WE NEED YOU!

Leveraging Neuropathologically Verified Cases & Controls in the Genetic Study of AD

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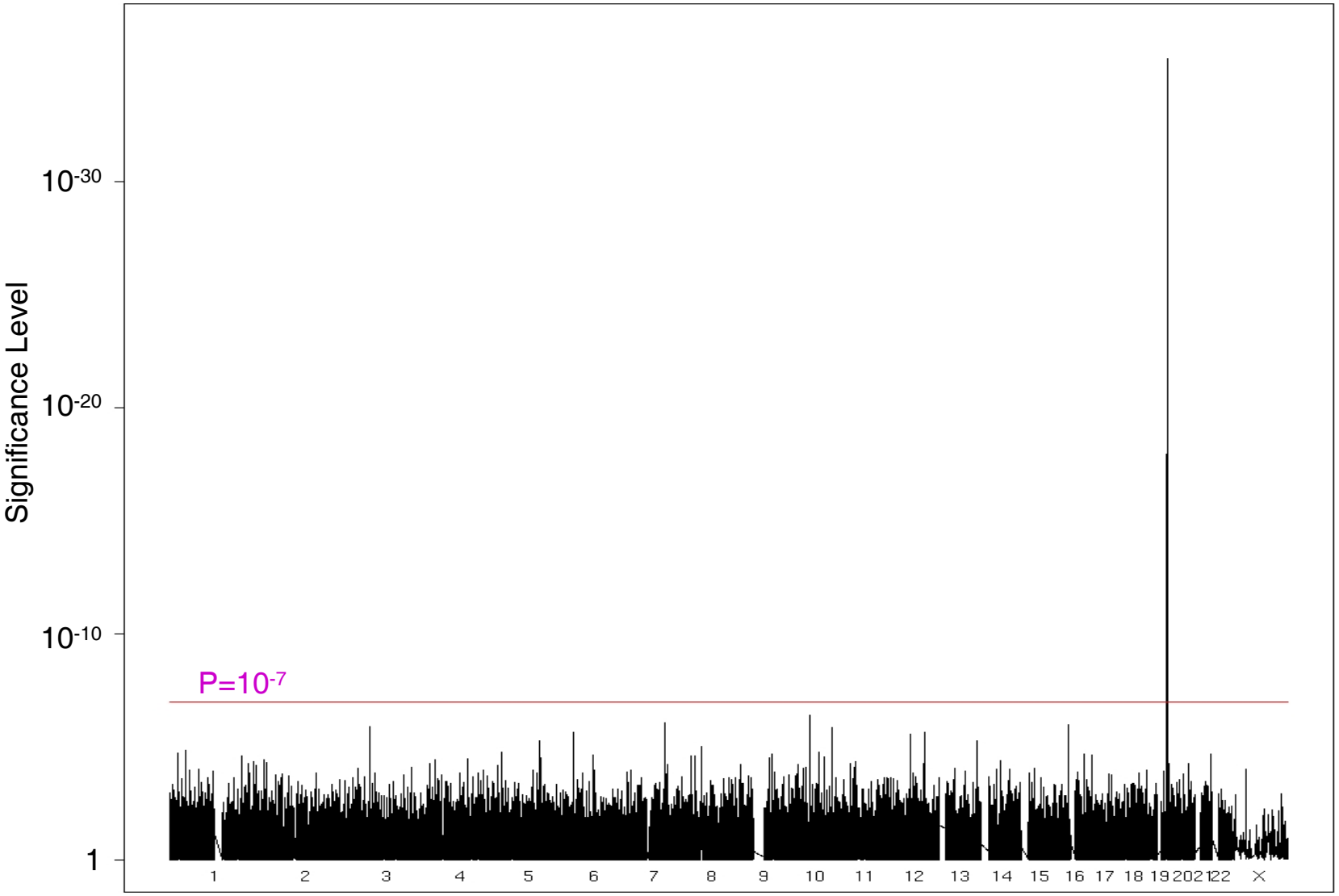
Entering the Era of Genome-Wide Association (GWA) Studies



Reiman et al, *Neuron* 2007

The Genetic Study of Neuropathologically Verified Cases & Controls

- Advantages
  - fewer misclassifications
  - quantitative endophenotypes
  - other neuropathological data
  - other neurobiological studies
- Disadvantages
  - availability of samples (especially controls)
  - availability & reliability of assessments
  - selection biases
- Complementary Role

APOE Genotype	Odds Ratio[1] Meta-analysis	Odds Ratio[2] Neuropathology
ε2ε2	0.6	0.4
ε2ε3	0.6	0.4
ε3ε3	1.0	1.0
ε2ε4	2.6	3.5
ε3ε4	3.2	4.3
ε4ε4	14.9	25.3

[1]Farrer et al, *JAMA* 1997: Meta-analysis of 14,537 cases & controls

[2]Coon et al, *J Clin Psychiatry* 2007: 1,080 neuropathologically verified cases & controls

AD Genetics Consortium
Neuropathology Work Group

Our Goal

To establish a central resource of DNA & data from neuropathologically verified late-onset AD cases & controls for GWA, replication & other genetic studies of late-onset AD

Our Immediate Need

Information & brain samples from up to 6,000 expired donors within the next few months!*

*Including as many controls as possible & up to 4x the number of AD cases

Criteria for AD Cases

1. Clinical diagnosis of probable or possible AD
2. Minimum age at dementia onset: 50
3. If evaluated for AD using NIA-Reagan criteria:

   Intermediate or high probability that AD accounts for dementia
4. If not evaluated using NIA-Reagan criteria:
   a. Braak III-IV or V-VI and
   b. moderate or frequent neocortical neuritic plaques (highest neocortical plaque density)

*Cases will be included whether or not they have comorbid neuropathology (e.g., infarcts)

Criteria for Controls

1. Clinical confirmation of non-dementia within 12 months of death
2. Minimum age at death: 50
3. If evaluated for AD using NIA-Reagan criteria:

   Low probability that AD accounts for dementia
4. If not evaluated using NIA-Reagan criteria:

   a. Braak 0-III and

   b. No or sparse neocortical neuritic plaques (highest neocortical plaque density)

*Controls will be included whether or not they have comorbid neuropathology (e.g., infarcts)

We Need Your Help!

1. Send us information about your cases & controls ASAP
   - Find as many suitable cases & controls from your ADC & affiliated brain banks
   - Include number of controls that meet other criteria but have not been assessed for criteria 1 or 4
   - Compare your numbers to those NACC will send you next week
2. Ship requested frozen brain samples to NCRAD ASAP
   - 3-5 g from the frontal pole is strongly preferred, but as little as 1 g from any region (e.g., cerebellum) would be acceptable
   - Send data & invoice to NACC (per Bud)
     - MDS & Neuropath forms for non-NACC samples
3. Provide additional information (TBD) later

Overcoming the Paucity of Control Samples

1. Reach out to affiliated & non-affiliated brain banks with controls (& cases) who meet our criteria
2. Information about additional controls who are thought to be non-demented, meet other control criteria, but were not evaluated in the last 12 months before death
3. Information about number of controls who meet other criteria but were not yet assessed for both criteria 4a & 4b
4. Include donors with Braak ratings irrespective of their clinical diagnosis at a later time
5. Other suggestions?

What We Can Do For You

1. $50 per brain sample
2. On-site sample help (if wanted)
3. Virtually unlimited supply of extracted DNA
   - Delegate DNA storage & distribution to NCRAD
   - Return up to 100 μg of DNA to interested sites
     (depending on amount of tissue provided)
4. APOE genotypes
5. Meeting the NIH/NIA/ADC sample & data sharing requirement
6. The science itself

Lending a Hand

AD Genetics Consortium
Neuropathology Work Group

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- You!