One Hundred Years of Solitude

Macondo
Family Trees with PS1 E280A

Source: Lopera et al, JAMA 1997

~5000 individuals
Fully penetrant dominant mutation

E280A

Thèse de Cécile Dumanchin-Njock, Rouen, 1999
Medellin
Yarumal
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
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.

Admixture Dynamics in Antioquia

Amerindian

\[ G_0 \]

\[ G_1 \]

\[ G_2 \]

\[ G_t \]

Spanish

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
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.

6 homozygotes with the E280A gene mutation [g.50024A>C]
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 $0.718 \pm 0.228$ 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

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