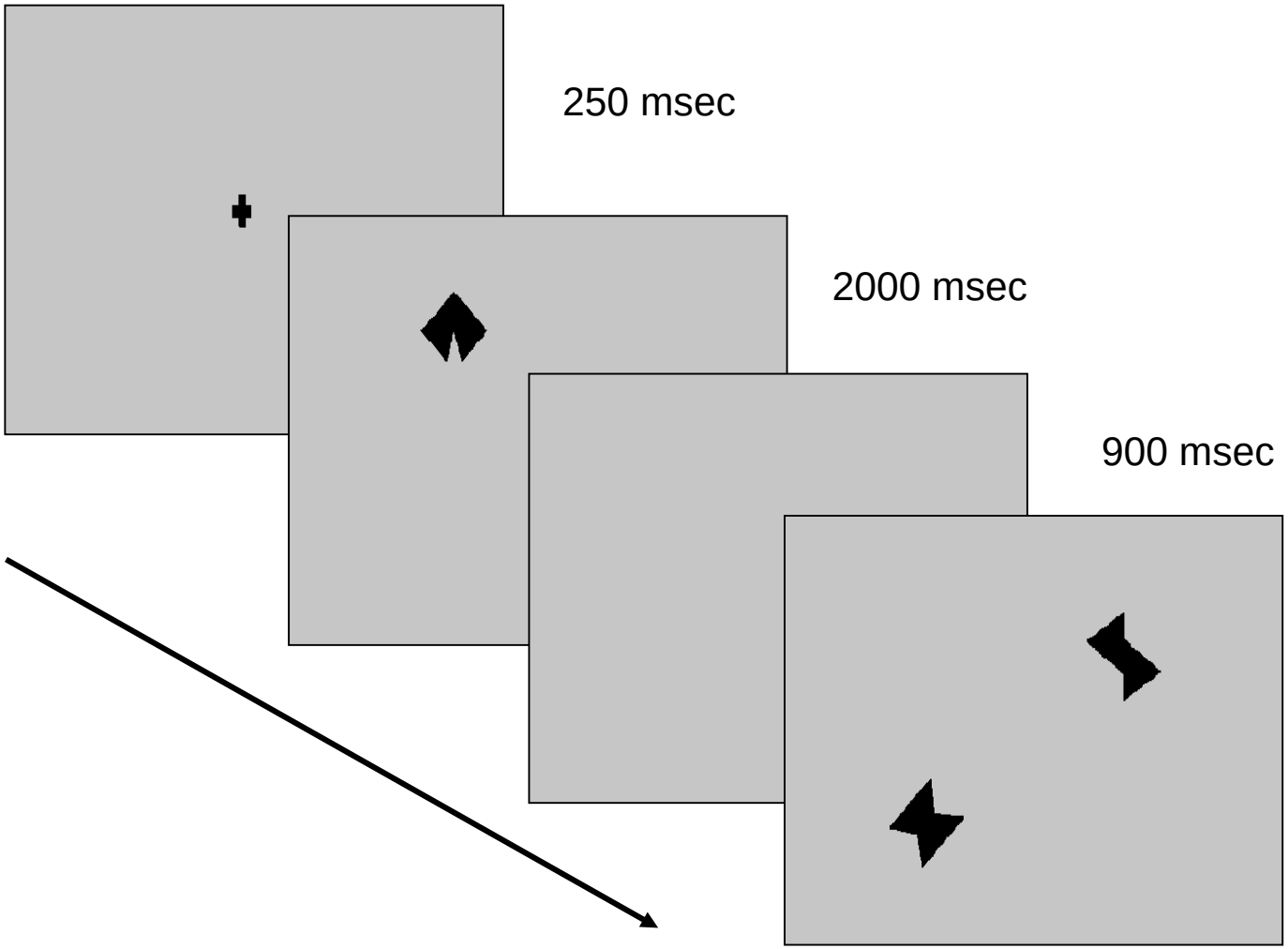
1. Memory for Shapes

2. Memory for Colors

3. Memory for shape + color

Experiment 1

Memory for Shapes



Respuesta

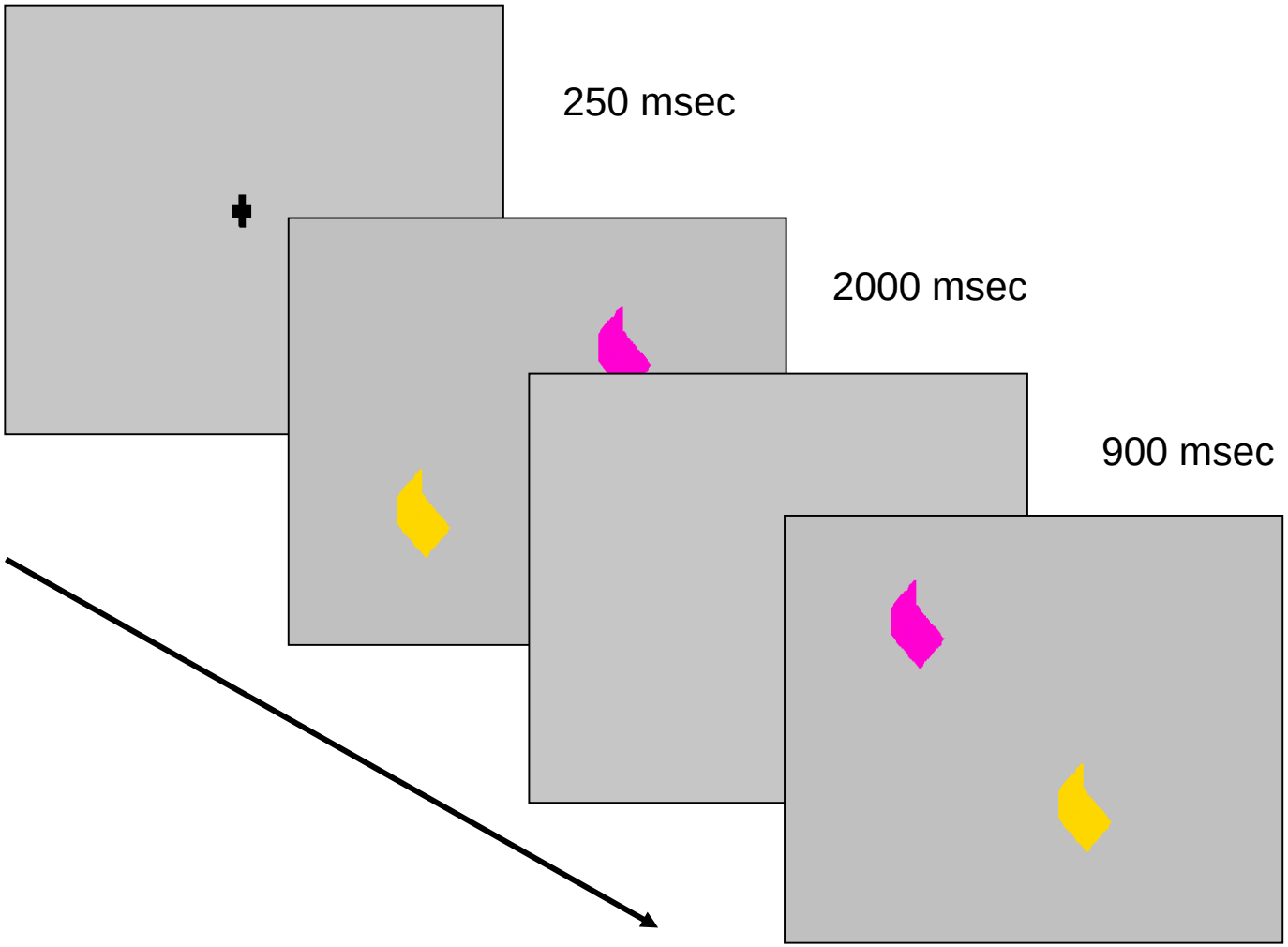
“Igual”

O

“Diferente”

Experiment 2

Memory for Colors



Respuesta

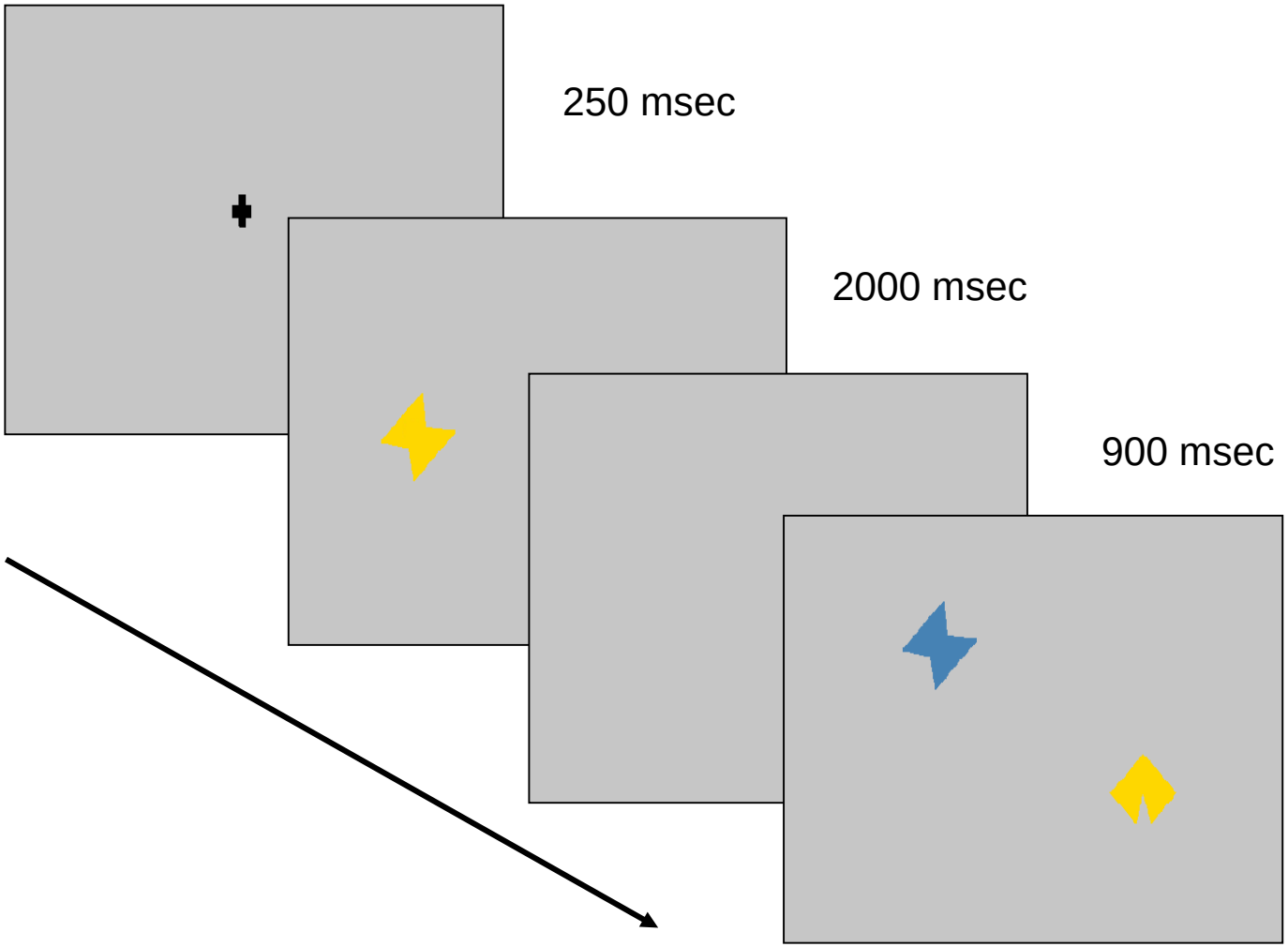
“Igual”

O

“Diferente”

Experiment 3

Memory for shape + color



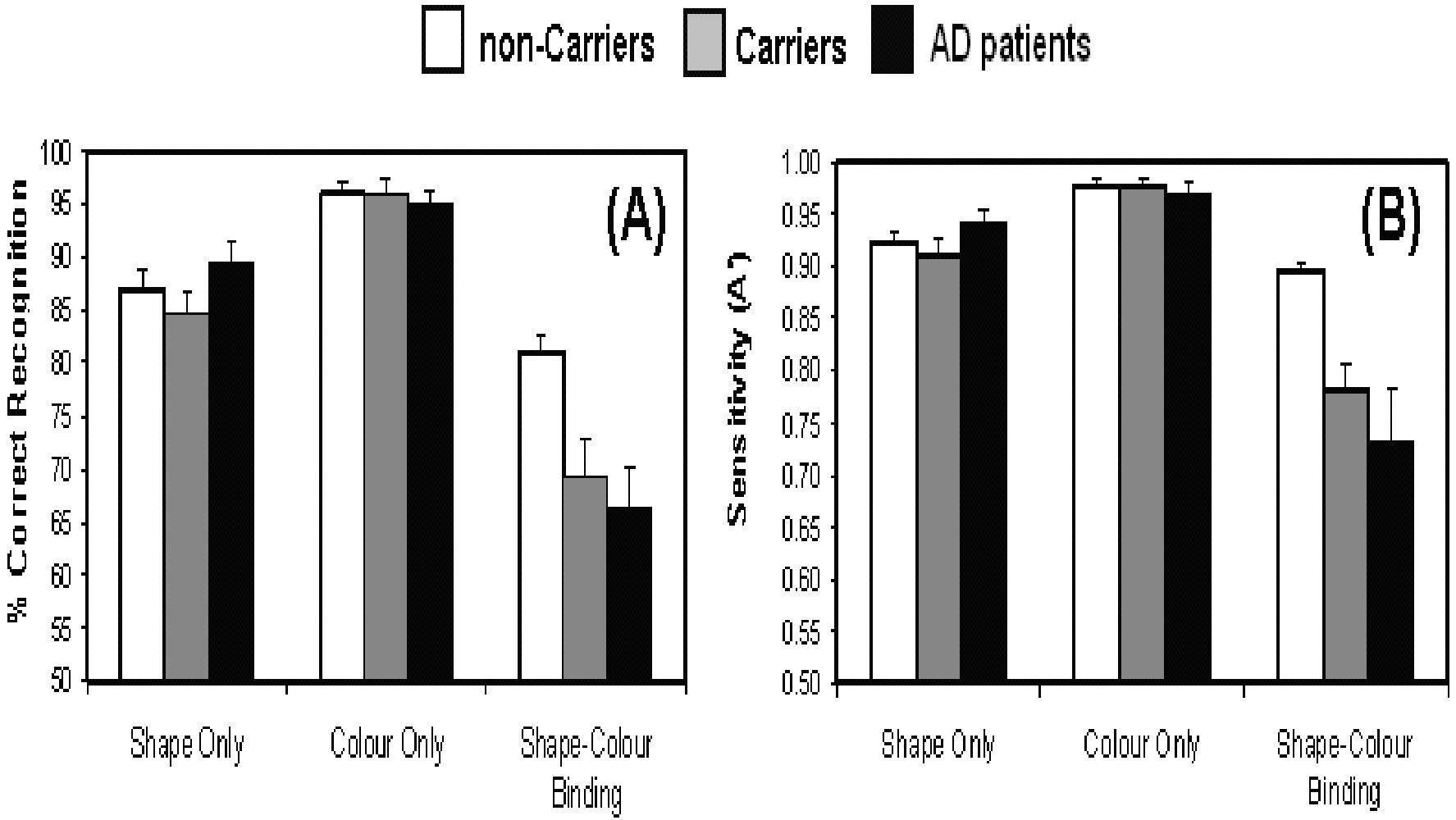
Respuesta

“Igual”

O

“Diferente”

Carriers: 22, No Carriers: 20, AD:15



Preclinical Alzheimer Disease

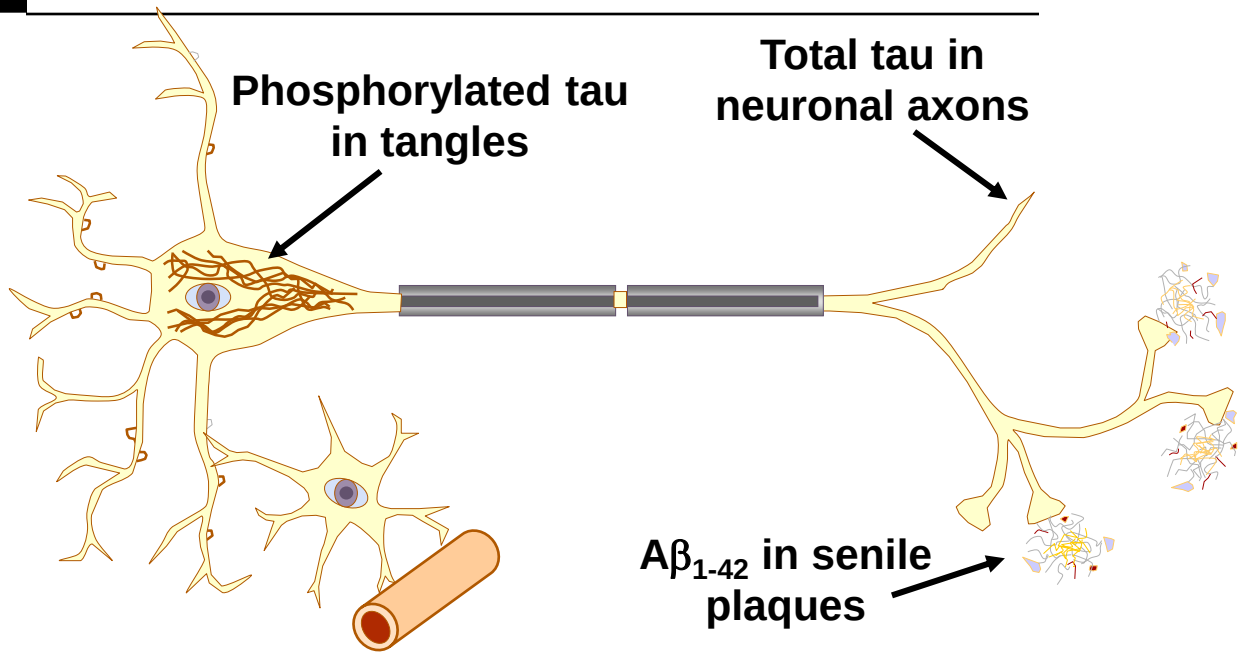
BIOMARKERS

- BIOCHEMICAL

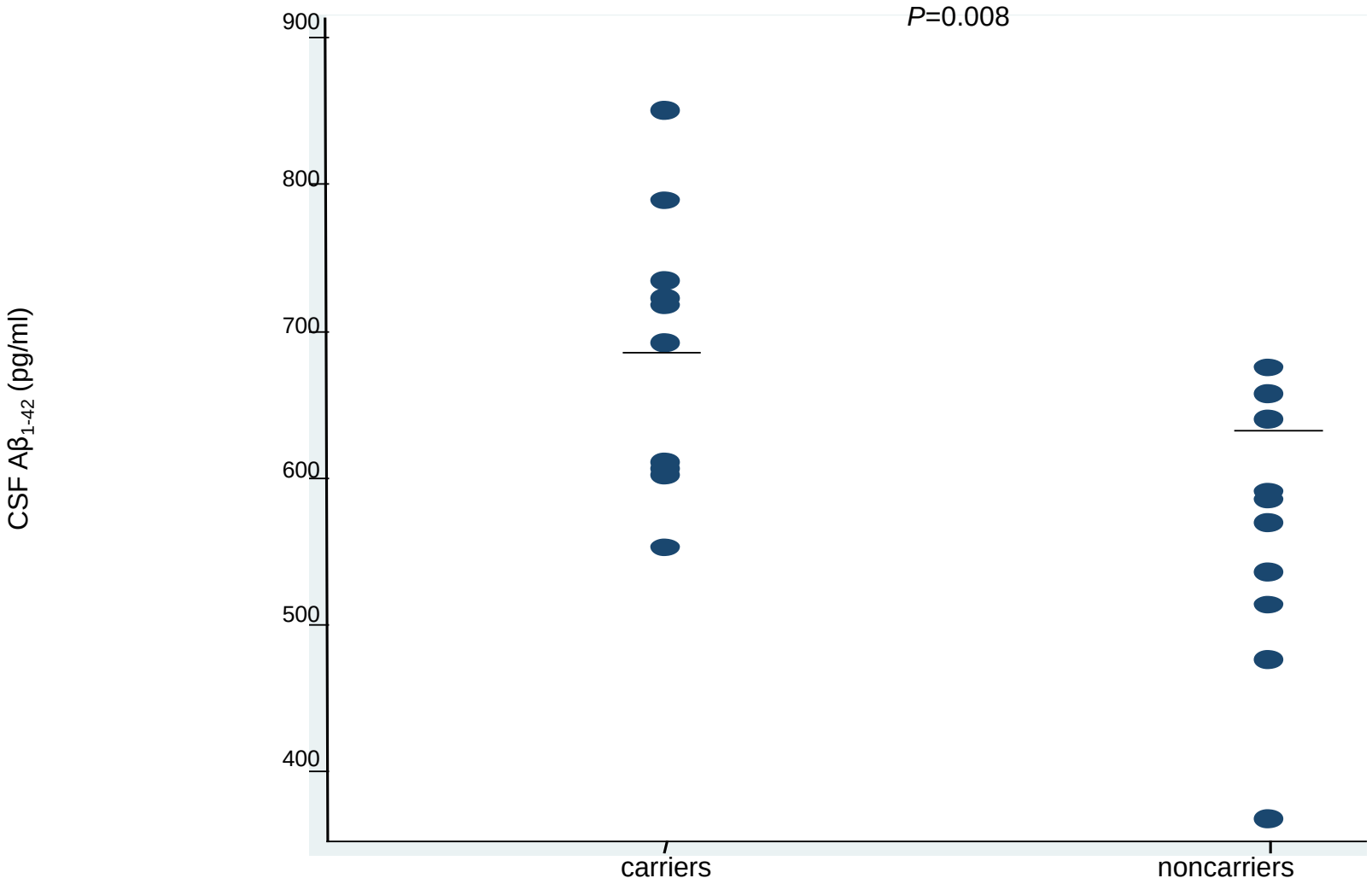
Levels of CSF $A\beta_{1-42}$

Biomarkers in CSF in AD

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



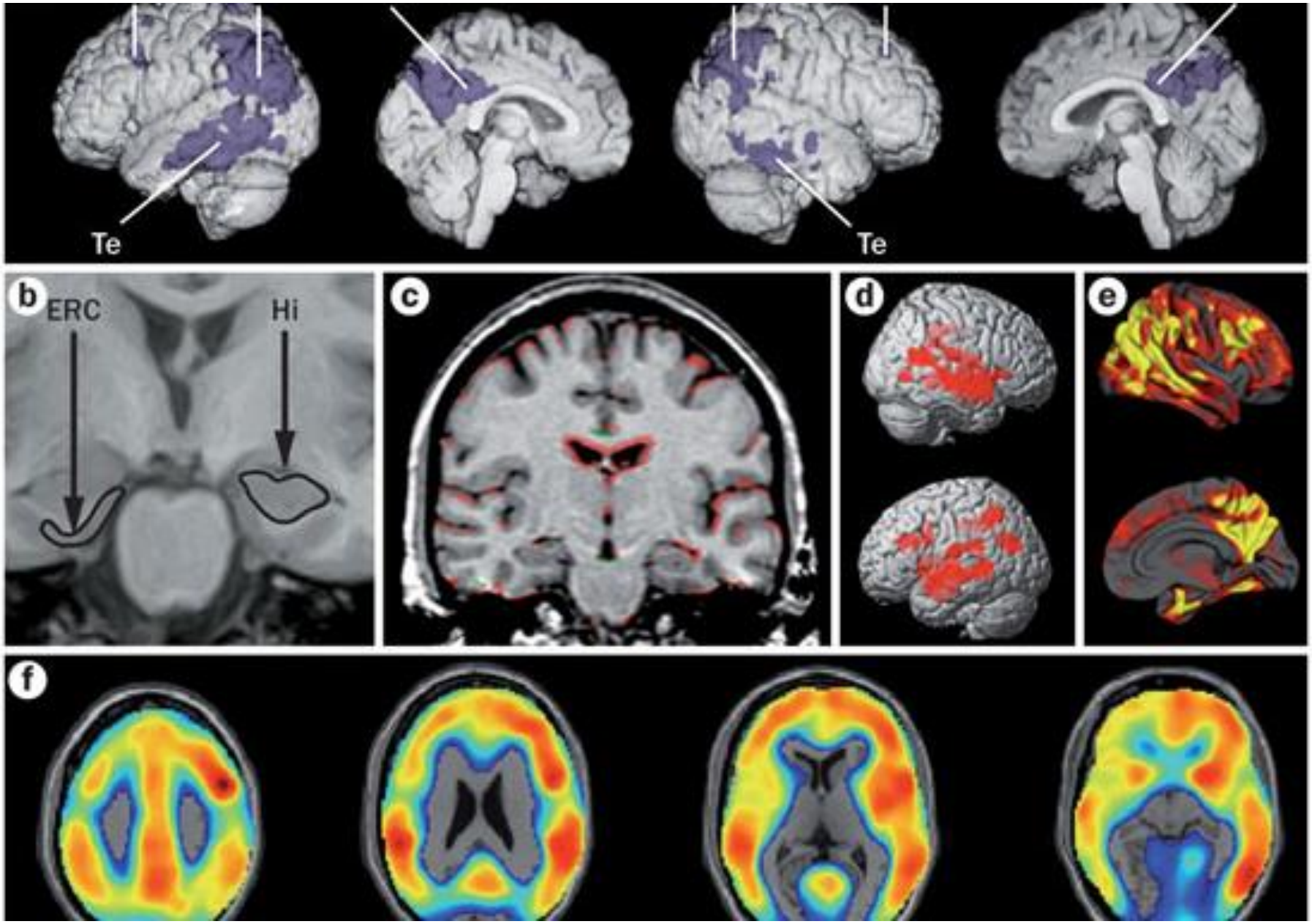
Higher (not lower) CSF $A\beta_{1\text{-}42}$ Levels in E280A Population



Preclinical Alzheimer Disease

IMAGES BIOMARKERS

1. Structural, anatomical (RM)
2. Funcionals Images: MRI, PET amiloide, PET FDG



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

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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

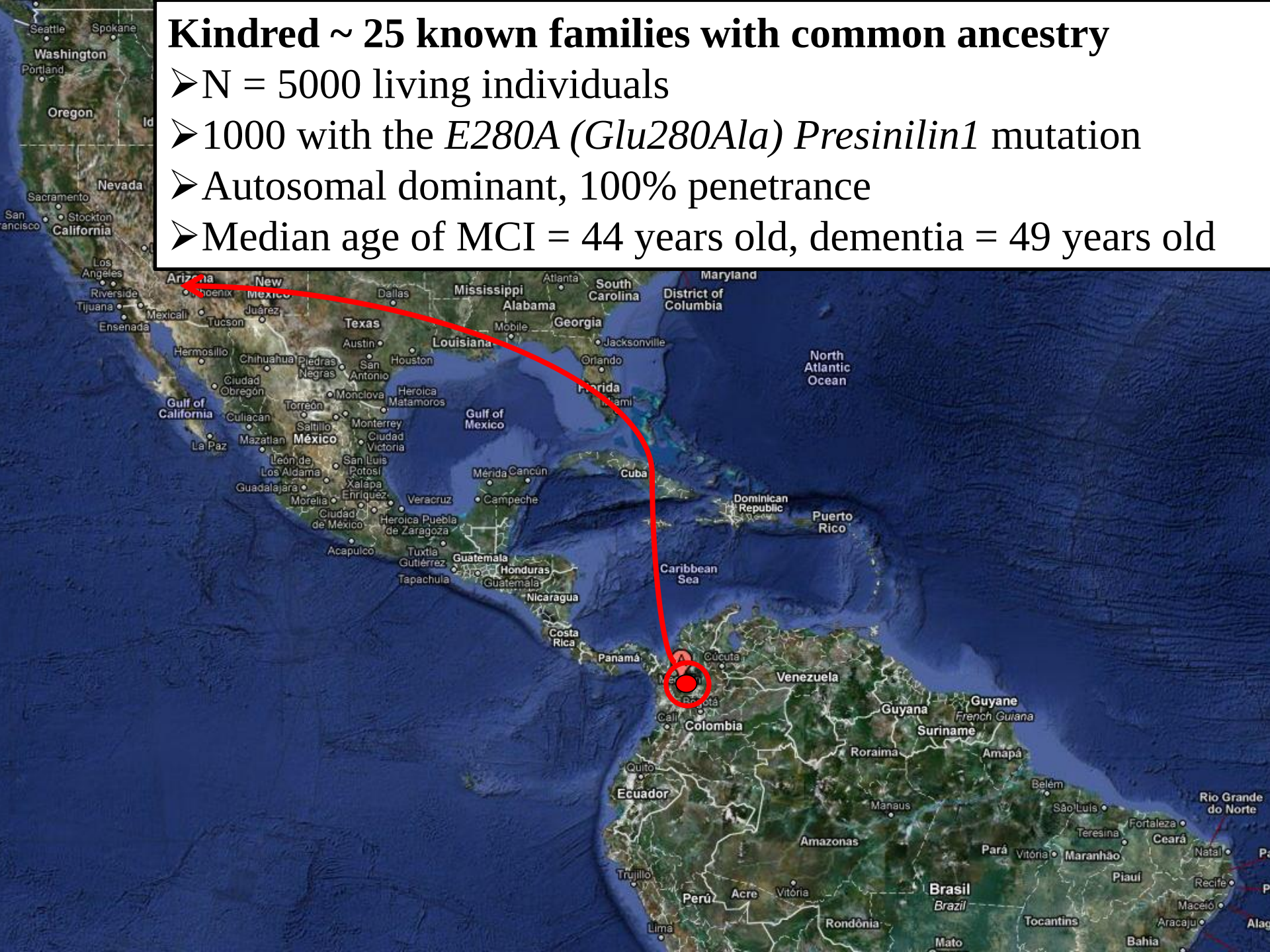
Summary

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

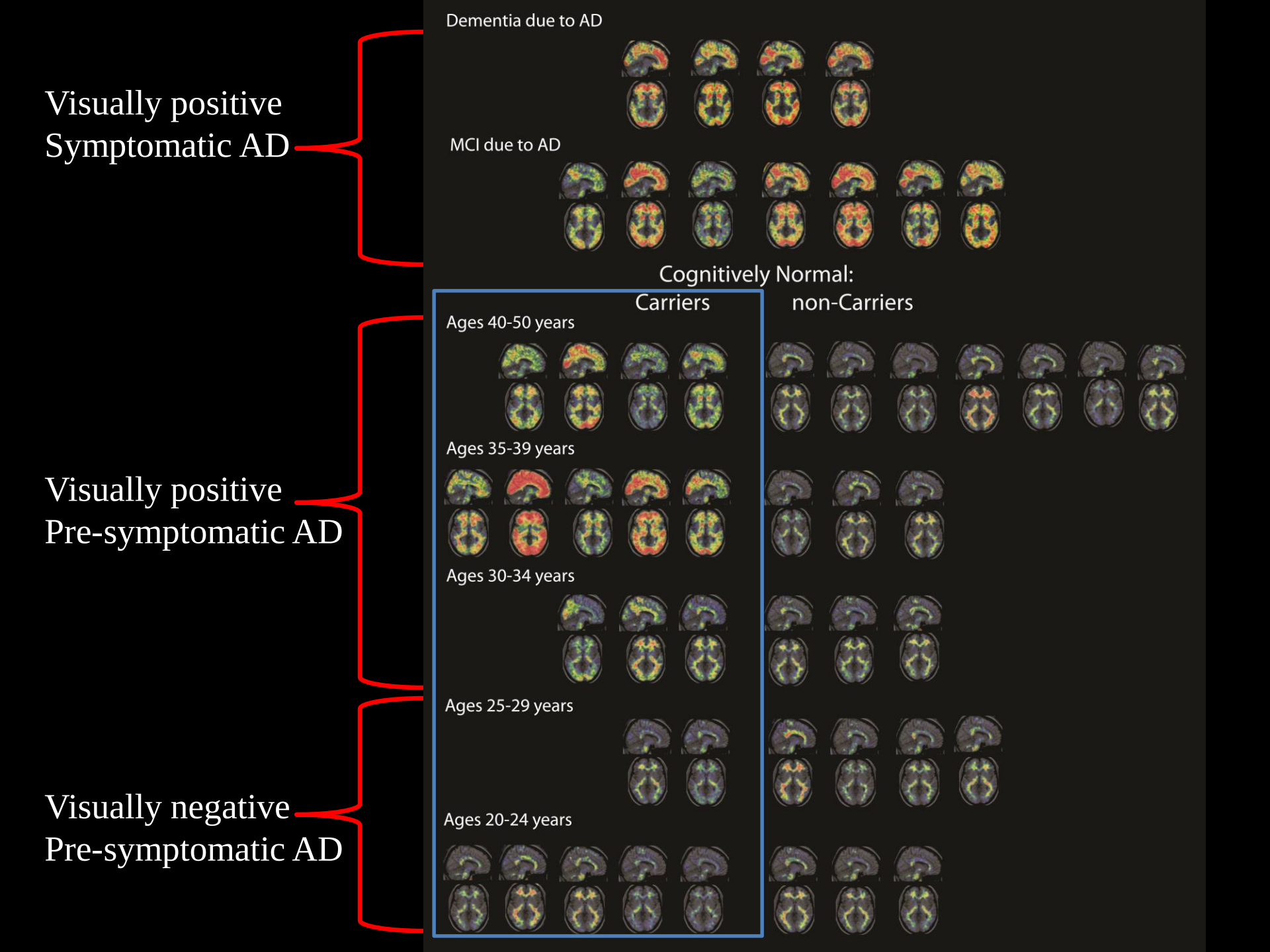
Published Online November 6, 2012 http://dx.doi.org/10.1016/S1474-4422(12)70227-2

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, dementia = 49 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
Hermosillo
Chihuahua
Ciudad Obregón
Culiacan
Mazatlan
La Paz
Gulf of California
Piedras Negras
Monclova
Torreón
Saltillo
Monterrey
México
Ciudad Victoria
León de los Aldama
San Luis Potosí
Guadalajara
Morelia
Xalapa Enríquez
Veracruz
Ciudad de México
Heroica Puebla de Zaragoza
Acapulco
Heroica Matamoros
Texas
Dallas
Austin
San Antonio
Houston
Laredo
Mississippi
Alabama
Atlanta
Georgia
Mobile
Louisiana
Gulf of Mexico
South Carolina
Jacksonville
Orlando
Florida
Miami
Maryland
District of Columbia
North Atlantic Ocean
Mérida
Cancún
Campeche
Tuxtla Gutiérrez
Tapachula
Guatemala
Honduras
Nicaragua
Costa Rica
Panamá
Cuba
Dominican Republic
Puerto Rico
Caribbean Sea
Cúcuta
Venezuela
Guyana
French Guiana
Suriname
Roraima
Amapá
Colombia
Cali
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
Lima
Rondônia
Tocantins
Aracaju
Mato
Bahia

Demographics

	Non-Carriers	Pre-symptomatic Carriers	Symptomatic Carriers	P-value
Number of subjects	20	19	11	
Age (range)	33.9±8.7 (20-50)	32.6±8.2 (20-43)	47.5±4.6 (41-56)	<0.001
Gender (M/F)	7/13	7/12	3/8	0.86
Education	11.2±3.3	12.3±2.8	8.8±3.5	0.02
MMSE	29.8±0.5	29.8±0.4	23.1±3.5	<0.001


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

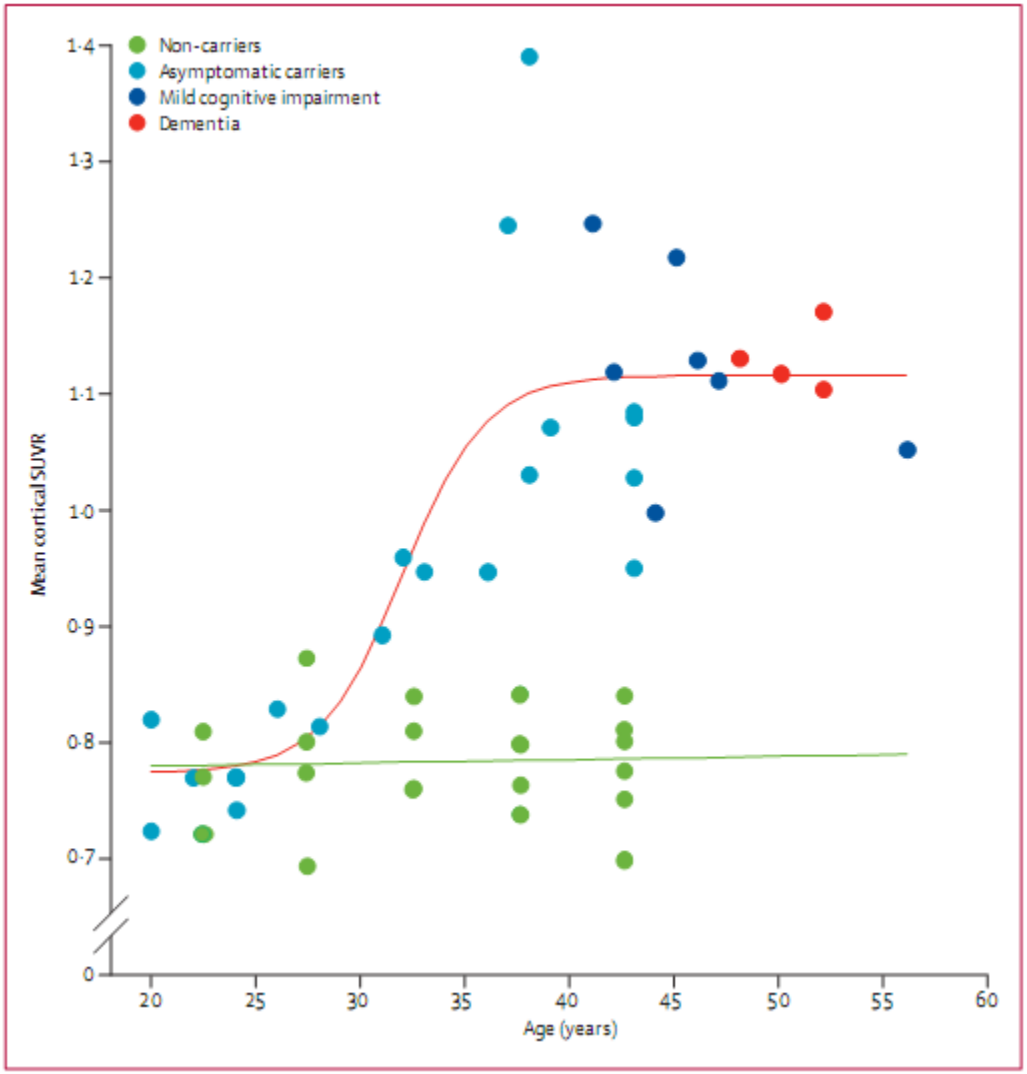
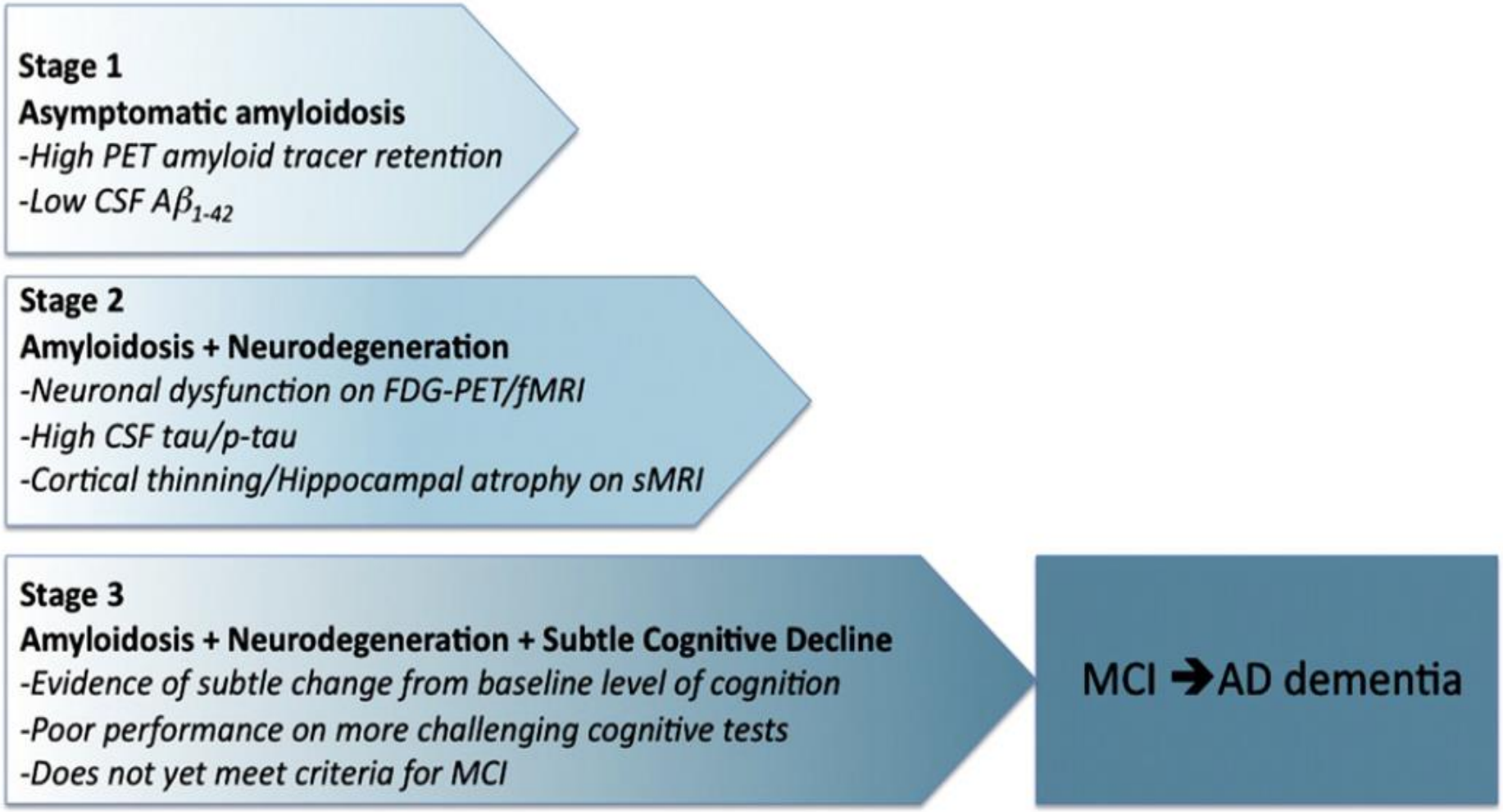


Figure 3: **Mean cortical standard uptake value ratios at different ages**
The individual values of non-carriers are shown as artificially clustered at 5-year intervals to help preserve anonymity of carriers versus non-carriers related to specific ages. All datapoints over age 40 years are clustered at 42·5 years on the x axis because of limited non-carrier datapoints above age 40 years. SUVR=standard uptake value ratio.

PRECLINICAL ALZHEIMER DISEASE- (2011)

Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup
Reisa A. Sperling



THE LANCET Neurology

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

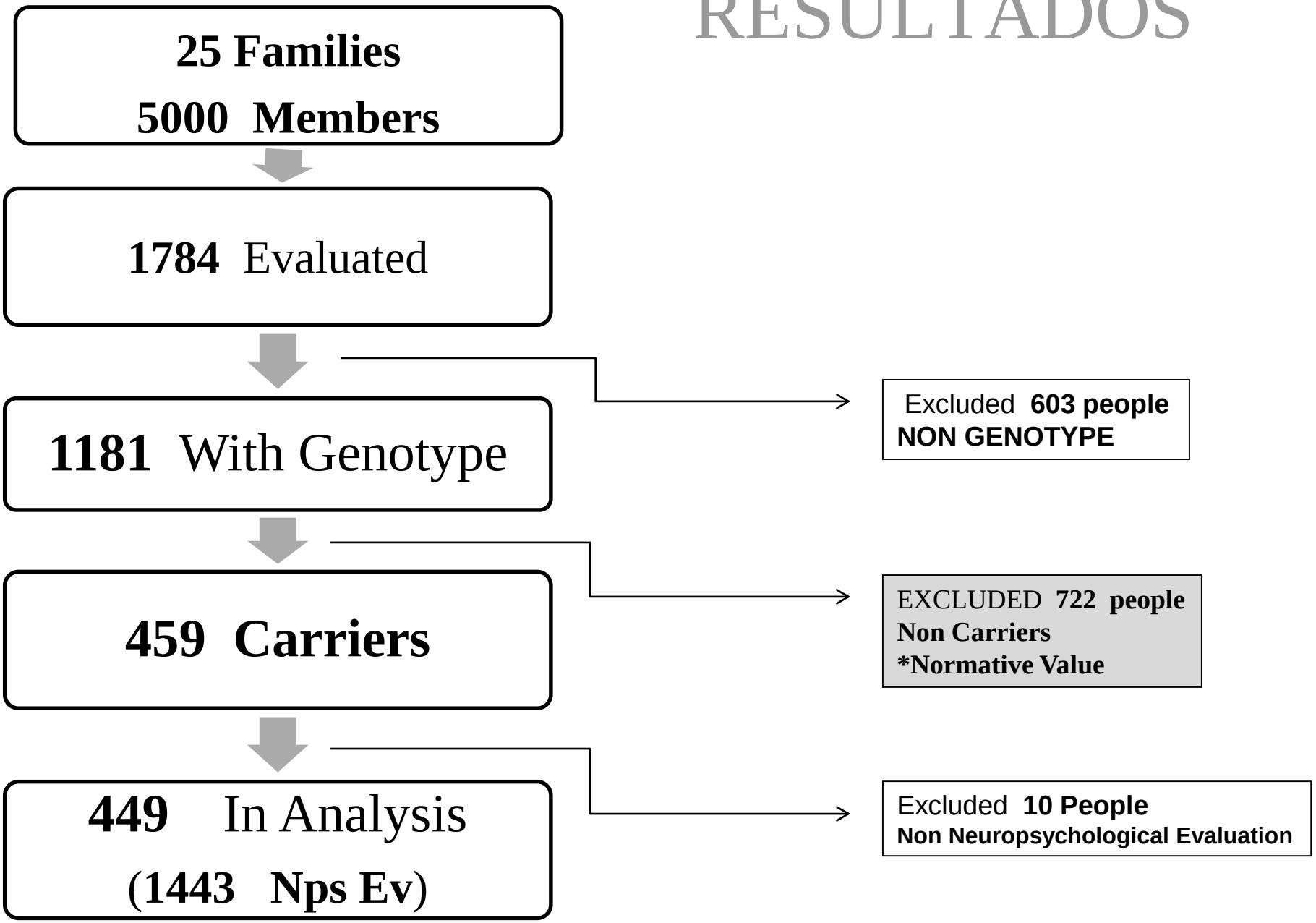
Natalia Acosta-Baena MD [a b c], Diego Sepulveda-Falla MD [a d], Carlos Mario Lopera-Gómez MSc [e], Mario César Jaramillo-Elorza MSc [e], Sonia Moreno MSc [a], Daniel Camilo Aguirre-Acevedo MSc [a b], Amanda Saldarriaga BSc [a], Prof Francisco Lopera MD [a]

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

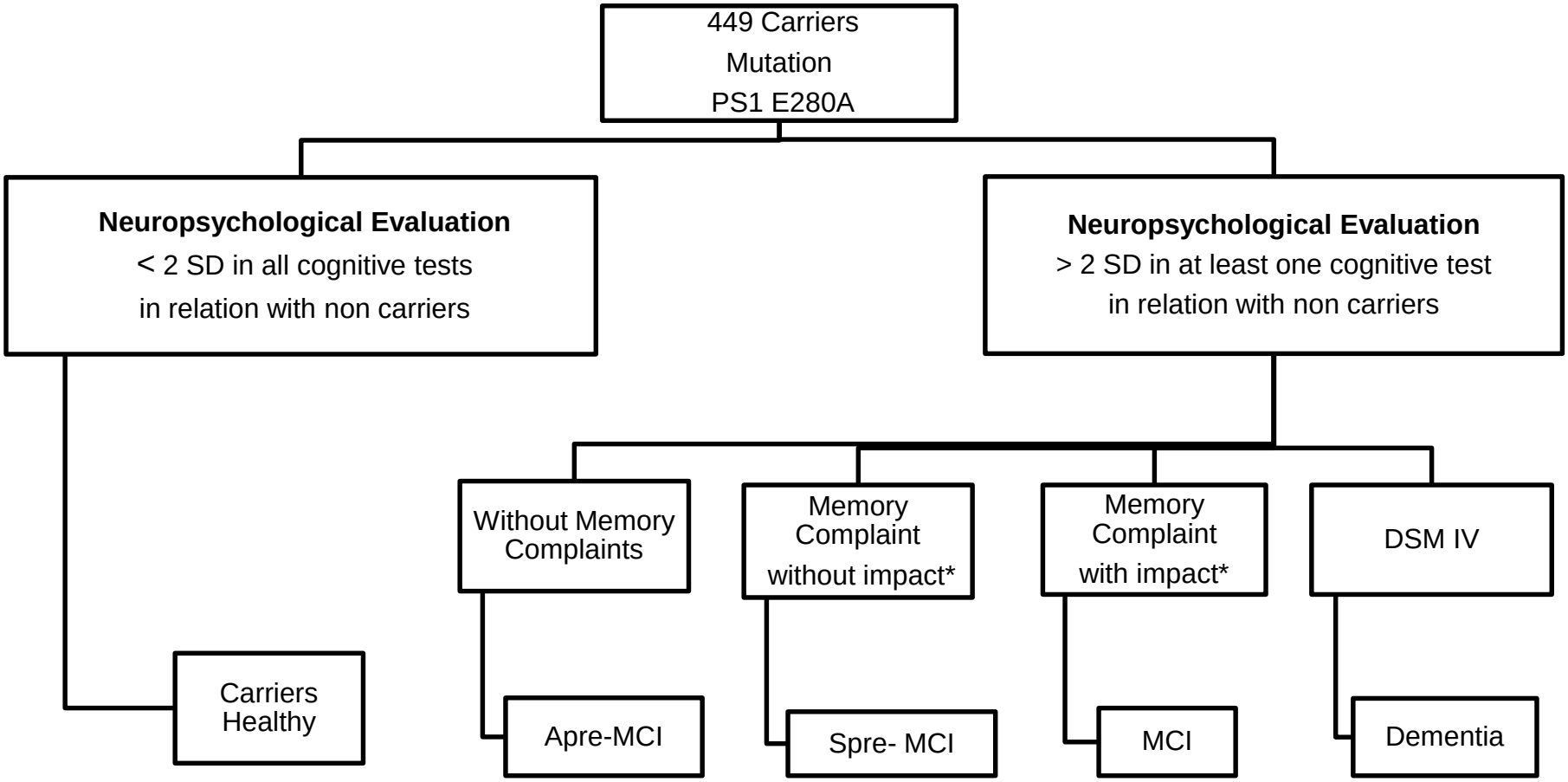
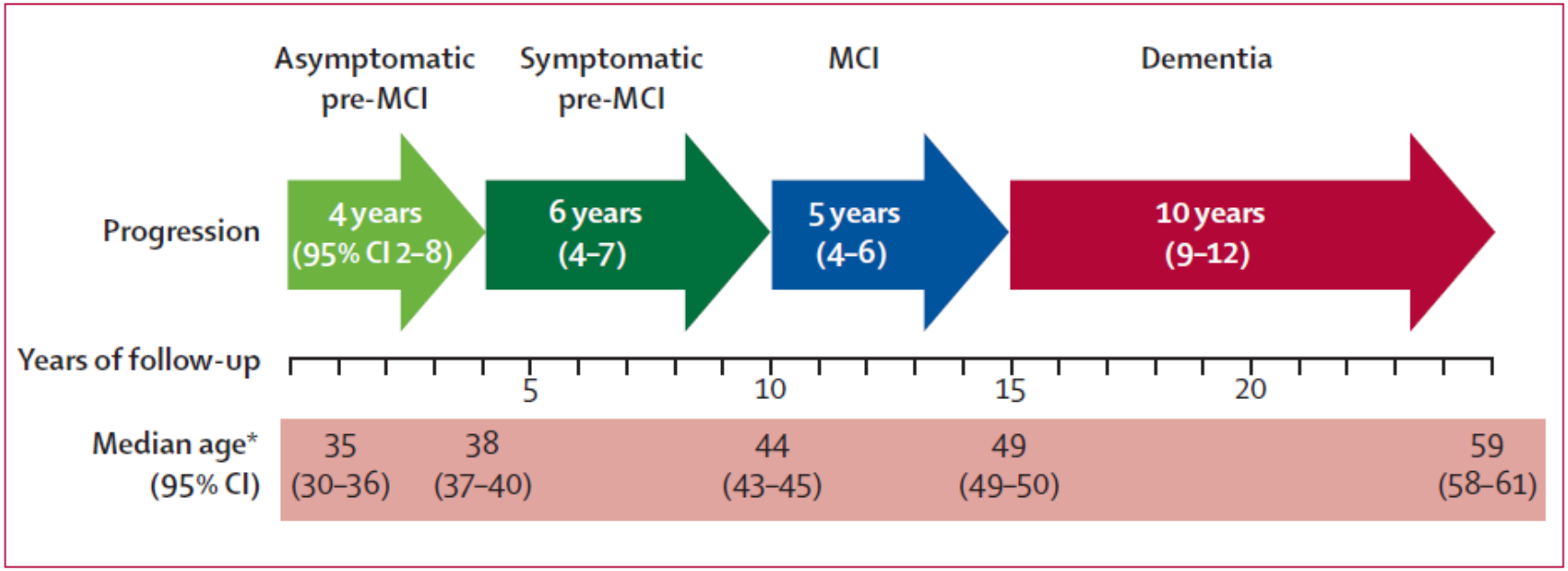


Figure 2: Clasifiación restrospectiva de los portadores E280A de acuerdo con los criterios de cada estado.
Portadores sanos: asintomáticos con puntajes en evaluación neuropsicológica menos de 2SD del promedio de acuerdo a la edad y educación.
*Impacto: Alto puntaje en la escala de quejas subjetivas de 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.



JAMA Neurology

Original Investigation | February 22, 2016

Cognitive Decline in a Colombian Kindred With Autosomal Dominant Alzheimer Disease

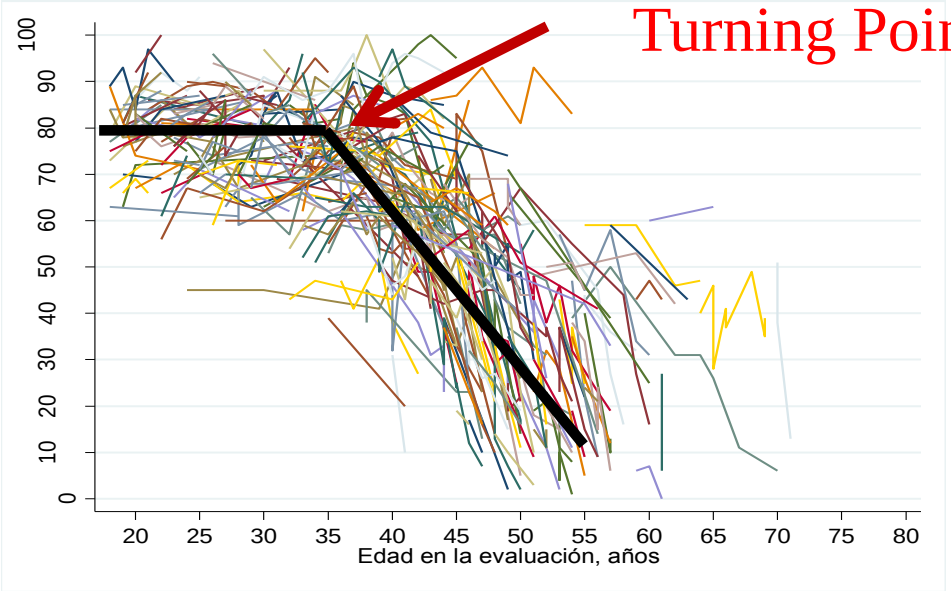
A Retrospective Cohort Study ONLINE FIRST

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



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

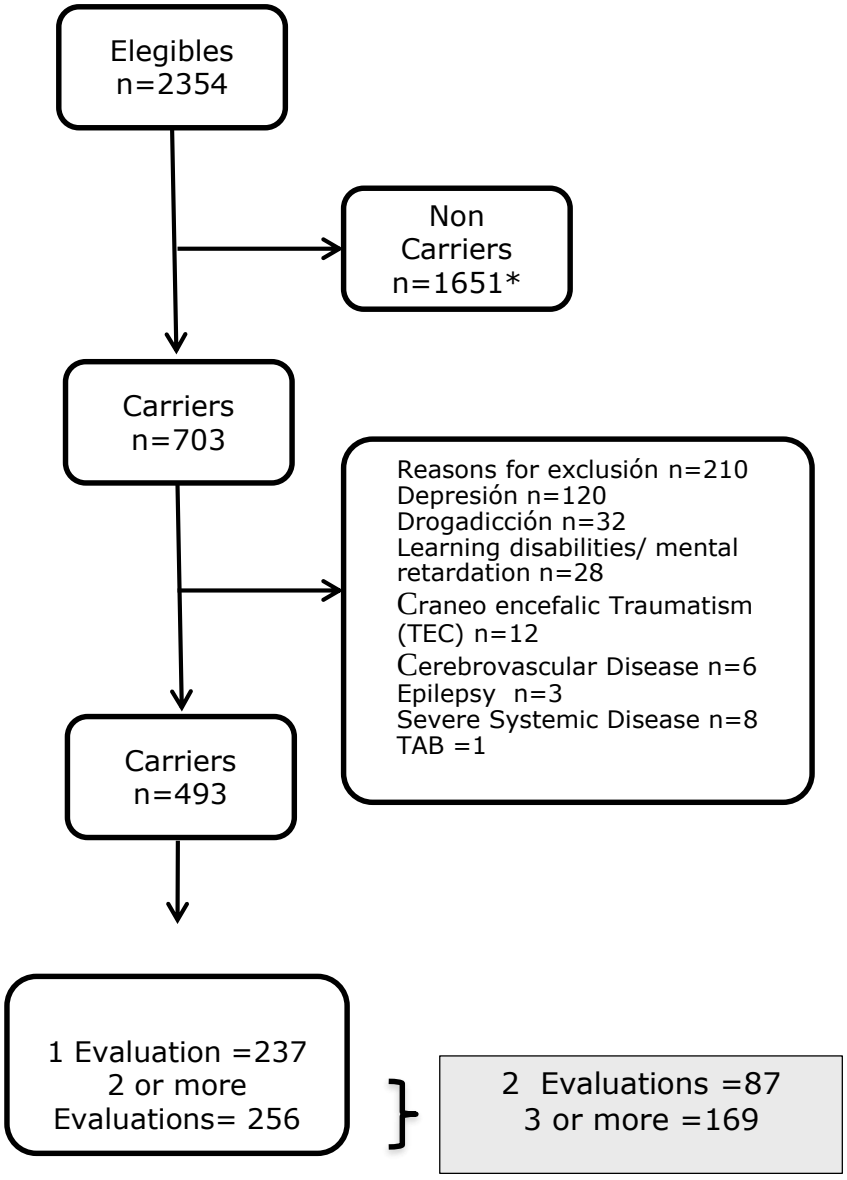
$$E(Y_{it}) = \begin{cases} \beta_{01i} + \beta_{11i}t & \text{If } t \le \tau \\ \beta_{02i} + \beta_{12i}t & \text{If } t > \tau \end{cases}$$

Función antes del punto de cambio

Función después del punto de cambio

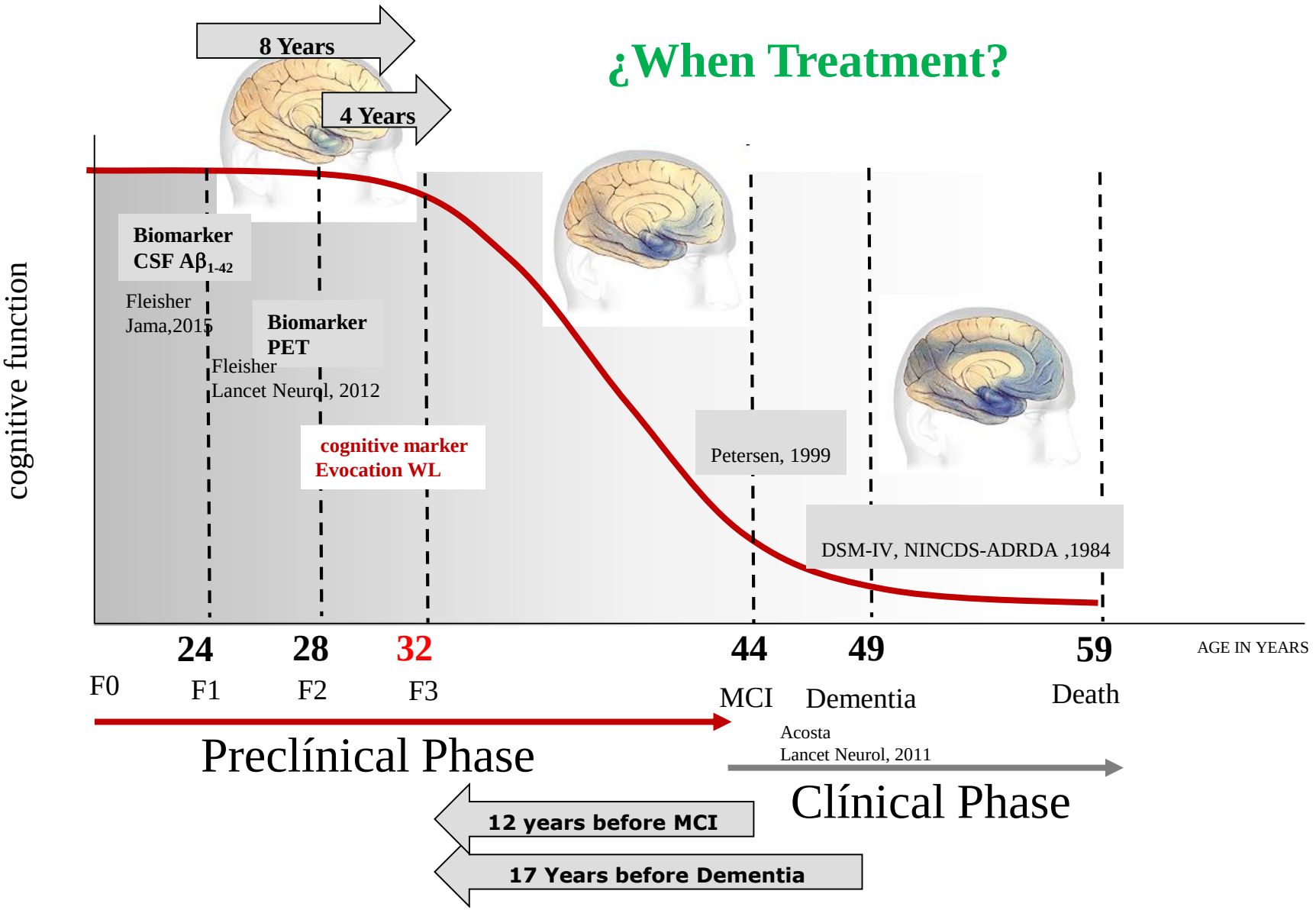
Hall CB, et al. Stat Med. 2000;19(11):1555-1566

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.

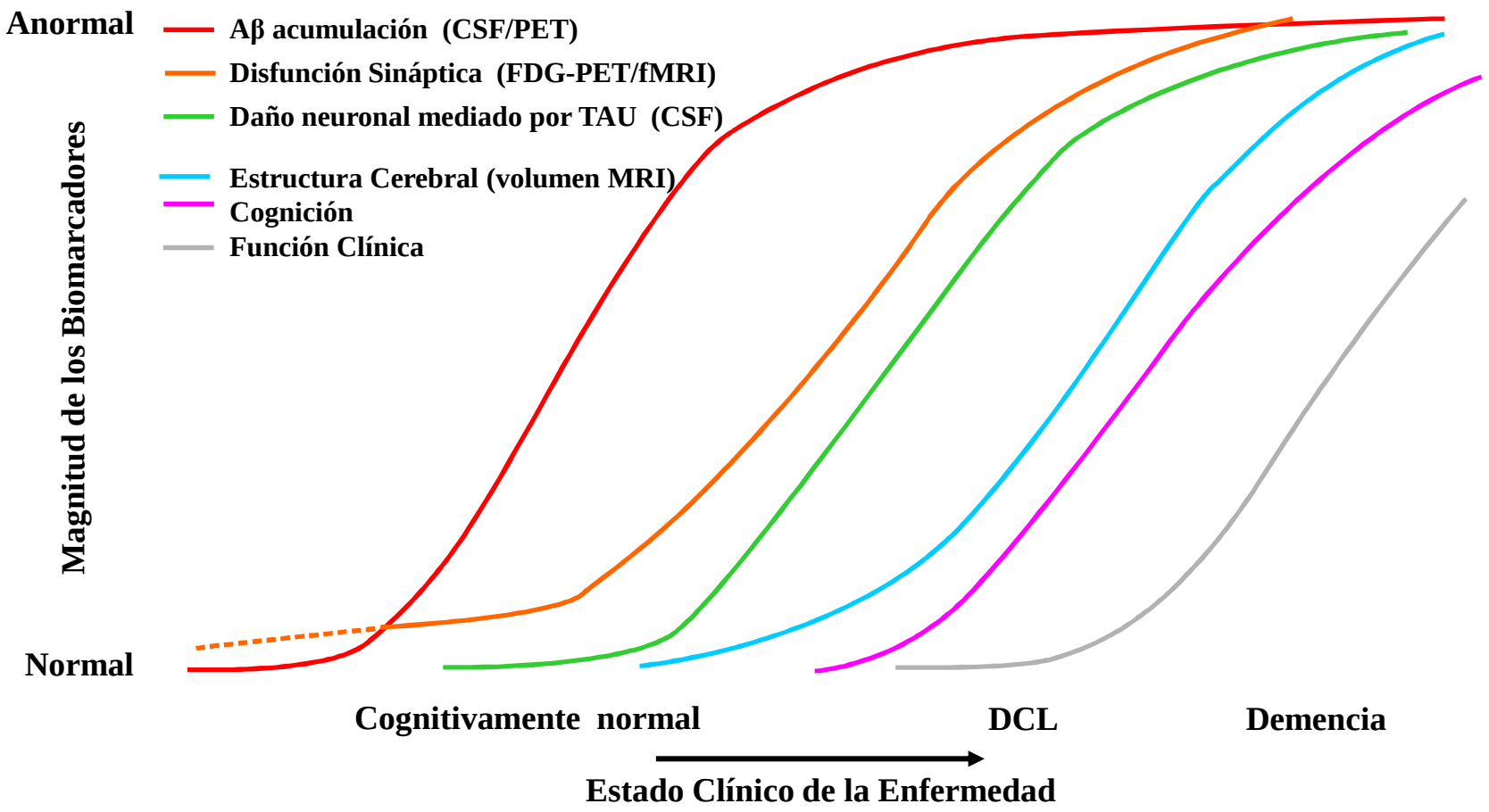
Clinical and Preclinical phases in FAD caused by E280A PS1 Mutation (Aguirre et al, 2015)



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

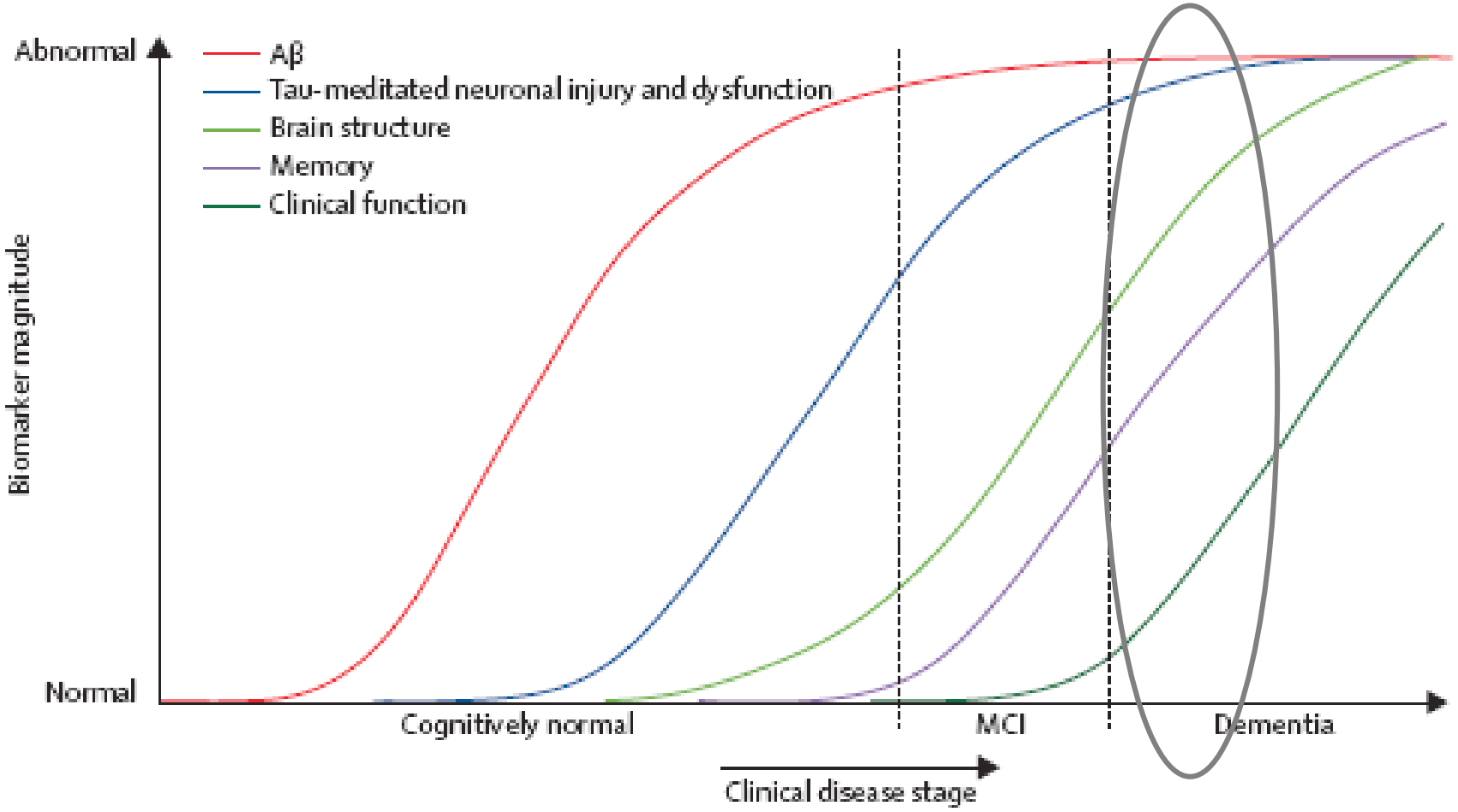
ALZHEIMER'S PREVENTION INITIATIVE

Alzheimer's disease is a continuum



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

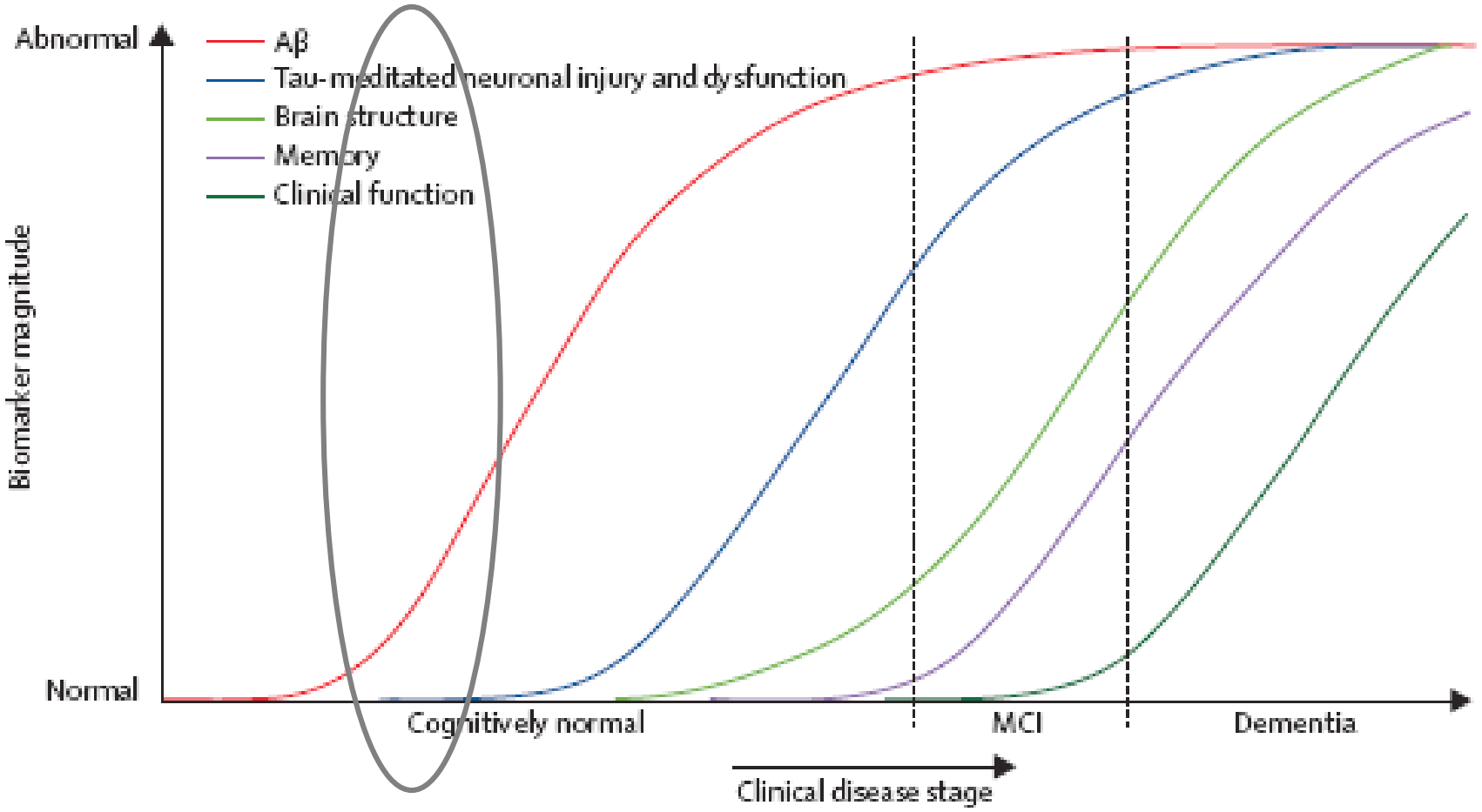
Pathological cascade implications for therapy: treatment and prevention



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

Pathological cascade implications for therapy: treatment and prevention



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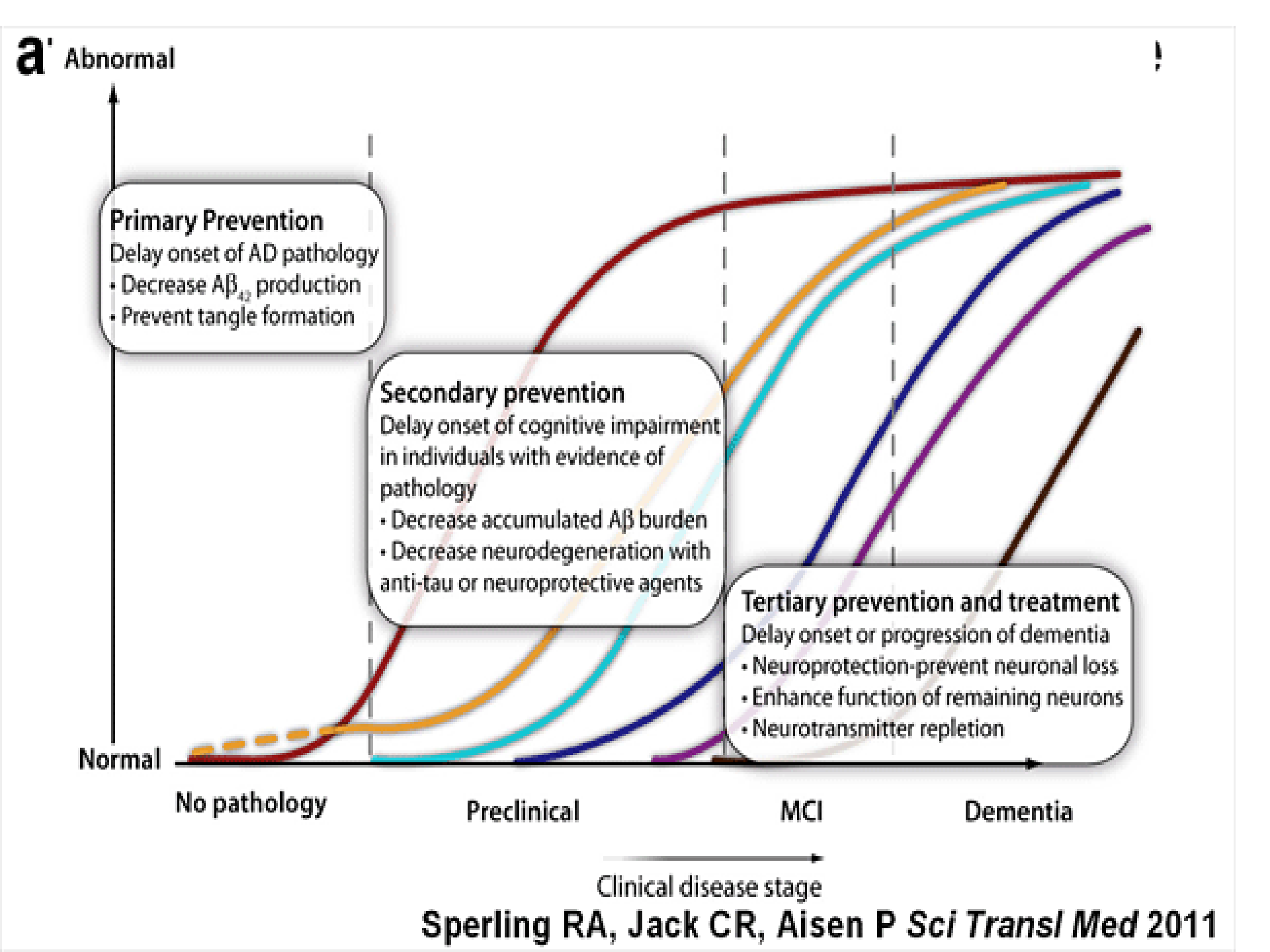
Ab Amyloid = CSF Ab42 or amyloid PET imaging; Tau Mediated Neuron Injury and Dysfunction = CSF tau or FDG PET; Brain Structure = structural MRI

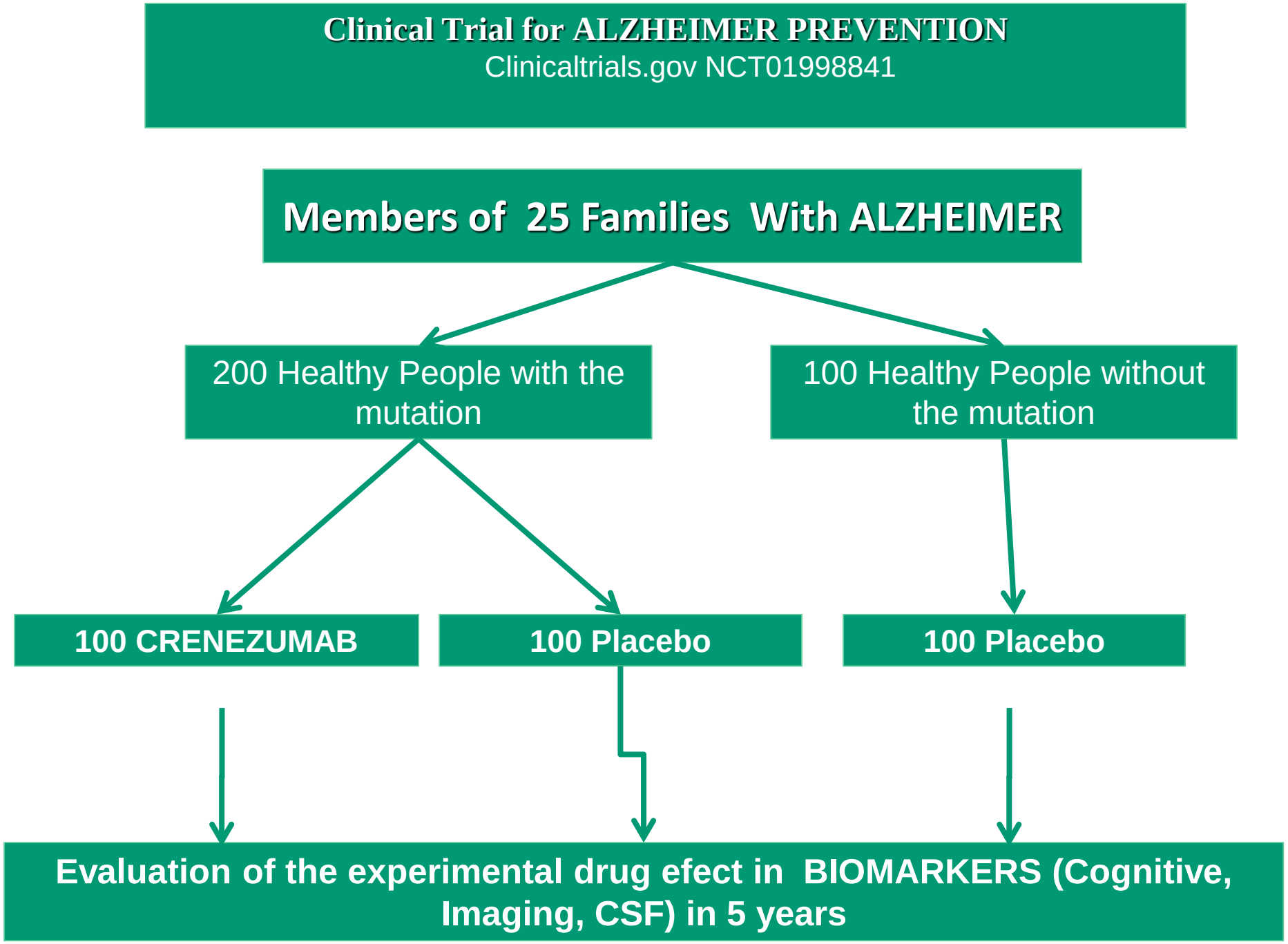


Sperling RA, Jack CR, Aisen P *Sci Transl Med* 2011

CLNICAL TRIAL
API COLOMBIA
GN28352

Conducted by Neurosciences Group of Antioquia:
in partnership with /supported by NIA, Banner, Genentech & Roche
Launched 2nd half 2013

INICIATIVA DE PREVENCIÓN DEL ALZHEIMER COLOMBIA


Clinical Trial for ALZHEIMER PREVENTION
Clinicaltrials.gov NCT01998841
Members of 25 Families With ALZHEIMER
200 Healthy People with the mutation
100 Healthy People without the mutation
100 CRENEZUMAB
100 Placebo
100 Placebo
Evaluation of the experimental drug efect in BIOMARKERS (Cognitive, Imaging, CSF) in 5 years

Interdisciplinary Team of Neuroscience Group of Antioquia.