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

MCI Symposium

Workshop - Miami January 15, 2017

Francisco Lopera, MD
University of Antioquia, Medellin (Colombia)
flopera@une.net.co
CONFLICT OF INTERESTS

Project: API COLOMBIA (IP)

Financed by:

NIH, Banner and Genentech
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.
Location of the affected population with EOFAD PSEN1 E280A mutation

(Some members are living in Caracas, Sidney, USA)
Genetics of Alzheimer’s Disease

**Early-onset AD:**
- APP
- PSEN1
- PSEN2

Altered Aβ-production

**NEURODEGENERATION**

**Late Onset (≥65 Years):**
- APOE
- CLU

**Genetics:**
- **Simple Genetics** (<5%)
- “Complex Genetics” (>95%)
Most of the mutations that cause FAD are in the PSEN1 gene

<table>
<thead>
<tr>
<th>Gene</th>
<th># Mutations</th>
<th># Families</th>
</tr>
</thead>
<tbody>
<tr>
<td>APP</td>
<td>32 (14.3%)</td>
<td>86 (17.2%)</td>
</tr>
<tr>
<td>PSEN1</td>
<td>177 (78.4%)</td>
<td>392 (78.2%)</td>
</tr>
<tr>
<td>PSEN2</td>
<td>14 (6.3%)</td>
<td>23 (4.6 %)</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>501</td>
</tr>
</tbody>
</table>

AD mutation database:  
Paisa Mutation E280A is a substitution of ALANINE FOR GLUTAMIC ACID in CODON 280 OF THE PRESENLIN 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.
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; Lucía Madrígala; 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
## Symptoms and Clinical Signs in PSEN1 E280A

Lopera et al, Jama 1997

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory disturbance</td>
<td>118 (100)</td>
</tr>
<tr>
<td>Personality and behavioral changes</td>
<td>111 (94)</td>
</tr>
<tr>
<td>Language difficulty</td>
<td>96 (81)</td>
</tr>
<tr>
<td>Symptoms of depression</td>
<td>93 (79)</td>
</tr>
<tr>
<td>Headache</td>
<td>86 (73)</td>
</tr>
<tr>
<td>Gait difficulty</td>
<td>77 (65)</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>77 (65)</td>
</tr>
<tr>
<td>Wandering</td>
<td>74 (63)</td>
</tr>
<tr>
<td>Convulsions and myoclonus</td>
<td>53 (45)</td>
</tr>
<tr>
<td>Suck reflex</td>
<td>49 (42)</td>
</tr>
<tr>
<td>Babinski reflex</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Grasp reflex</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>22 (19)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>22 (19)</td>
</tr>
</tbody>
</table>
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
Neuropsychological Profile of a Large Kindred with Familial Alzheimer’s Disease Caused by the E280A Single Presenilin-1 Mutation

Álfredo Ardila

Instituto Colombiano de Neuropsicología

Francisco Lopera

University of Antioquia

Mónica Rosselli

Florida Atlantic University

Sonia Moreno, Lucia Madrigal, Juan C. Arango-Lasprilla, Mauricio Arcos, Clara Murcia, Juan C. Arango-Viana, and Jorge Ossa

University of Antioquia

Alison Goate

Washington University

Kenneth S. Kosik

Harvard Medical School
Preclinical Cognitive markers

Study Design

- **E280A**
- **122 Asymptomatic**
- **Group 1**
  - Carriers = 40
- **Group 2**
  - Non Carriers = 82
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

<table>
<thead>
<tr>
<th>TEST (CERAD)</th>
<th>E280A (-) N = 82</th>
<th>E280A (+) N = 40</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRUSIONS trial 2</td>
<td>0.12 (0.32)</td>
<td>0.30 (0.56)</td>
<td>2.19</td>
<td>.030</td>
</tr>
<tr>
<td>INTRUSIONS Total</td>
<td>0.67 (1.12)</td>
<td>1.48 (1.72)</td>
<td>3.09</td>
<td>.002</td>
</tr>
<tr>
<td>INTRUSIONS Remembering Words</td>
<td>0.36 (0.69)</td>
<td>1.05 (1.58)</td>
<td>3.32</td>
<td>.001</td>
</tr>
</tbody>
</table>
Cognitive changes in the preclinical phase of familial Alzheimer’s disease

Juan Carlos Arango-Lasprilla,¹ Fernando Cuetos,² Claudia Valencia,¹,³ Claramonika Uribe,¹ and Francisco Lopera¹

¹Neuroscience Group, University of Antioquia, Medellín, Colombia
²University of Oviedo, Oviedo, Spain
³Cognitive Psychology Group, University of Antioquia, Medellín, Colombia

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 non-carriers 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


• **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

<table>
<thead>
<tr>
<th></th>
<th>Non-carriers (n = 21)</th>
<th>Carriers (n = 19)</th>
<th>U</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>45.29 (3.68)</td>
<td>43.16 (3.00)</td>
<td>-1.9</td>
<td>0.061</td>
</tr>
<tr>
<td>Years of education</td>
<td>5.57 (3.82)</td>
<td>5.05 (3.05)</td>
<td>-0.3</td>
<td>0.768</td>
</tr>
</tbody>
</table>
### Carrier vs. non-carrier scores on lexical and semantic tasks

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

FERNANDO CUETOS,1 JUAN CARLOS ARANGO-LASPRILLA,2 CLARAMÓNNIKA URIBE,2 CLAUDIA VALENCIA,2,3 AND FRANCISCO LOPERA2

1Department of Psychology, University of Oviedo, Oviedo, Spain
2Neuroscience Group, University of Antioquia, Medellín, Colombia
3Cognitive Psychology Research Group, University of Antioquia, Medellín, Colombia

(Received July 10, 2006; Final Revision December 13, 2006; Accepted December 13, 2006)
Table 1. Performance of carriers and noncarriers on variables from the Boston Cookie Theft Picture Card

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carriers</td>
</tr>
<tr>
<td>Semantic units</td>
<td>4.26 (2.10)</td>
</tr>
<tr>
<td>Objective situations</td>
<td>5.68 (2.73)</td>
</tr>
<tr>
<td>Inferences</td>
<td>0.05 (0.23)</td>
</tr>
<tr>
<td>Total number of sentences</td>
<td>12.10 (4.03)</td>
</tr>
<tr>
<td>Average sentence length</td>
<td>9.61 (2.67)</td>
</tr>
<tr>
<td>Open-class/closed-class words ratio</td>
<td>0.89 (0.17)</td>
</tr>
<tr>
<td>Total number of simple verbs</td>
<td>14.11 (8.20)</td>
</tr>
<tr>
<td>Total number of compound verbs</td>
<td>6.68 (3.76)</td>
</tr>
</tbody>
</table>

*Significant $p$ value (Bonferroni corrected $\alpha = .0035$).
Visual short-term memory binding deficits in familial Alzheimer’s disease

Mario A. Parra, Sharon Abrahams, Robert H. Logie, Luis G. Méndez, Francisco Lopena and Sergio Della Sala

1 Human Cognitive Neuroscience, Centre for Cognitive Ageing and Cognitive Epidemiology, Psychology, University of Edinburgh, Edinburgh, UK
2 Neuroscience Group, University of Antioquia, SITI (Cede de Investigaciones Universitarias), Cali, #52-99, Antioquia, Medellín, Colombia

Correspondence to: Mario A. Parra,
Psychology Department,
University of Edinburgh,
7 George Square,
Edinburgh EH8 9JF, UK
E-mail: mappar@ed.ac.uk

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 90 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

250 msec

2000 msec

900 msec

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

(A) % Correct Recognition

(B) Sensitivity (A')

<table>
<thead>
<tr>
<th>Condition</th>
<th>非携带者</th>
<th>携带者</th>
<th>AD患者</th>
</tr>
</thead>
<tbody>
<tr>
<td>形状 Only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>颜色 Only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>形状-颜色绑定</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Preclinical Alzheimer Disease

BIOMARKERS

• BIOCHEMICAL

Levels of CSF $\text{A} \beta_{1-42}$
## Biomarkers in CSF in AD

<table>
<thead>
<tr>
<th></th>
<th>Aβ42</th>
<th>Tau</th>
<th>Ptau</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>DCL</td>
<td>↓ or N</td>
<td>↑ or N</td>
<td>↑ or N</td>
</tr>
<tr>
<td>Control</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

- **Aβ42** refers to the concentration of Aβ in the cerebrospinal fluid (CSF).
- **Tau** indicates the total tau protein levels.
- **Ptau** refers to phosphorylated tau, which is associated with neurofibrillary tangles.

**Neurodiagram:**
- Phosphorylated tau in tangles
- Total tau in neuronal axons
- Aβ1-42 in senile plaques
Higher (not lower) CSF Aβ$_{1-42}$ Levels in E280A Population

$P = 0.008$

CSF Aβ$_{1-42}$ (pg/ml)
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
Florbetapir PET analysis of amyloid-\(\beta\) deposition in the presenilin 1 E280A autosomal dominant Alzheimer’s disease kindred: a cross-sectional study


Summary

Background  Fibrillar amyloid-\(\beta\) (A\(\beta\)) 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 A\(\beta\) 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 A\(\beta\) deposition in presenilin 1 (PSEN1) E280A mutation carriers across the spectrum of preclinical disease.
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
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Non-Carriers</th>
<th>Pre-symptomatic Carriers</th>
<th>Symptomatic Carriers</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>20</td>
<td>19</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td><strong>Age (range)</strong></td>
<td>33.9±8.7</td>
<td>32.6±8.2</td>
<td>47.5±4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(20-50)</td>
<td>(20-43)</td>
<td>(41-56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender (M/F)</strong></td>
<td>7/13</td>
<td>7/12</td>
<td>3/8</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>11.2±3.3</td>
<td>12.3±2.8</td>
<td>8.8±3.5</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>29.8±0.5</td>
<td>29.8±0.4</td>
<td>23.1±3.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Visually positive Symptomatic AD

Visually positive Pre-symptomatic AD

Visually negative Pre-symptomatic AD
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

**Stage 1**
*Asymptomatic amyloidosis*
- High PET amyloid tracer retention
- Low CSF Aβ_{1-42}

**Stage 2**
*Amyloidosis + Neurodegeneration*
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

**Stage 3**
*Amyloidosis + Neurodegeneration + Subtle Cognitive Decline*
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

\[\text{MCI} \rightarrow \text{AD dementia}\]
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

We retrospectively assessed a Cohort of descendants of *PSEN1 E280A mutation carriers* from 1995 to 2010
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: Clasificación retrospectiva 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.
Figure 2: Survival analysis of disease progression in PSEN1 E280A carriers
MCI = mild cognitive impairment.

Conclusions
Cognitive Decline in a Colombian Kindred With Autosomal Dominant Alzheimer Disease

A Retrospective Cohort Study

Daniel C. Aguirre-Acevedo, PhD¹,²; Francisco Lopera, MD¹; Eliana Henao, MS¹; Victoria Tirado, MS¹; Claudia Muñoz, MS¹; Margarita Giraldo, MD¹; Shrikant I. Bangdiwala, PhD³; Eric M. Reiman, MD⁴; Pierre N. Tariot, MD⁴; Jessica B. Langbaum, PhD⁴; Yakeel T. Quiroz, PhD¹,⁵; Fabian Jaimes, PhD²,⁶

[+] Author Affiliations

JAMA Neurol. Published online February 22, 2016. doi:10.1001/jamaneurol.2015.4851
Let $Y_{it} = \beta_0i + \beta_{1i}t + \beta_{02i} + \beta_{12i}t + \epsilon_{it}$

$$E(Y_{it}) = \begin{cases} 
\beta_0i + \beta_{1i}t & \text{If } t \leq \tau \\
\beta_{02i} + \beta_{12i}t & \text{If } t > \tau 
\end{cases}$$

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

Elegibles
n=2354

Non Carriers
n=1651*

Carriers
n=703

Reasons for exclusion n=210
Depresión n=120
Drogadicción n=32
Learning disabilities/ mental retardation n=28
Craneo encefalic Traumatism (TEC) n=12
Cerebrovascular Disease n=6
Epilepsy n=3
Severe Systemic Disease n=8
TAB =1

Carriers
n=493

1 Evaluation =237
2 or more Evaluations = 256

2 Evaluations = 87
3 or more = 169

*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)

- **Preclinical Phase**
  - **F0**: 17 Years before Dementia
  - **F1**: 12 years before MCI

- **Clinical Phase**
  - **MCI**: Petersen, 1999
  - **Dementia**: Fleisher, 2012
  - **Death**: Fleisher, 2012

- **Biomarker**
  - **PET**
  - **CSF Aβ1-42**
  - **Cognitive marker Evocation WL**

- **¿When Treatment?**
  - **Acosta**: Lancet Neurol, 2011
Alzheimer's disease is a continuum

Pathological cascade implications for therapy: treatment and prevention


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


Ab Amyloid = CSF Ab42 or amyloid PET imaging; Tau Mediated Neuron Injury and Dysfunction = CSF tau or FDG PET; Brain Structure = structural MRI
Primary Prevention
Delay onset of AD pathology
- Decrease Aβ_{42} production
- Prevent tangle formation

Secondary prevention
Delay onset of cognitive impairment in individuals with evidence of pathology
- Decrease accumulated Aβ burden
- Decrease neurodegeneration with anti-tau or neuroprotective agents

Tertiary prevention and treatment
Delay onset or progression of dementia
- Neuroprotection-prevent neuronal loss
- Enhance function of remaining neurons
- Neurotransmitter repletion

Clinical disease stage

CLINICAL TRIAL
API COLOMBIA
GN28352

Conducted by Neurosciences Group of Antioquia:
in partnership with /supported by NIA, Banner, Genentech & Roche
Launched 2nd half 2013
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 effect in BIOMARKERS (Cognitive, Imaging, CSF) in 5 years
Interdisciplinary Team of Neuroscience Group of Antioquia.