

Personalized Medicine and Alzheimer's Disease

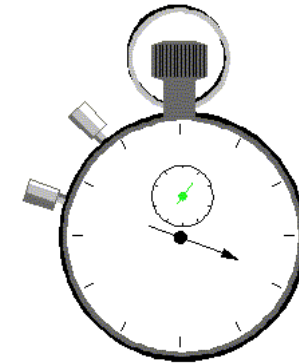
Philippe Amouyel, Lille, France

FONDATION PLAN ALZHEIMER

FONDATION DE COOPÉRATION SCIENTIFIQUE
POUR LA RECHERCHE SUR LA MALADIE D'ALZHEIMER
& LES MALADIES APPARENTÉES

IsaacSet test

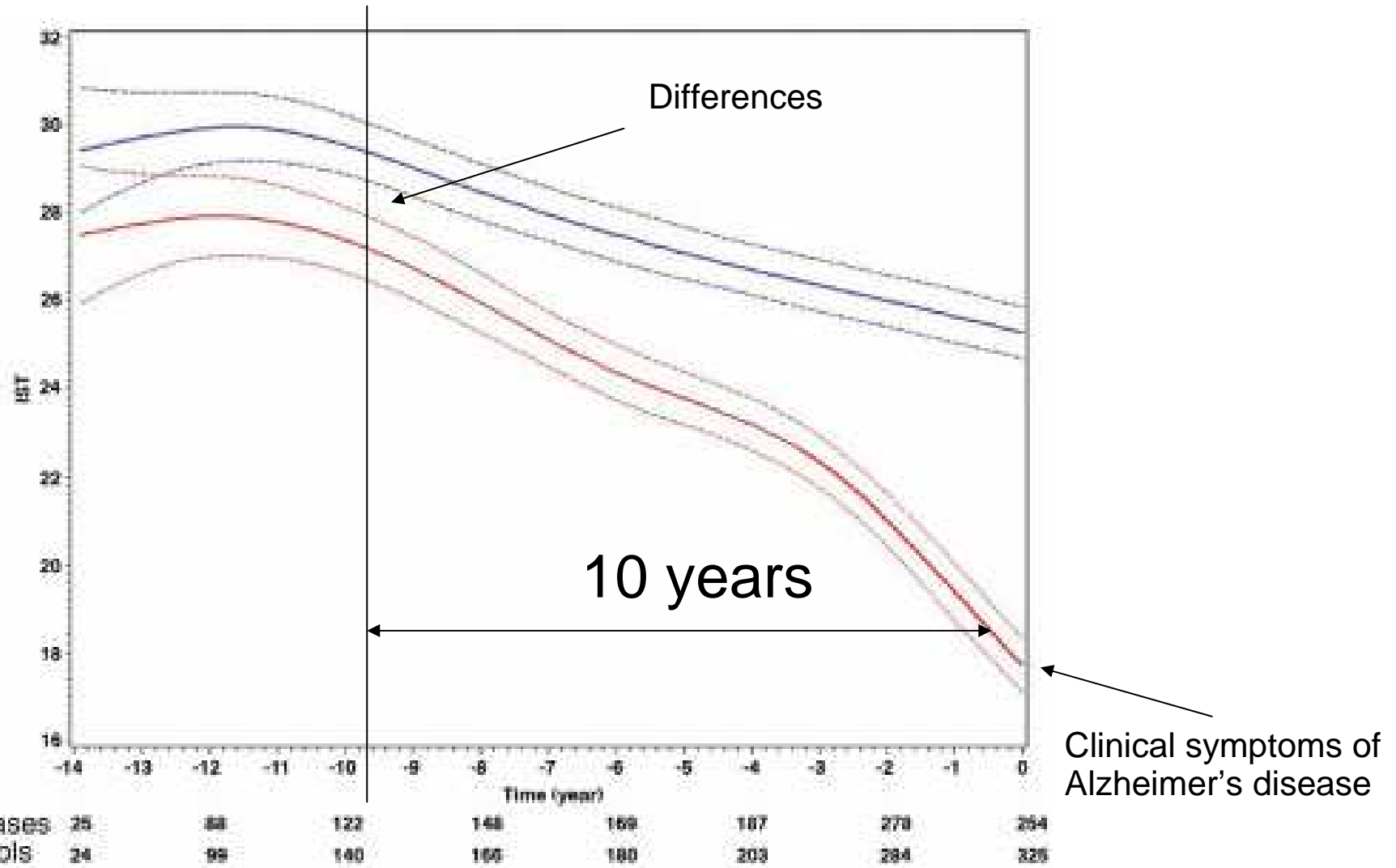
	Colors	Animals	Fruits	Towns
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15 seconds

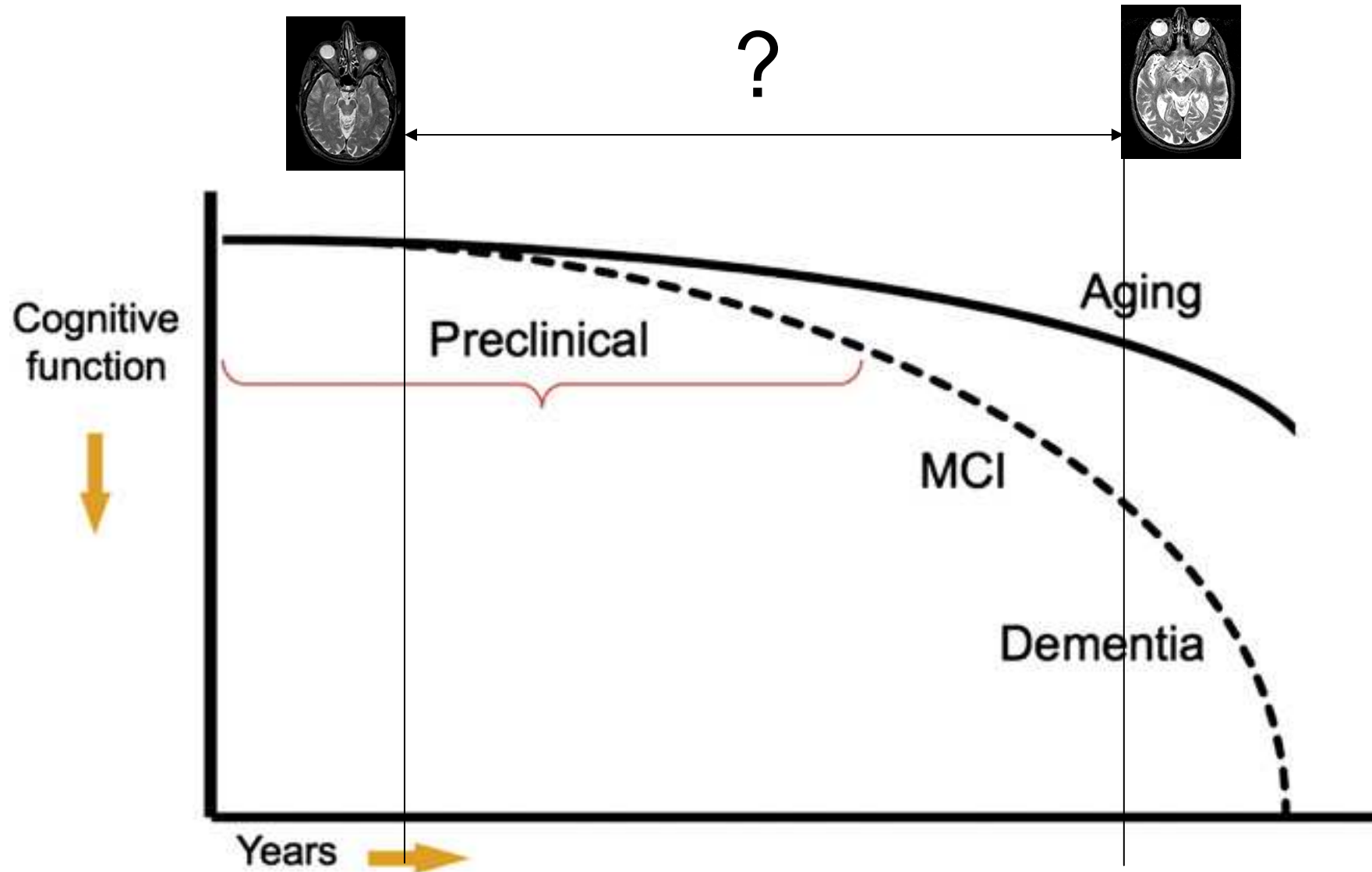
- Verbal fluency test
- Used in the testing for cognitive dysfunction in patients
- Normal > 37 ; $37 =$ monitoring ; $<34 =$ extended examination ; $<30 =$ pathological

PAQUID study, 14 year follow-up



D'après Amieva et al, Annals of Neurology, 2008

Alzheimer's disease evolution

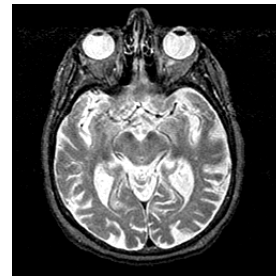
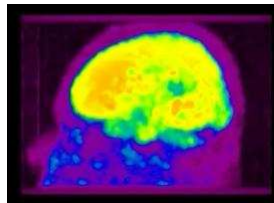


To diagnose as early as possible

- ◆ Neuropsychological examination

- Isaac Set test
- 5 word recall
-

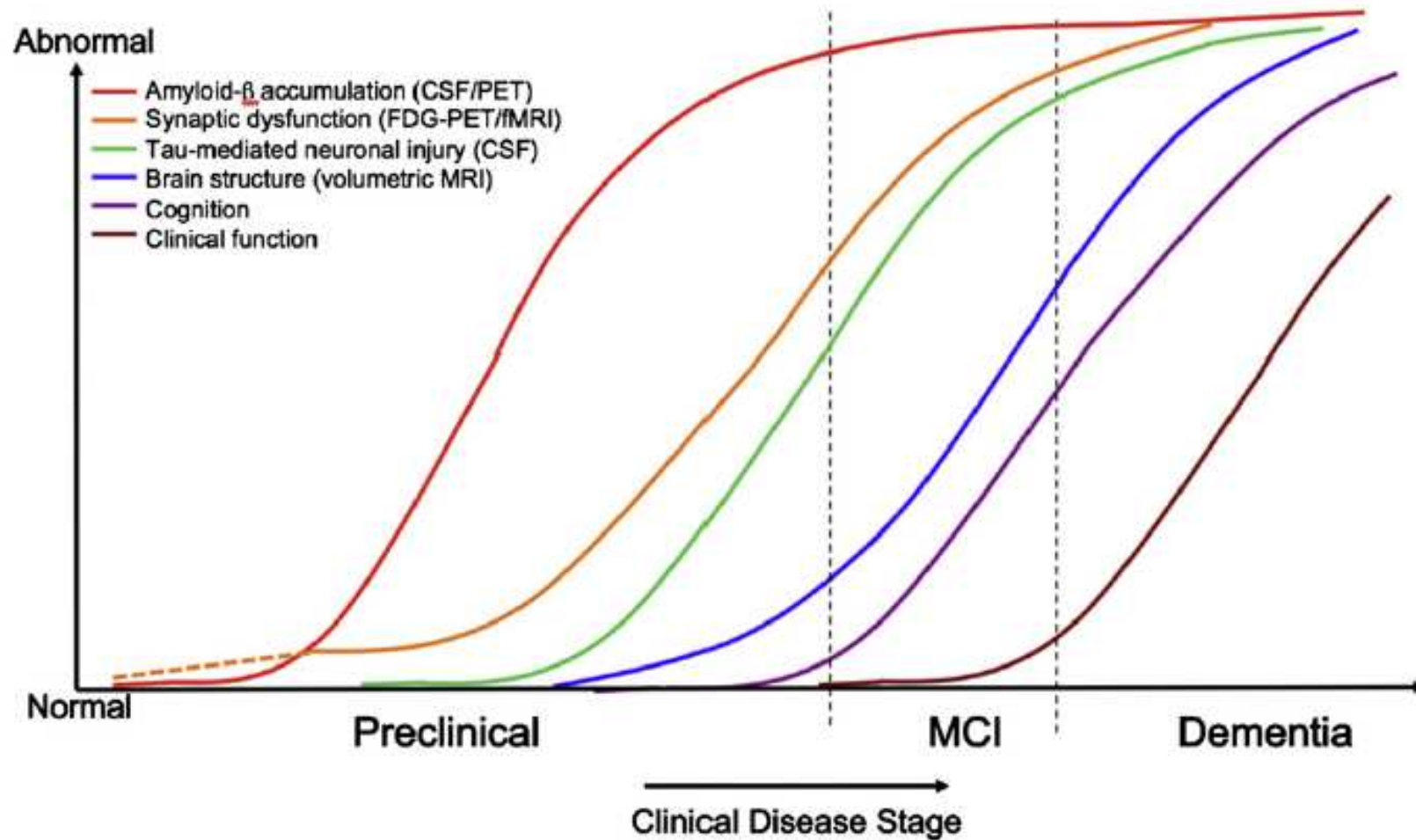
- ◆ Imaging



- ◆ Biology = A β peptide, Tau protein, P-Tau

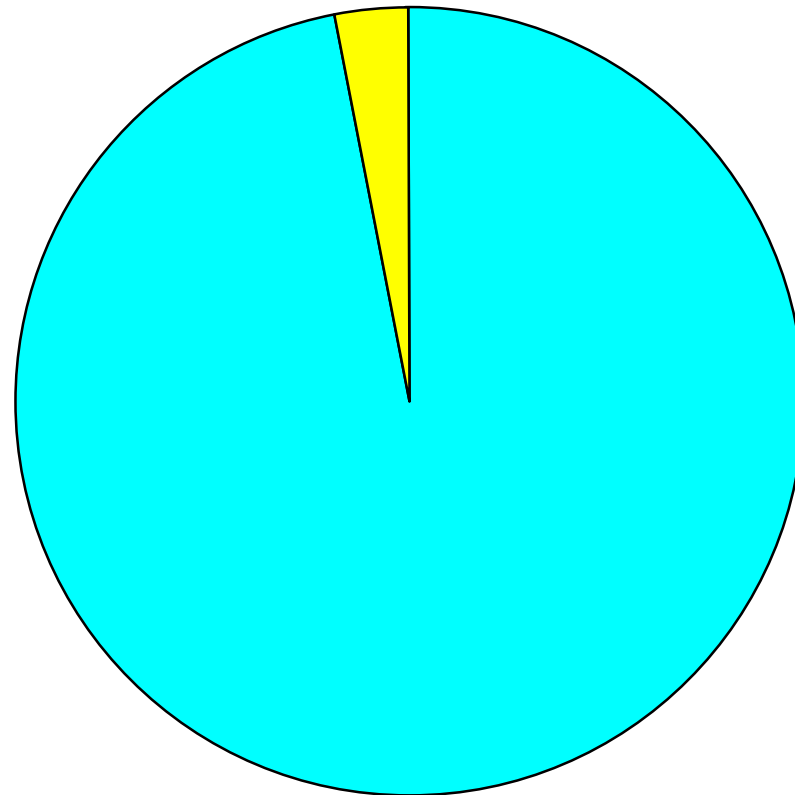
- CSF
- Blood

Biomarker Evolutions



D'après Sperling et al, Alzheimer & Dementia , 2011

Rare familial forms and a heritability over 60%



■ Sporadic ■ Inherited

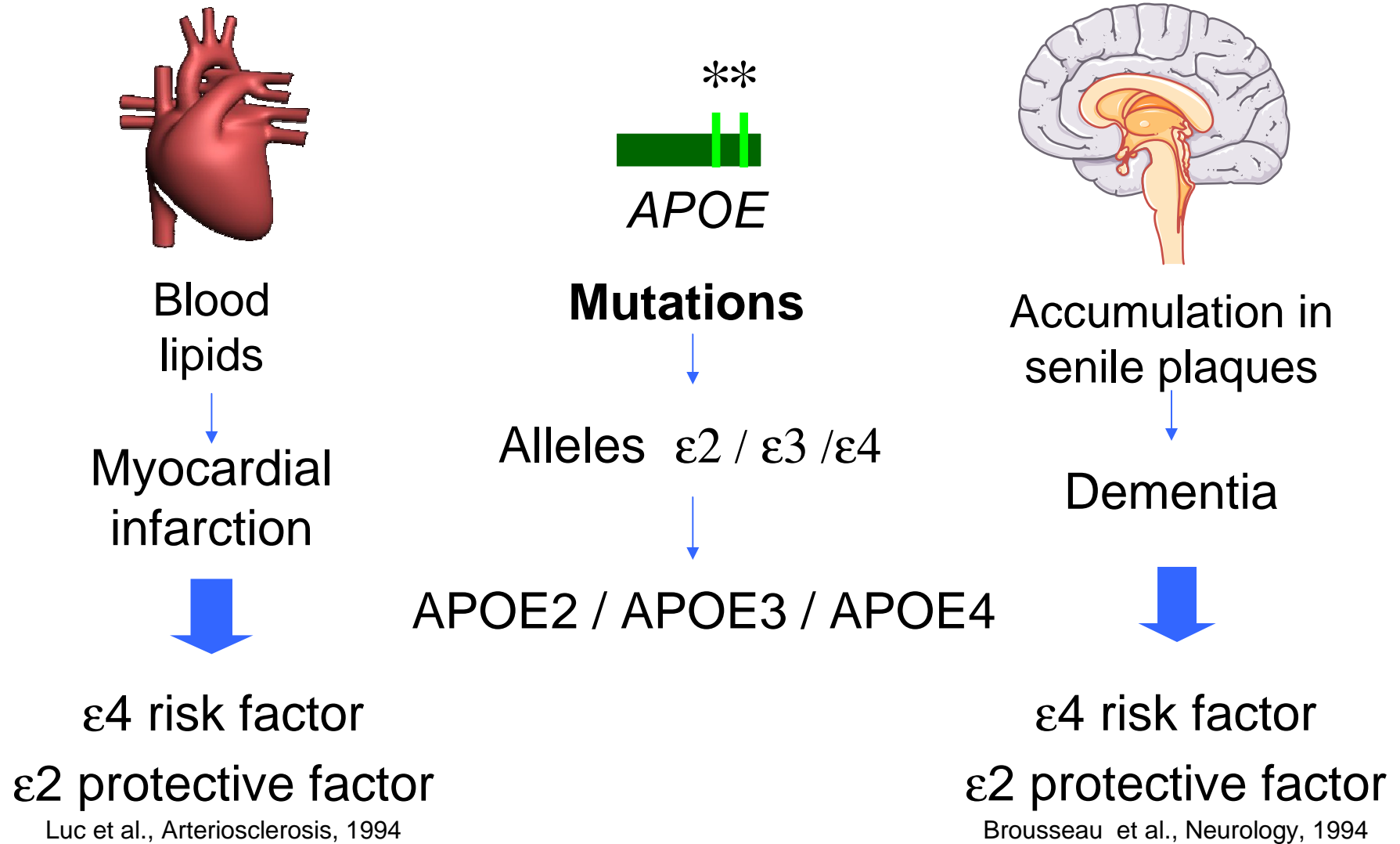
Hereditary forms

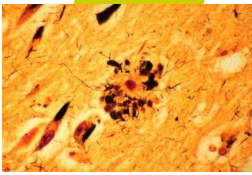
- ◆ Autosomal dominant transmission
- ◆ Less than 2% of all the cases
- ◆ Mainly early age-at-onset (before 65 y)
- ◆ Several major genes identified
 - Amyloid Protein Precursor (APP)
 - Presenilin 1 (PS1)
 - Presenilin 2 (PS2)

Sporadic forms

- ◆ Complex heredity
- ◆ 98% of all cases
- ◆ Mainly late age-at-onset (after 65 y)
- ◆ Until 2009 only one gene identified
 - Apolipoprotein E

From cardiovascular diseases to dementia





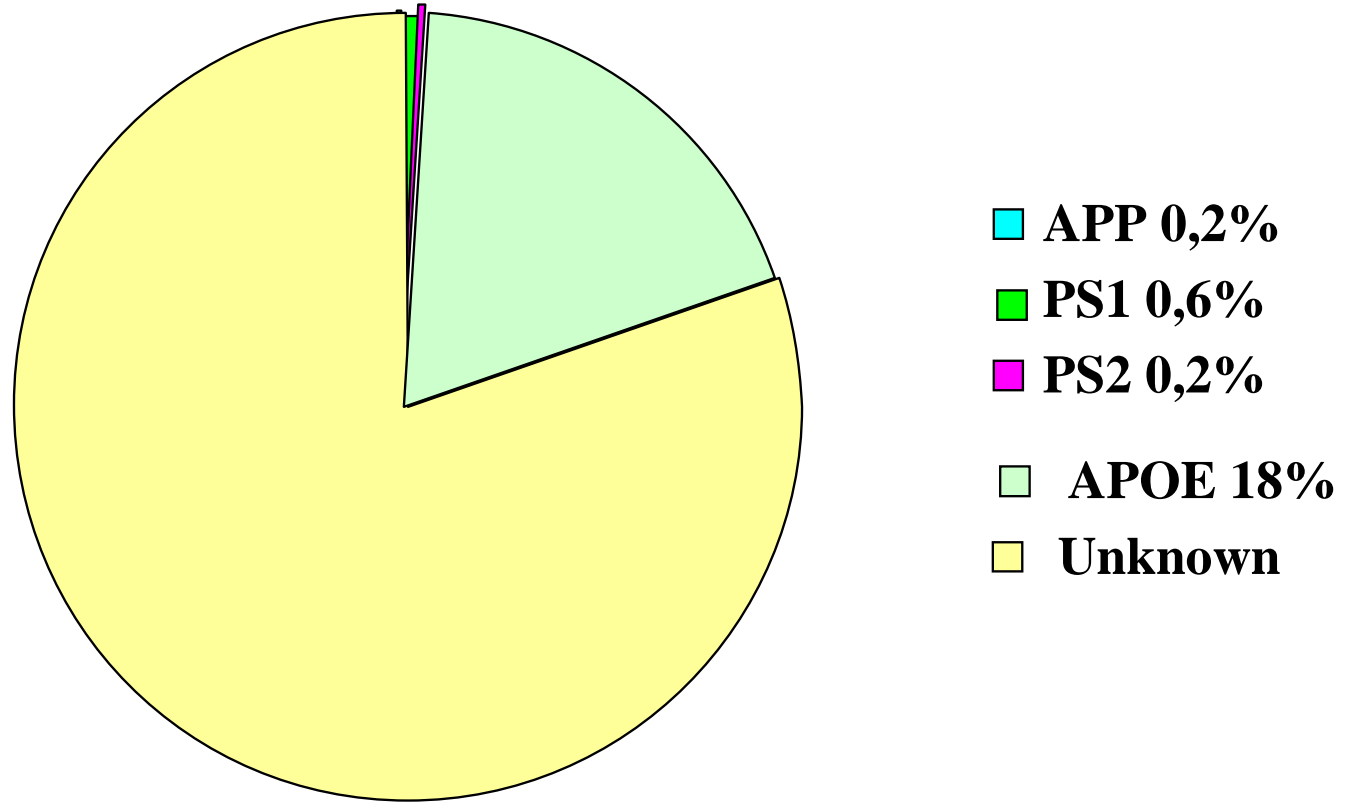
Apolipoprotein E



- ◆ 6 possible genotypes
- ◆ ε4 is a risk factor for late onset AD
- ◆ ε2 is a protective factor for late onset AD
- ◆ Replicated in almost all populations

APOE	OR (IC 95%)
ε2/ε2	0.6 [0.2-2.0]
ε2/ε3	0.6 [0.5-0.8]
ε3/ε3	1
ε2/ε4	2.6 [1.6-4.0]
ε3/ε4	3.2 [2.8-3.8]
ε4/ε4	14.9 [10.8-20.6]

From 1991 to 2009



Still 81% to characterize

Genome Wide Association Studies

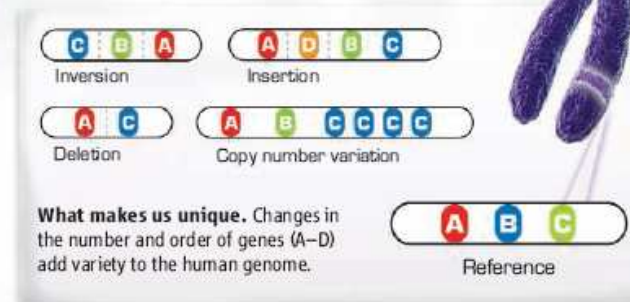
BREAKTHROUGH OF THE YEAR

Human Genetic Variation

Equipped with faster, cheaper technologies for sequencing DNA and assessing variation in genomes on scales ranging from one to millions of bases, researchers are finding out how truly different we are from one another

THE UNVEILING OF THE HUMAN GENOME ALMOST 7 YEARS AGO cast the first faint light on our complete genetic makeup. Since then, each new genome sequenced and each new individual studied has illuminated our genomic landscape in ever more detail. In 2007, researchers came to appreciate the extent to which our genomes differ from person to person and the implications of this variation for deciphering the genetics of complex diseases and personal traits.

Less than a year ago, the big news was triangulating variation between us and our primate cousins to get a better handle on genetic changes along the evolutionary tree that led to humans. Now, we have moved from asking what in our DNA makes us human to striving to know what in my DNA makes me me.



Experience from other major multifactorial diseases

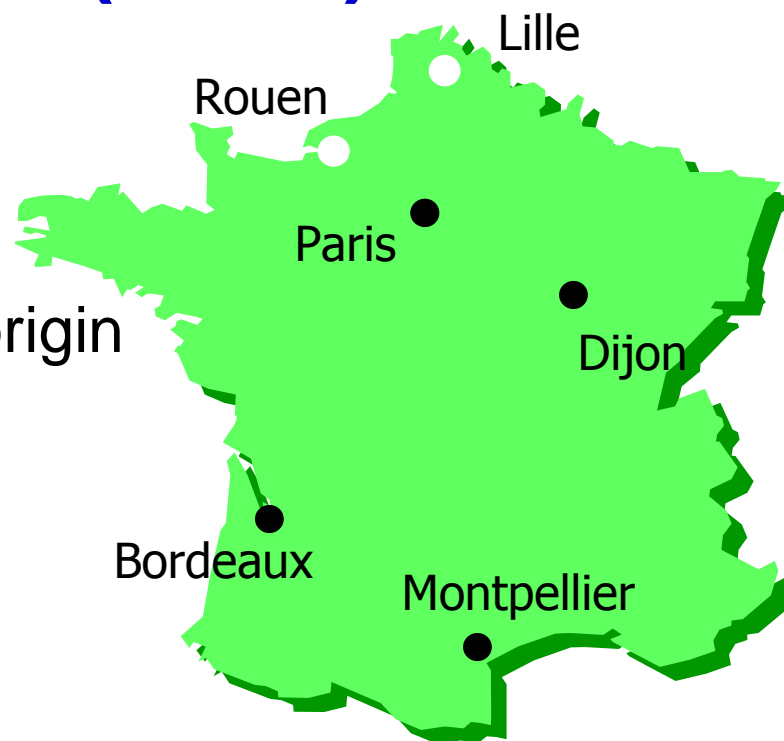
Methodological Issues to Solve

- ◆ Modest effects
- ◆ Statistical power
- ◆ Heterogeneity
- ◆ Replication

Increase sample sizes = collaboration

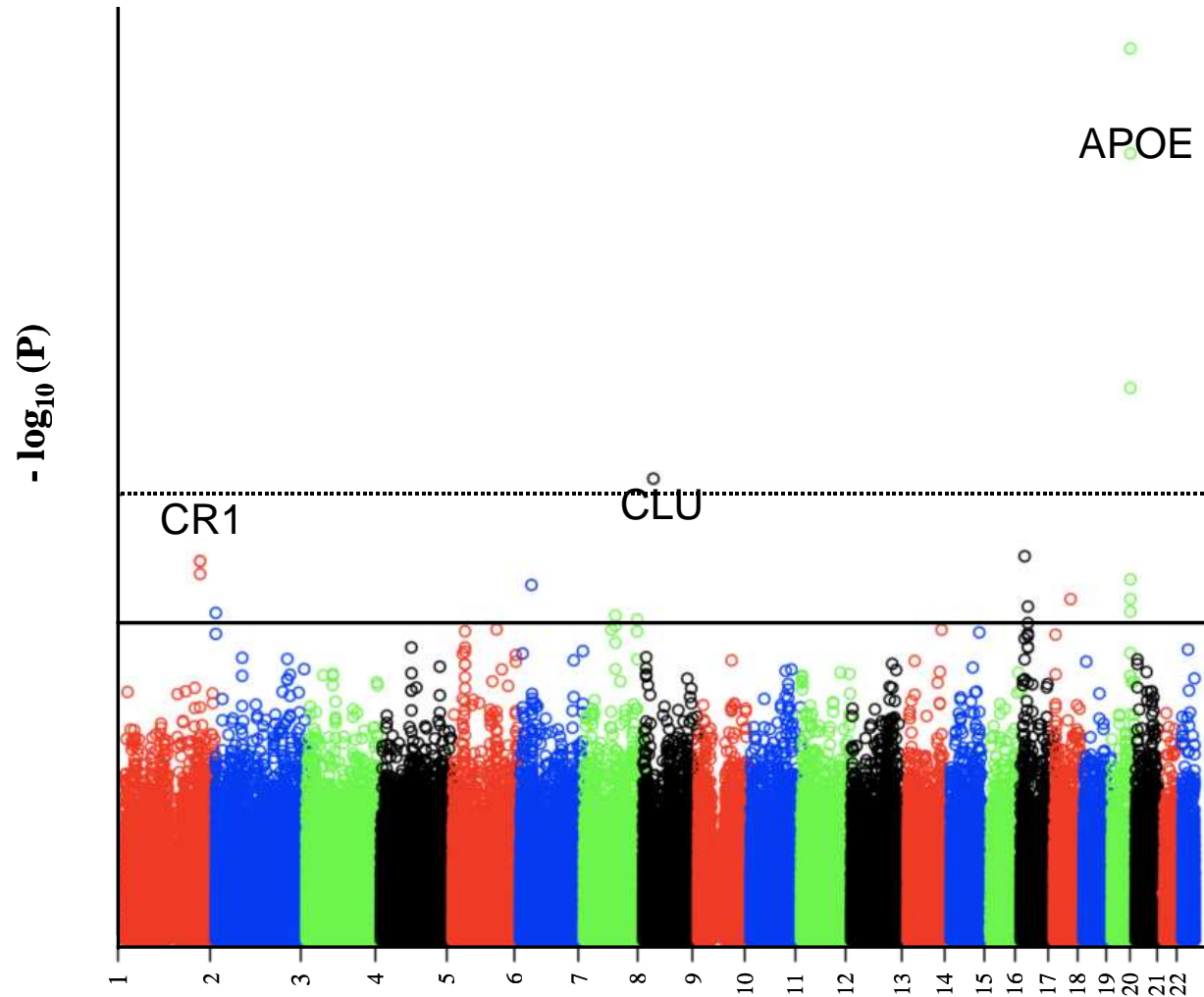
Genome Wide Association Study European Alzheimer's Disease Initiative (EADI)

- ◆ **Exploratory study** : GWAS
with populations from French origin



- ◆ **Follow-up study** : replication in independent samples from
European origin

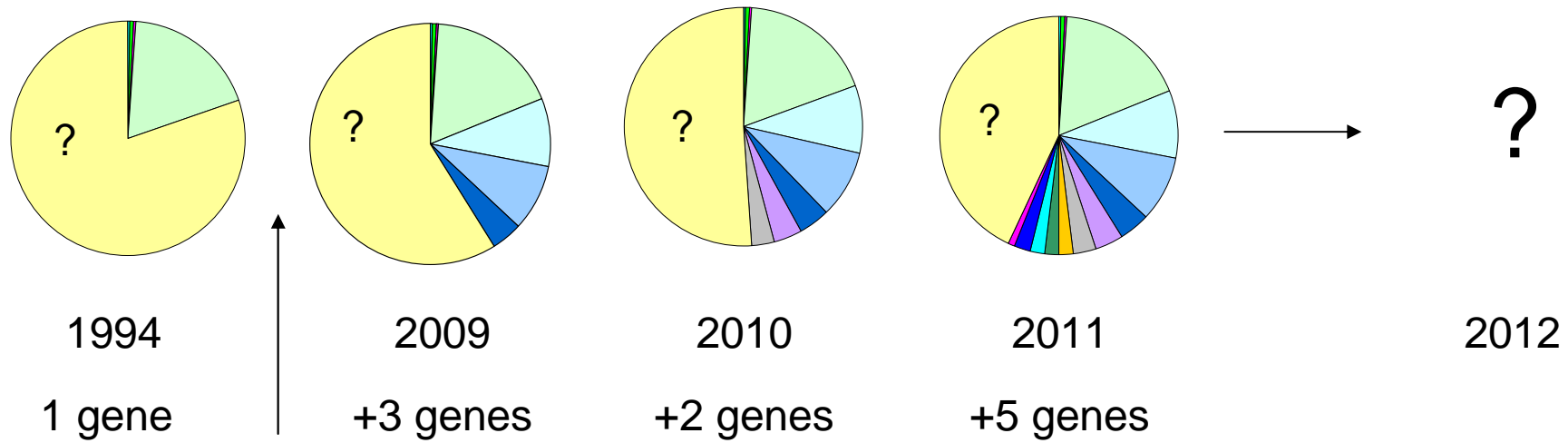
Manhattan plot EADI



D'après Lambert et al, Nature Genetics , 2009

Measure 30 High Throughput Genomics

Objective : to find new treatment clues for Alzheimer's disease by hunting for genes and genetic susceptibility for the occurrence of the disease in ageing populations



2008
Plan
Alzheimer

An acceleration of major discovery, with 10 new genes identified

Genetic background of AD

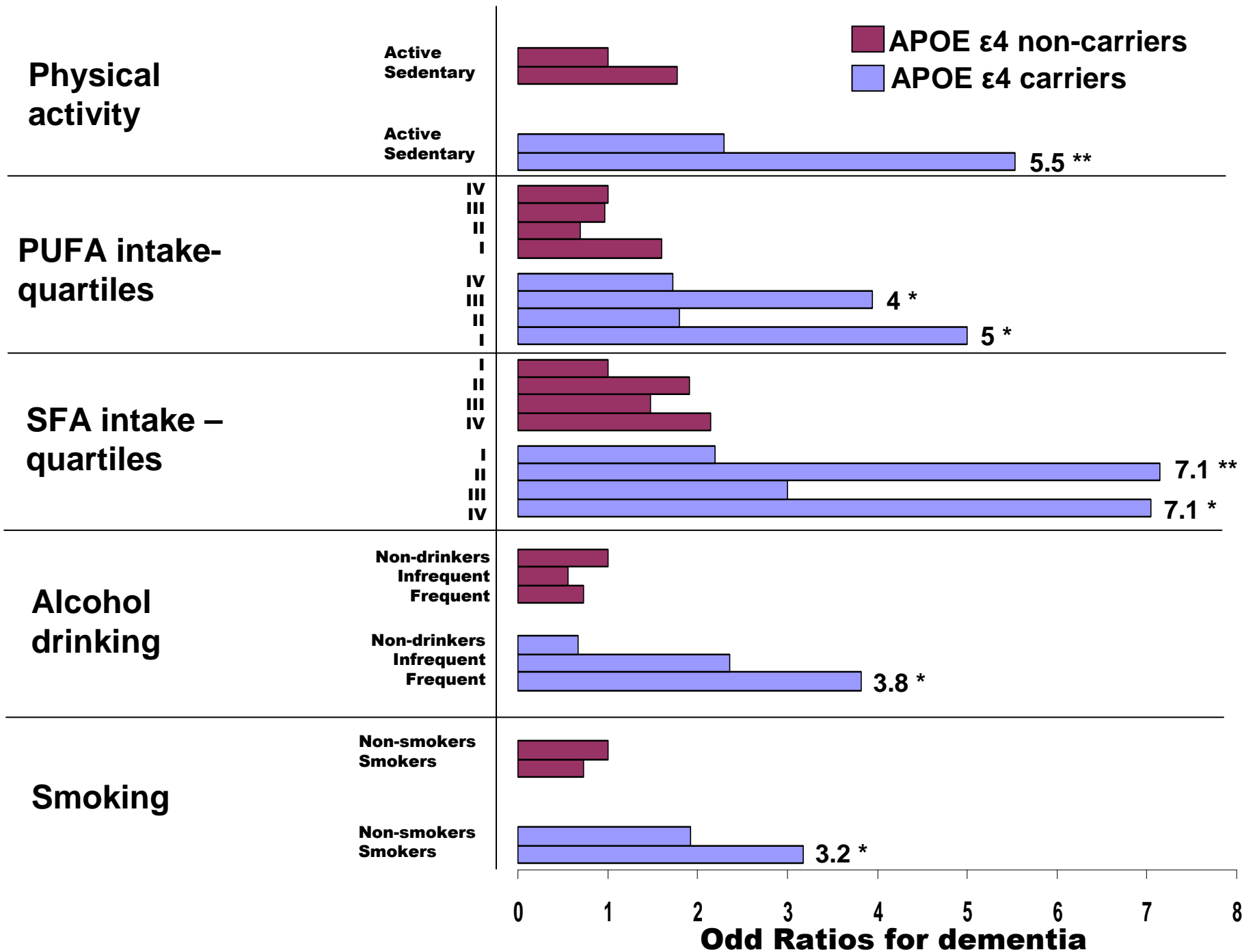
12th December 2011

➤ Rare autosomal dominant forms

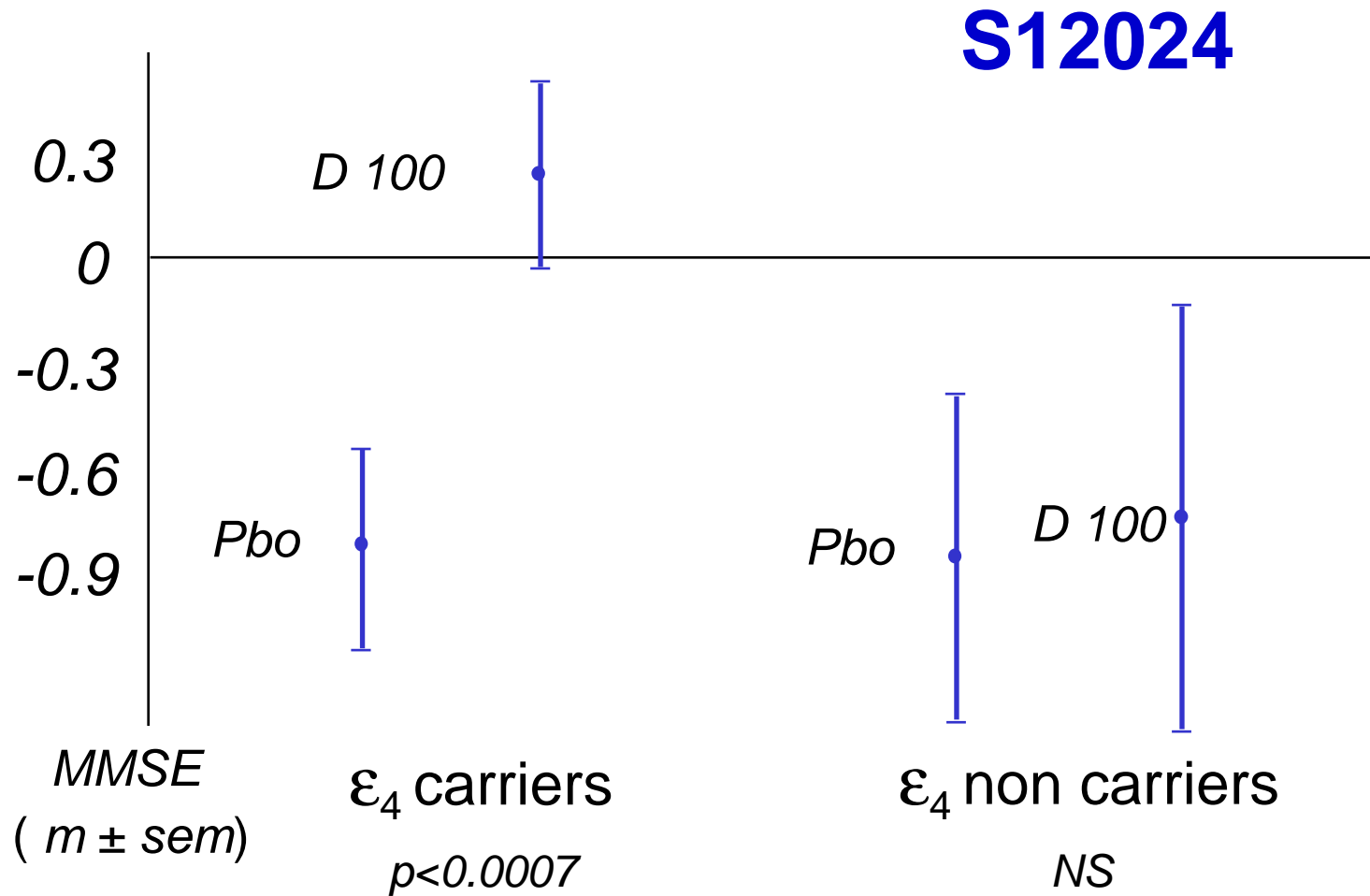
- APP
- PS1
- PS2

➤ Sporadic forms

- APOE
- CLU
- CR1
- PICALM
- BIN1
- ABCA7
- MS4A6A/MS4A4E
- EPHA1
- CD2AP
- CD33



APOE genotype and treatments



D'après Richard et al. Lancet 1997; 349: 539

Personalized Medicine and Alzheimer's Disease

- ◆ A need for such a complex disease whose latency period may last severeral years
- ◆ Tools allowing to identified disease at earlier stages
 - Neuropsychology
 - Genomics
 - Imaging
 - CSF biomarkers
 - Blood biomarkers
- ◆ Major ethical questions due to the lack of treatments

EADI Participants

Lille (F)

- JC. Lambert
- B. Grenier-Boley
- V Chouraki
- F. Pasquier
- N. Fiévet
- P. Amouyel

CNG (F)

- Y Katamani
- S. Heath
- D. Zelenika
- Y. Gut
- M. Lathrop

Paris (F)

- O. Hanon
- J Epelbaum
- A Brice

Montpellier (F)

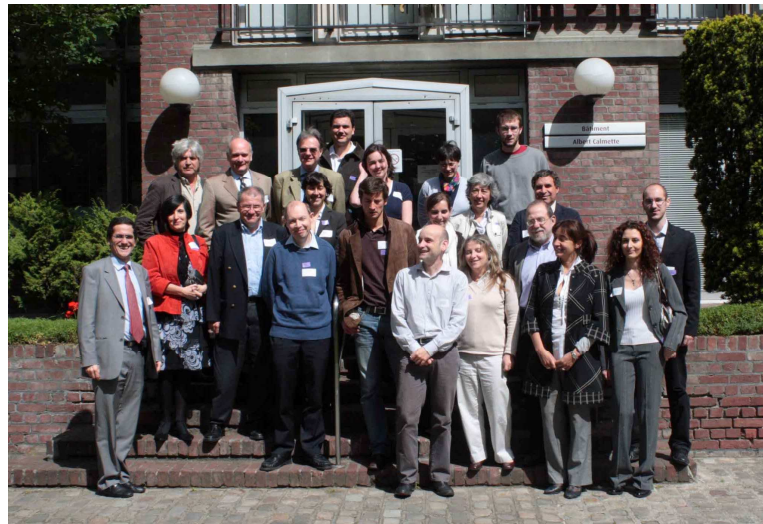
- C. Berr
- K. Ritchie

Bordeaux (F)

- L. Letenneur
- P. Barberger
- JF Dartigues

Dijon-Paris (F)

- B. Tavernier
- C. Dufouil
- C. Tzourio
- A. Alperovitch



Belgium

- K Slegers
- NBrouwers
- K Bettens
- S Engelborghs
- P De Deyn
- C Van Broeckhoven

Germany

- L. Bertram
- B M. Schjeide

Rouen (F)

- D. Champion
- D. Hannequin

Spain

- O Combarros
- M J Bullido
- E Coto
- I Mateoj,
- C Antunez
- J Lopez-Arrieta
- A Frank-Garcia
- F Valdivieso
- V Alvarez
- I Mateo
- F Sanchez-Garcia
- J Clarimon

Sweden

- M Ingelsson
- L Lannfelt
- C Graff
- J Prince

Finland

- M Hiltunen
- V Giedraitis
- S Helisalmi
- S Vepsäläinen
- H Soininen

Italy

- G Tognoni
- B Arosio
- M Del Zompo
- E Porcellini
- A Pilotto
- P Forti
- R Ferr
- E Scarpini
- G Siciliano
- V Solfrizzi
- S Sorbi
- G Spalletta
- G Ravaglia
- P Bosco
- M Mancuso
- F Panza
- B Nacmias
- P Bossù
- P Piccardi
- G Annoni
- D Seripa
- D Galimberti
- F Licastro
- P Cafarra