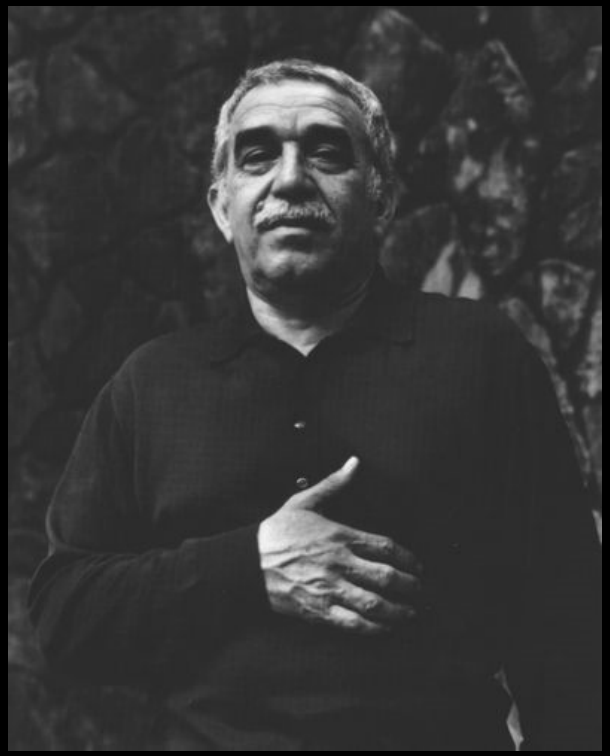
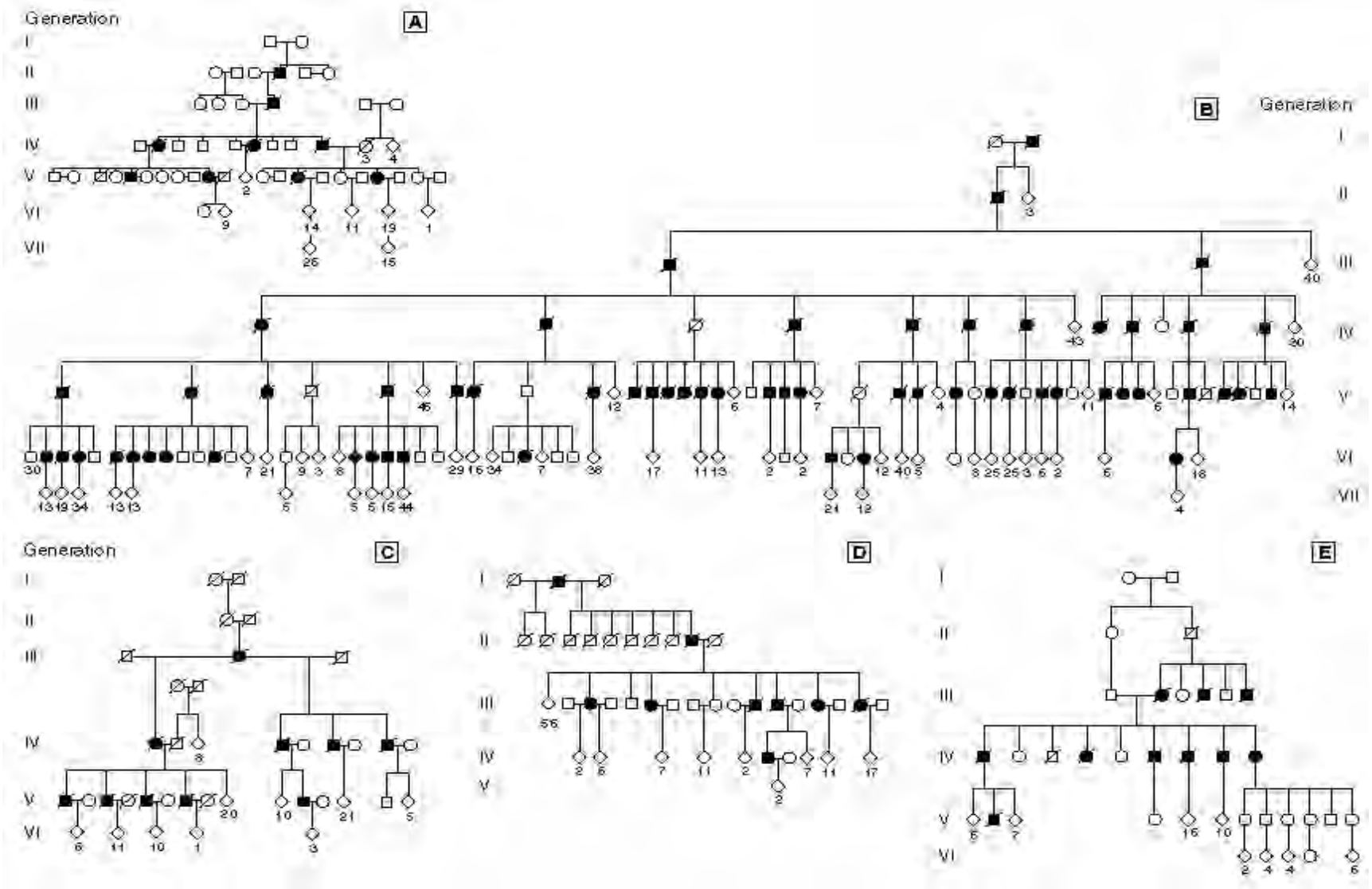
One Hundred Years of Solitude



Macondo

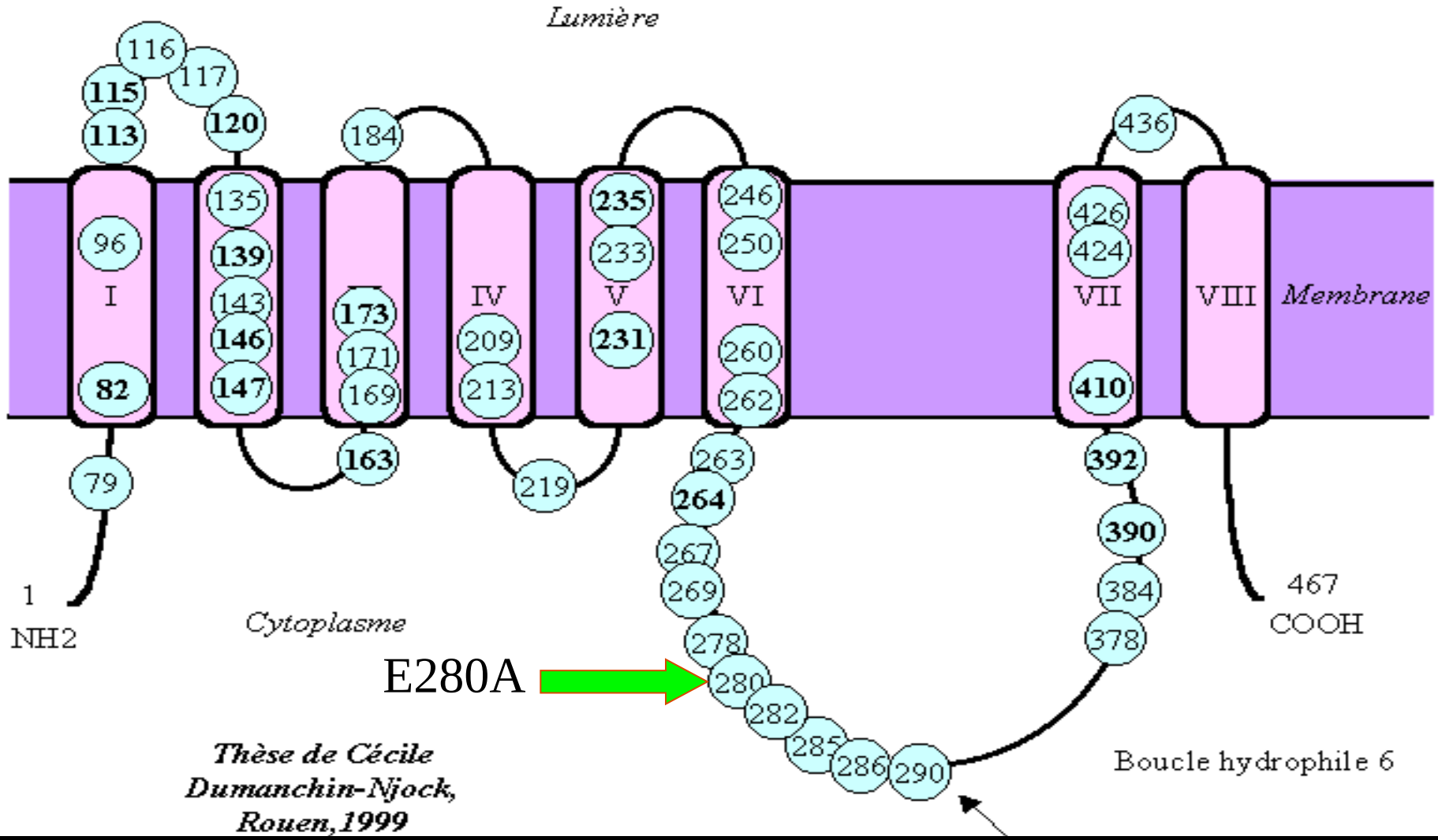
Family Trees with PS1 E280A



Source: Lopera *et al*, JAMA 1997

~5000 individuals

Fully penetrant dominant mutation




Barranquilla
Maracaibo
Cartagena
VENEZUELA
Medellin
COLOMBIA
Bogota
Cali

Medellin

Yarumal


NO FUME

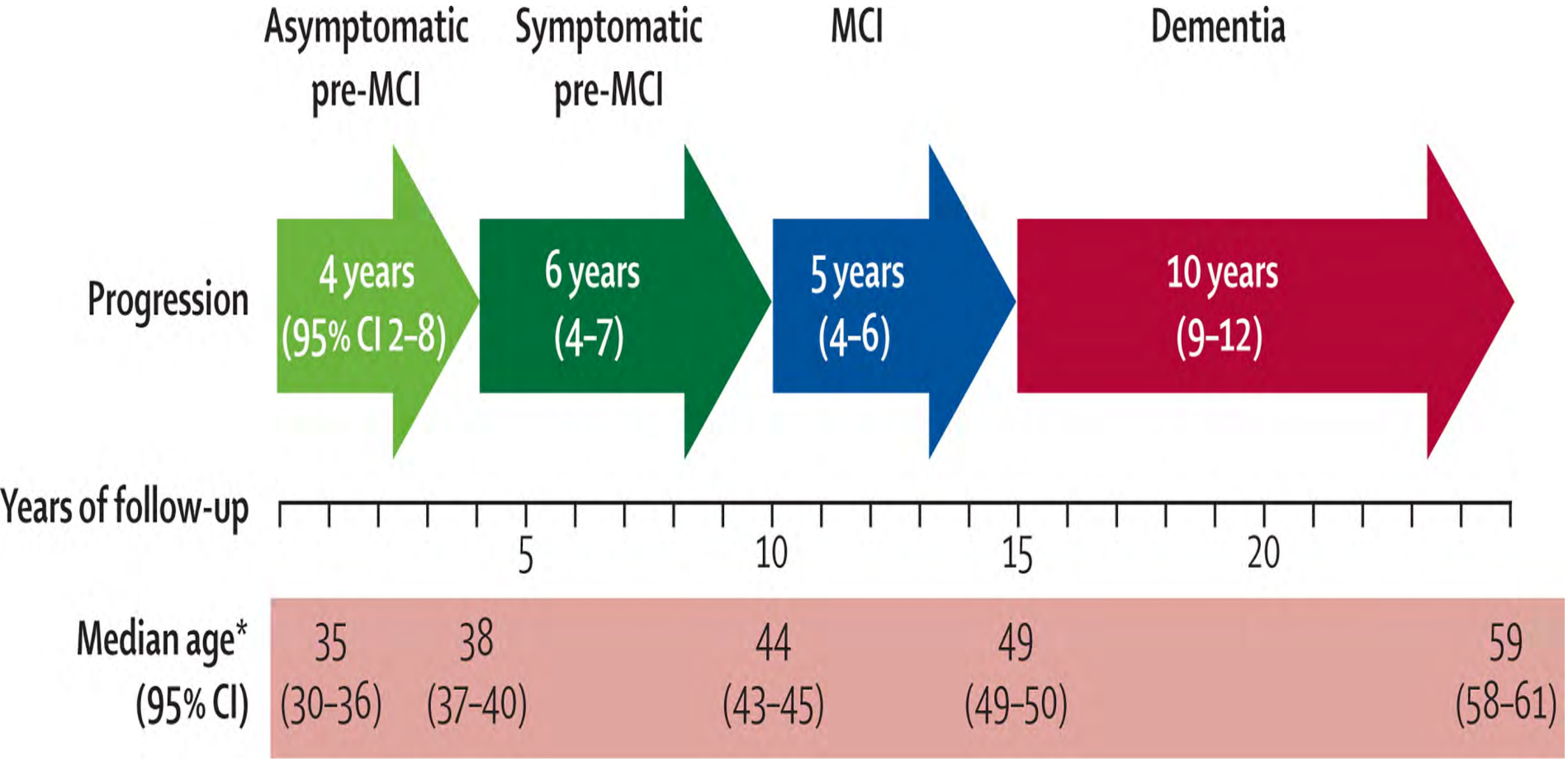
Moron

Sopetran


POR SU SEGURIDAD

Angostura

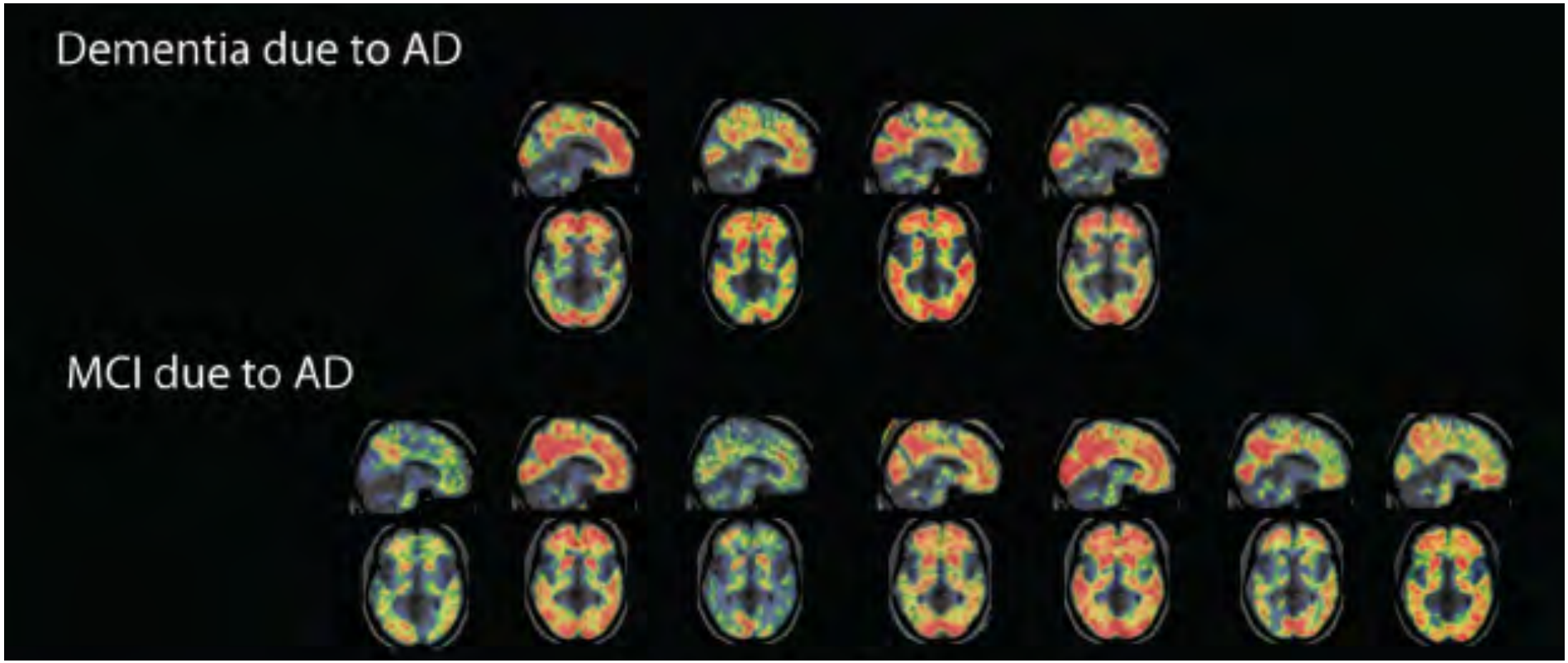

EST. 1960



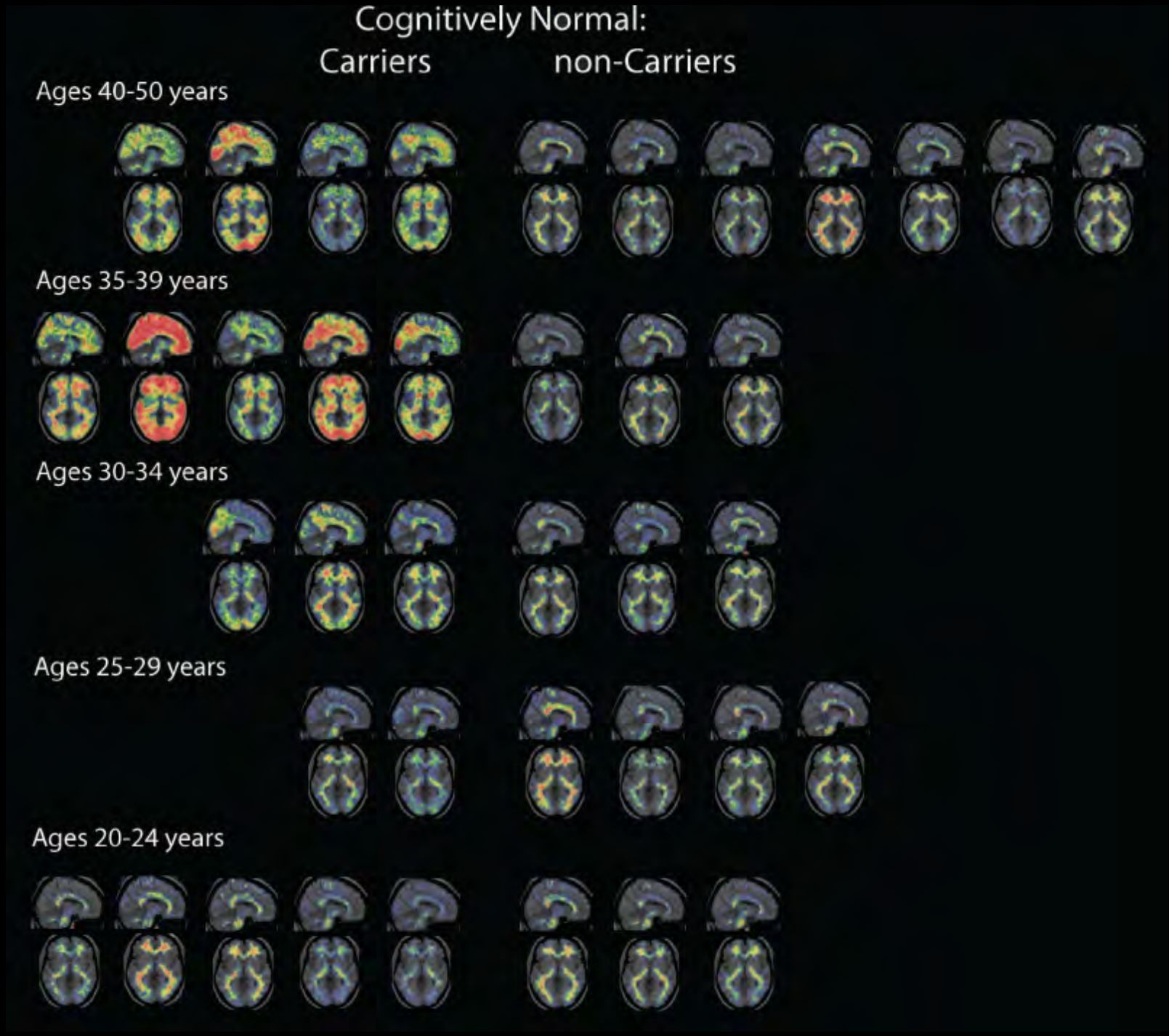
Acosta-Baena N, et al. *Lancet Neurol 10: 213-220, 2011*

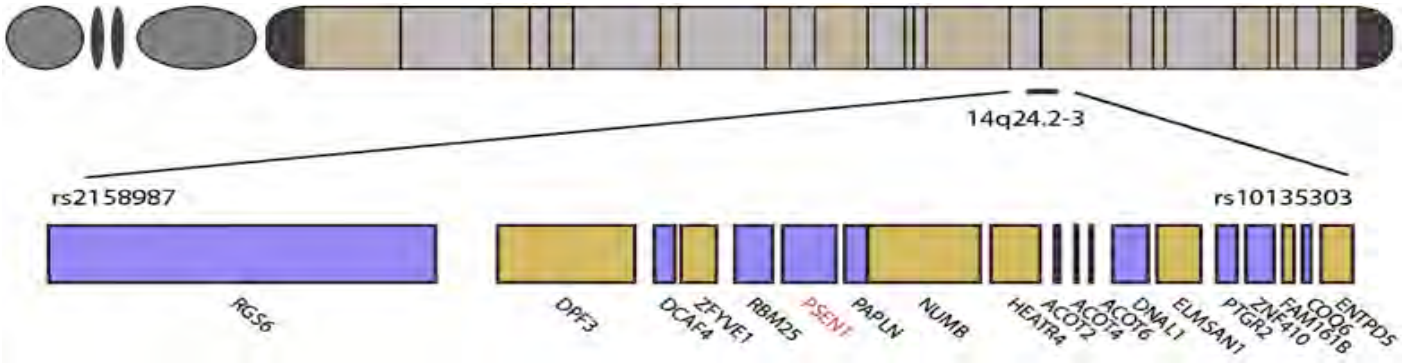
Florbetapir PET in 50 individuals age 20-56

11 symptomatic mutation carriers
19 asymptomatic carriers
20 asymptomatic non-carriers

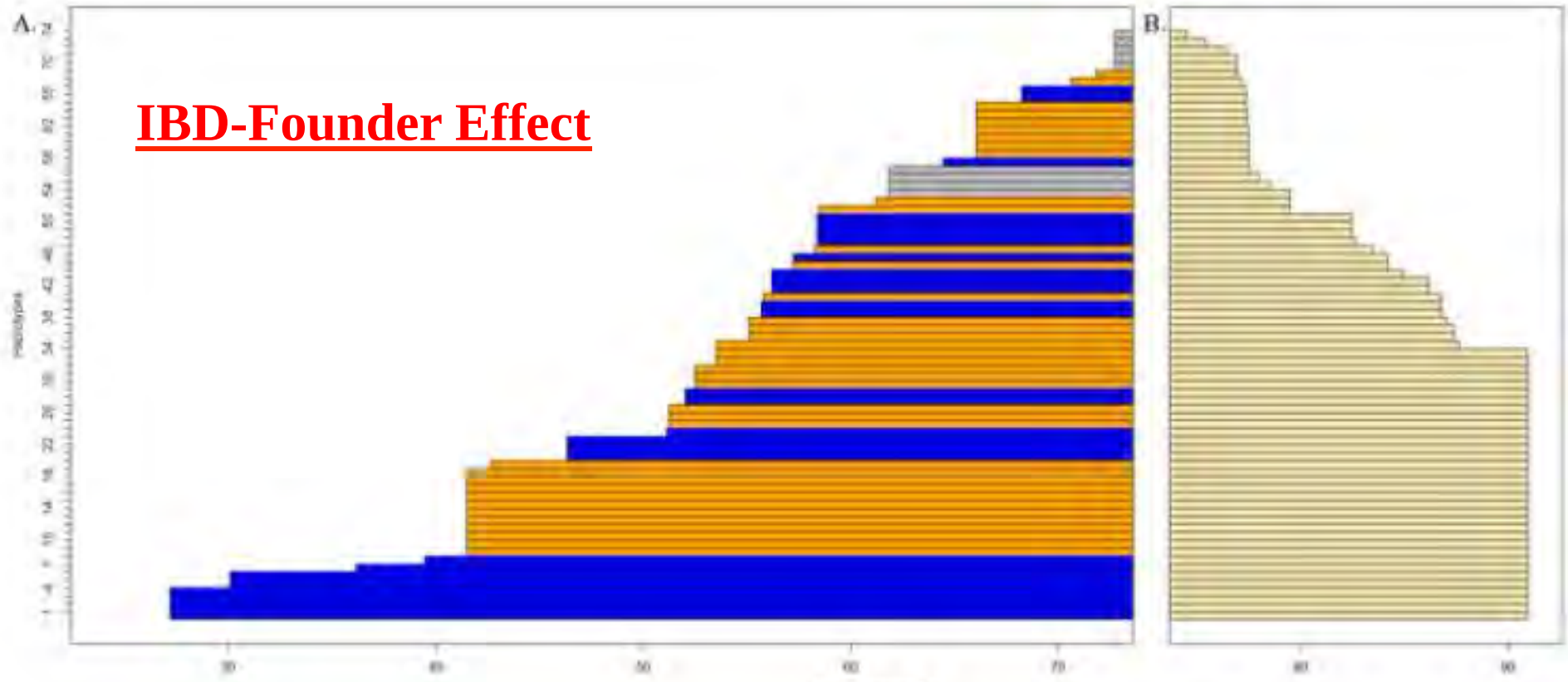


Adam S. Fleisher et al., Lancet Neurology

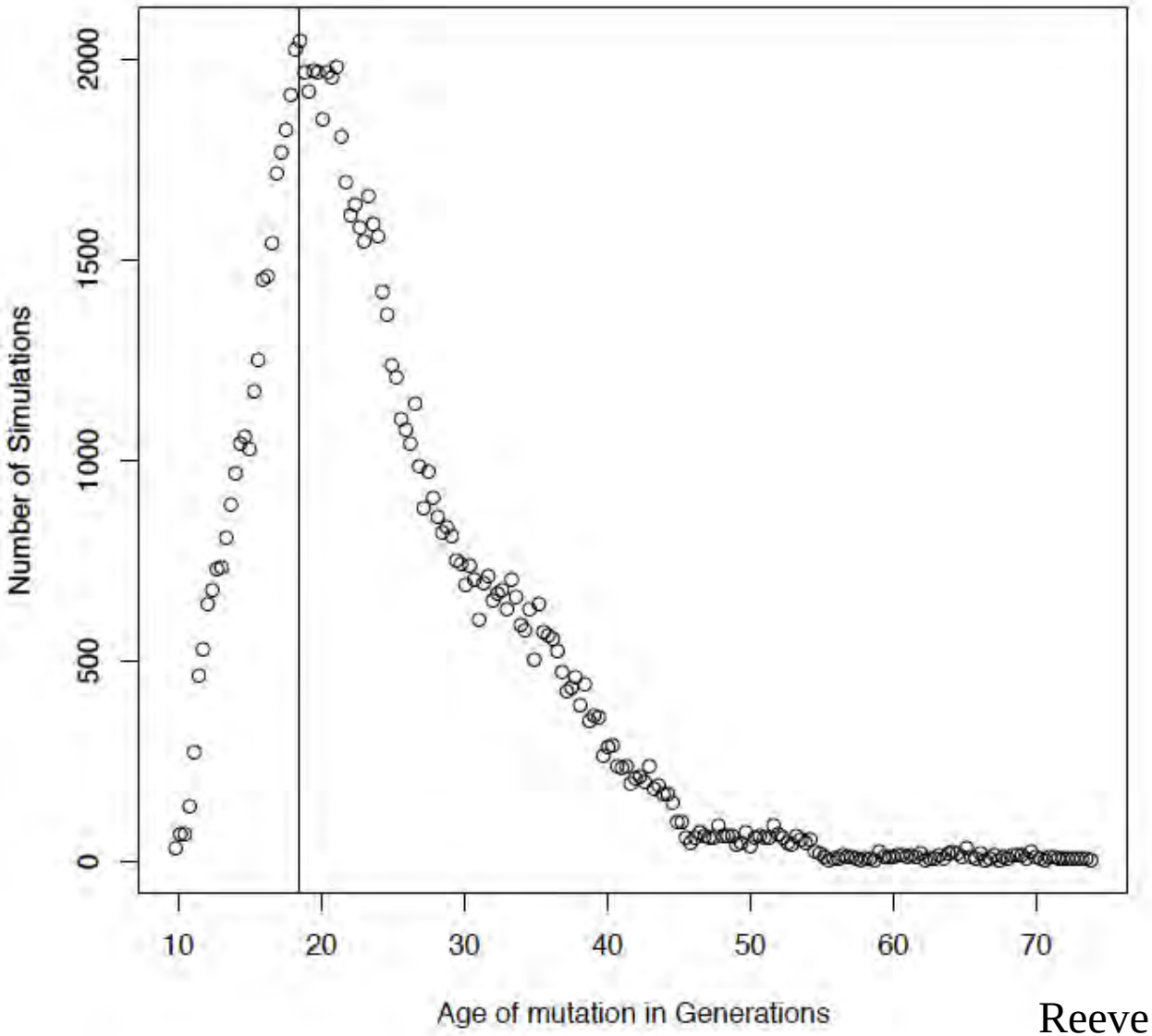

Cognitively Normal:
Carriers
non-Carriers
Ages 40-50 years
Ages 35-39 years
Ages 30-34 years
Ages 25-29 years
Ages 20-24 years



IBD-Founder Effect



the length of the haplotype suggests an origin of ~18 generations (360-450 years ago) corresponding to ~1550-1650

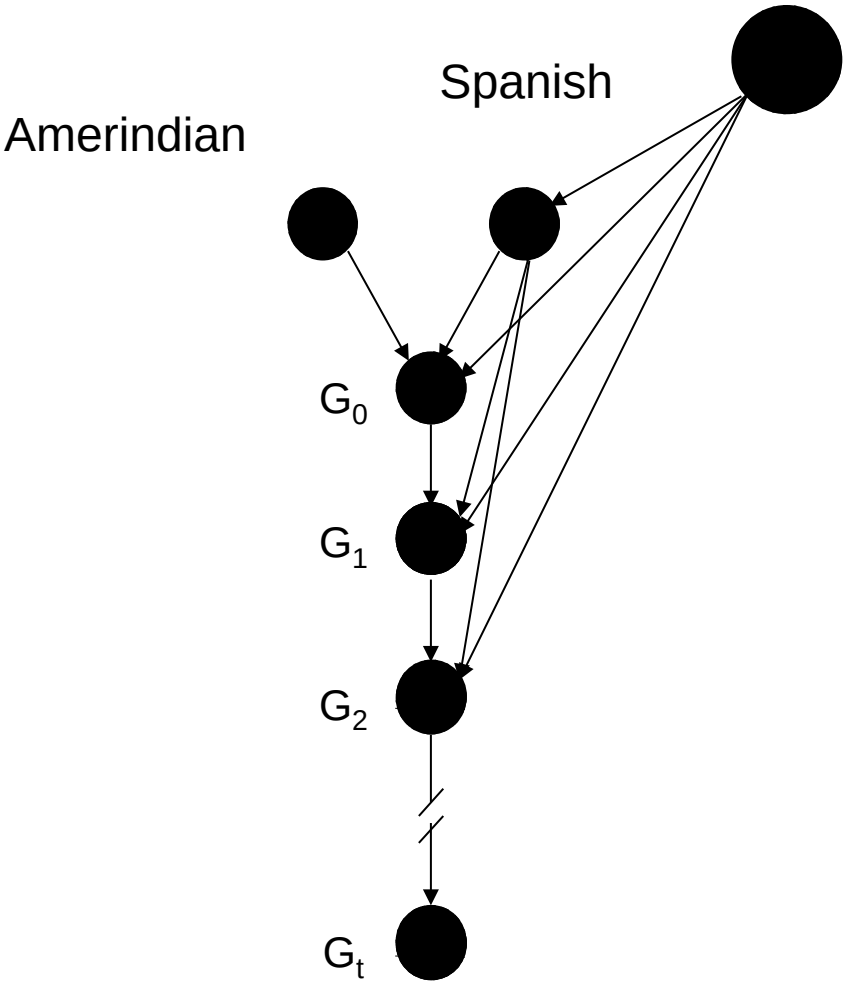


Intra-allelic coalescent modeling predicts mutation age of ~18 generations

Input is every haplotype in the study population

Reeve J, Rannala B:
DMLE+: Bayesian linkage disequilibrium gene mapping.
Bioinformatics 2002, 18:894-895

Admixture Dynamics in Antioquia

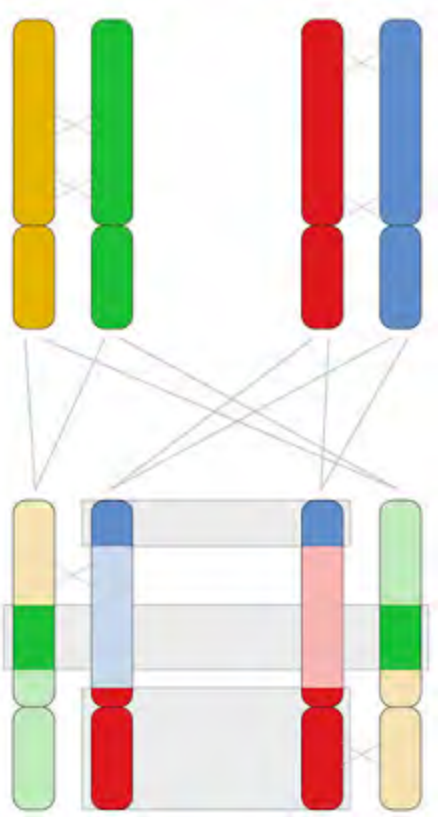


Andres Ruiz

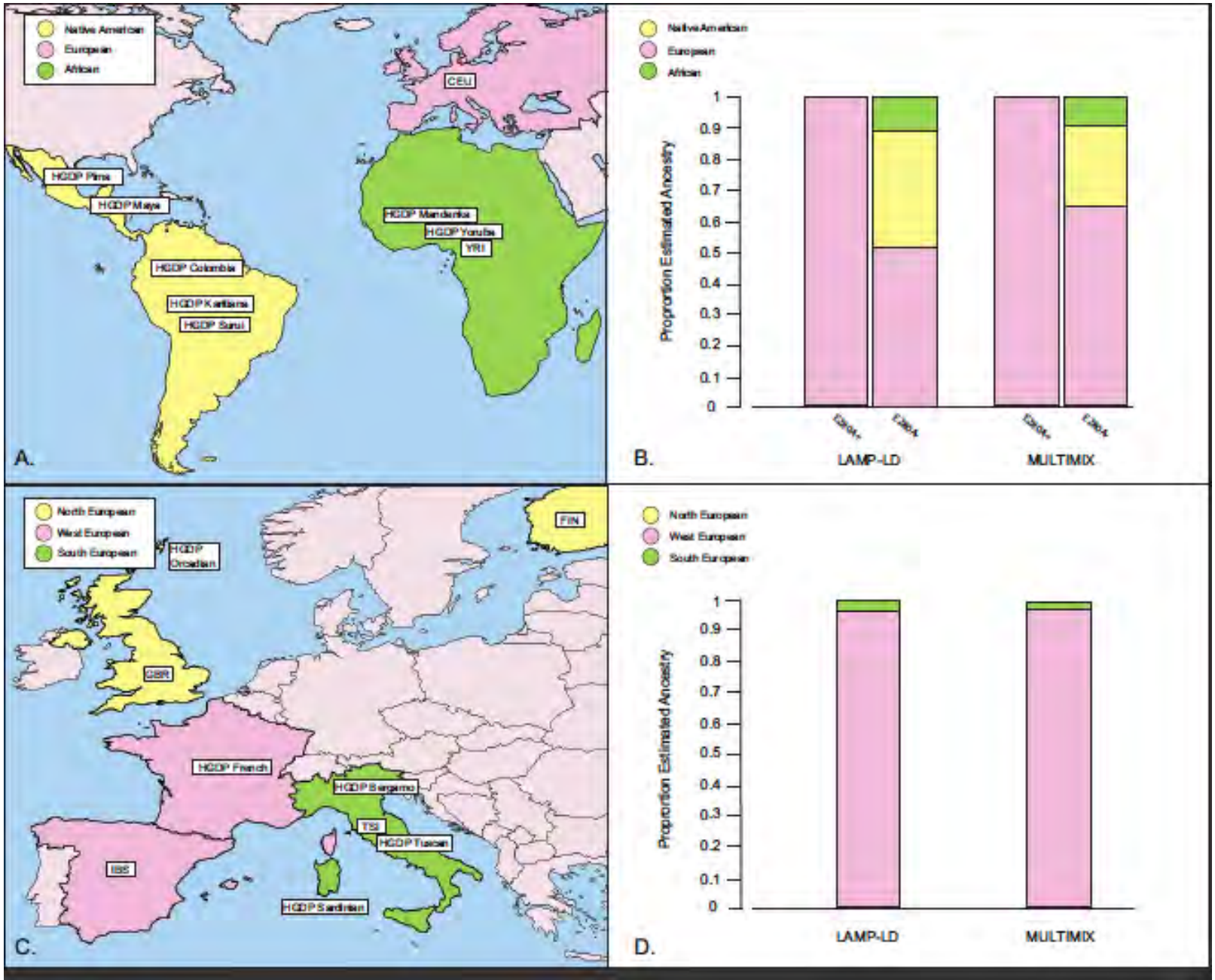
Local Ancestry Analysis

Recombination turns every chromosome into a mosaic

Compare reconstructed haplotype containing E280A to reference populations to determine its origin



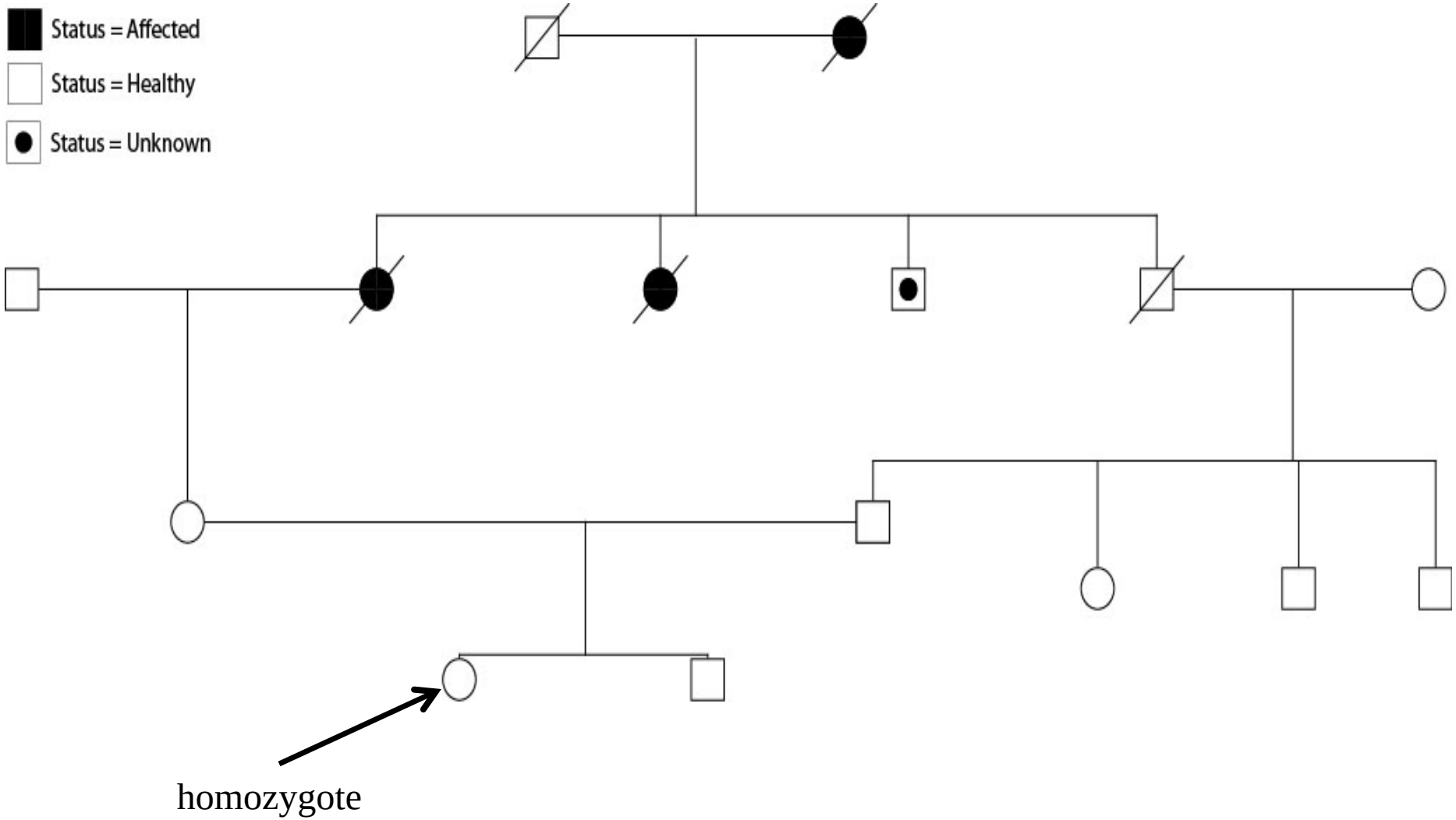
Local ancestry estimates a Mediterranean origin at the time of the Spanish Conquistadors



Darién Bay

Golfo de Urabá

Expediciones de los conquistadores y principales fundaciones en Antioquia


Status = Affected
Status = Healthy
Status = Unknown
homozygote

6 homozygotes with the E280A gene mutation [g.50024A>C]

Two have dementia with onset at ~35-40

Three without dementia range in age from 27-38

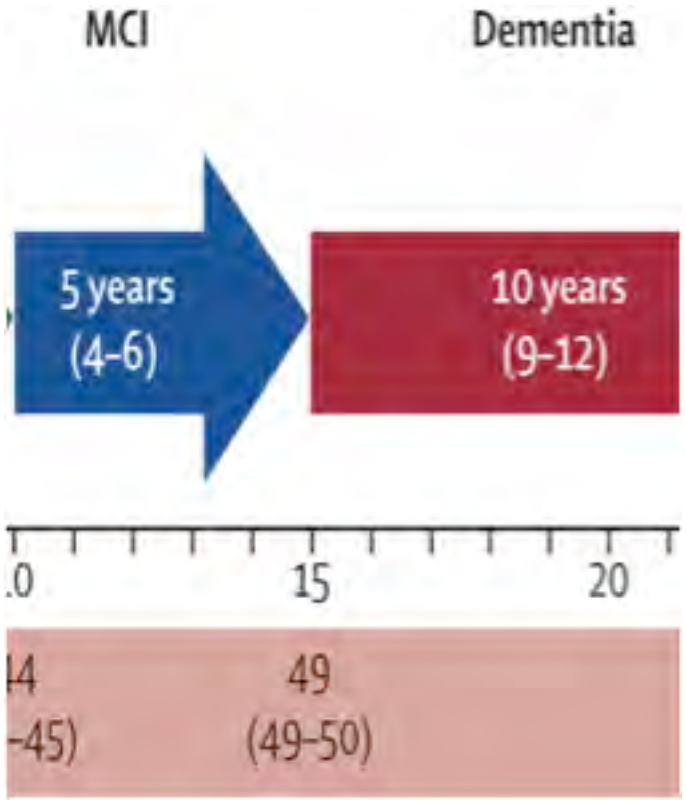
One child age 11 years old with mild mental retardation.

Among the six, five are female. (probability of 5 females out of 6 independent births = 0.09375).

The determination of cognitive status has been adjusted in those cases with minimal or no schooling by setting the cut-off at 1-1.5 SD below the mean for the population. Education and CERAD cutoffs were made based on data in the Antioquia cohort. Among the homozygous cases most live in a rural area and have had little or no schooling.

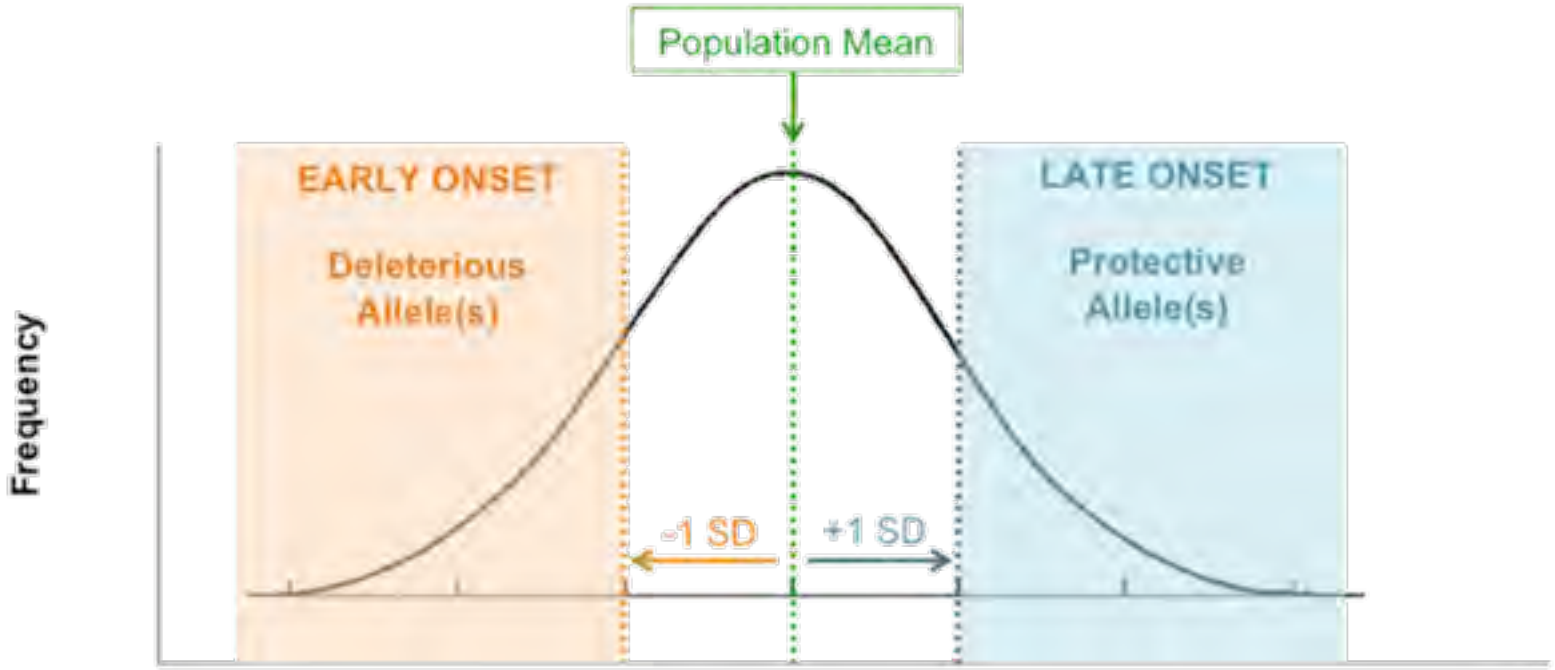
Identifying Genetic Modifiers of Age at Onset of Alzheimer's Disease

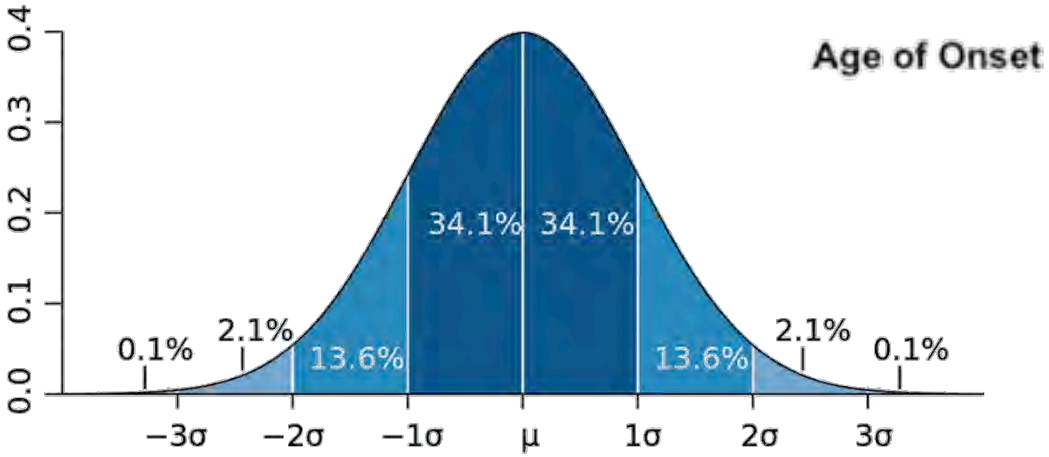
Use whole genome sequencing to find age-at-onset modifier genes?



Outliers are likely to be strong alleles

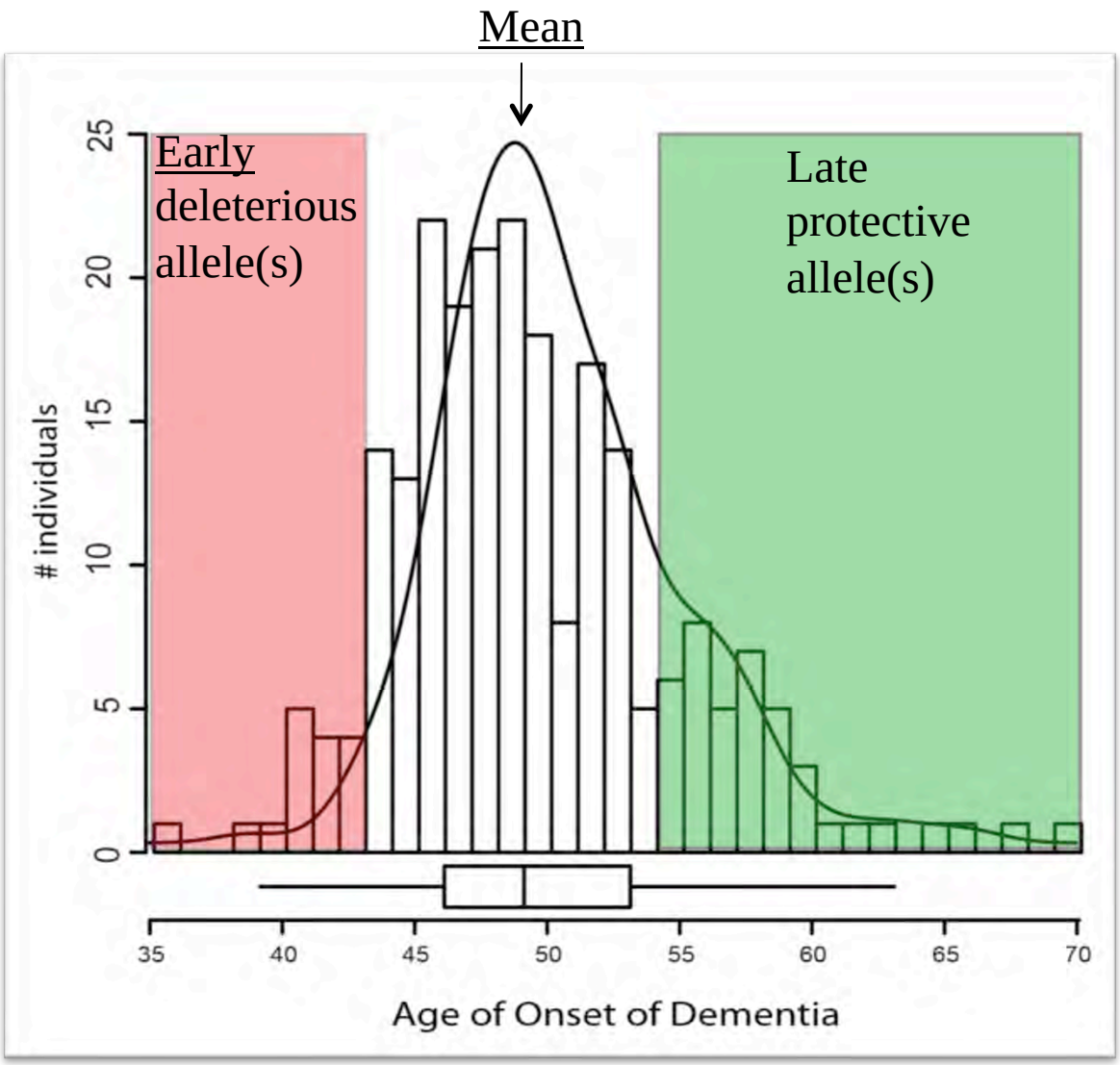
age at onset is heritable





Distribution of Dementia Onset

Heritability estimated as 0.718±0.228 for age at onset of dementia



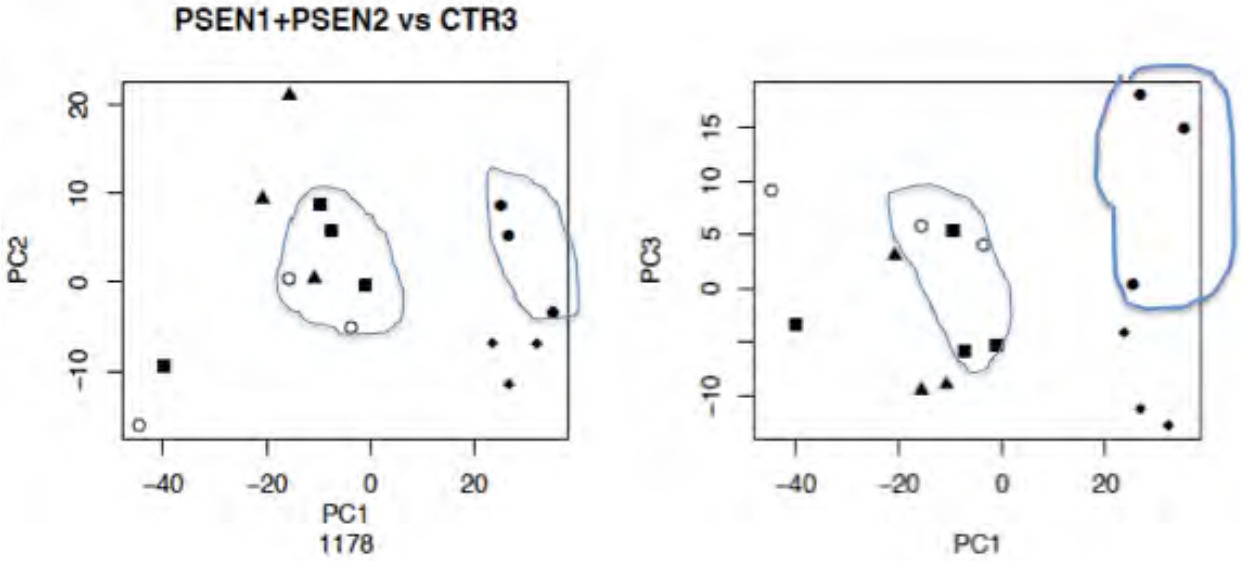
Spurious associations:

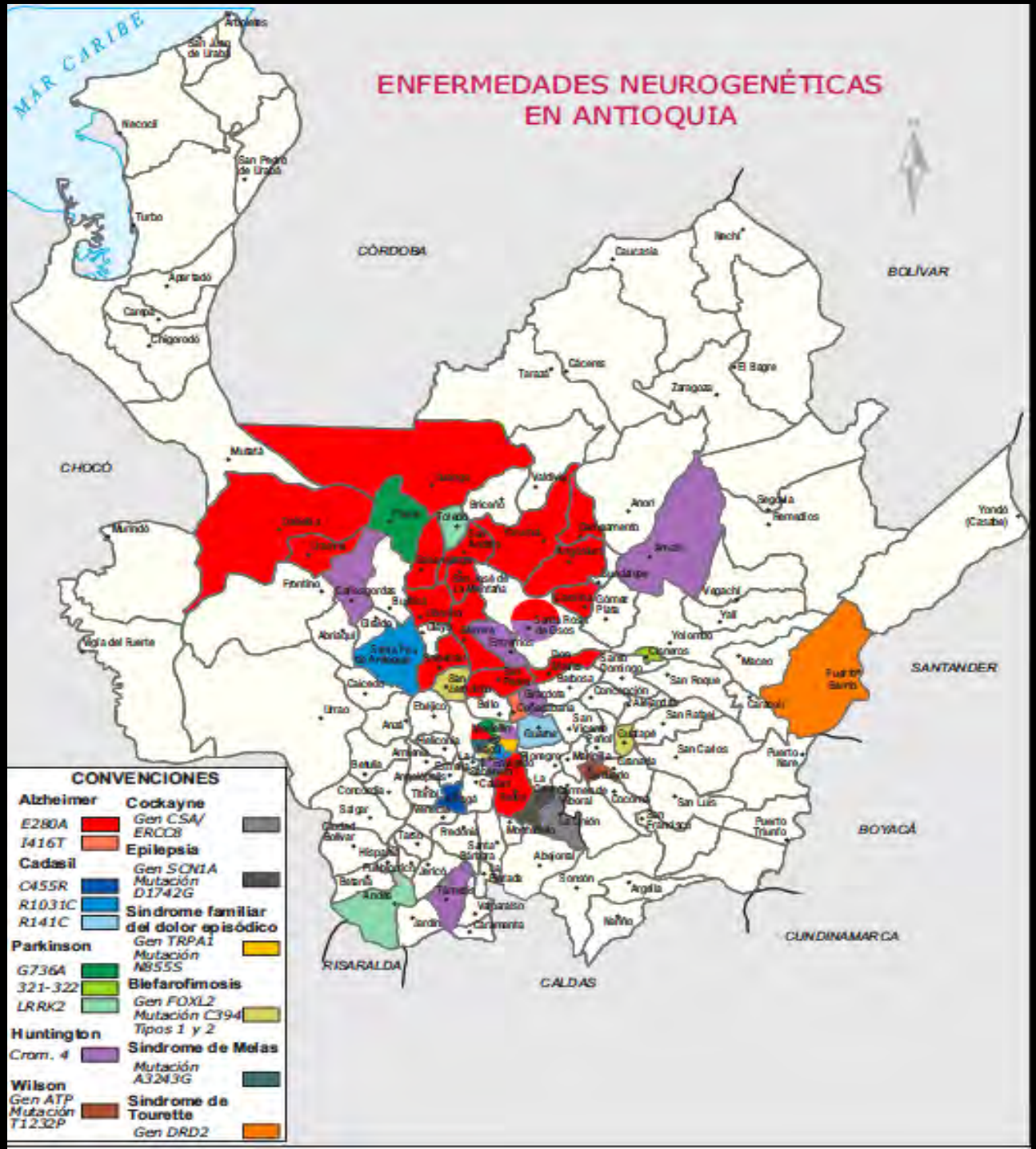
1. **Population stratification** = cases and controls are sampled disproportionately from different populations with distinct genetic ancestry.

2. **Admixture** = genetic mixing of two or more groups in the recent past.

As allele frequencies and disease frequencies are known to vary among populations of different genetic ancestry, population stratification or admixture can confound the association between the disease trait and the genetic marker; it can bias the observed association, or indeed can cause a spurious association.

Paisa population is an admixture but comparisons within the E280A kindred obviates this issue.





Multiple bottlenecks among founders of each settlement—high frequency deleterious mutations in healthy individuals

…una sustancia de color apacible…

Gabriel Garcia Marquez

Gracias

Institute for Systems Biology

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Hanna Cox
Jared Roach
Gustavo Gluzman
Leroy Hood

Banner/Tgen

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Eric Reiman
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