# ADNI and DIAN Neuropathology Core

**Update 10/10/2014**

**Nigel Cairns, PhD, FRCPath**

**Knight ADRC**
**Neuropathology Core Leader**

# ADNI and DIAN Longitudinal Observational Studies

1. The Alzheimer Disease Neuroimaging Initiative (ADNI) (**http://www.adni-info.org**/) was established to determine the relationships among the clinical, cognitive, imaging, genetic, and biochemical biomarker characteristics of sporadic, predominantly late-onset, Alzheimer disease (LOAD).
2. A complementary longitudinal observational study, the Dominantly Inherited Alzheimer Network (DIAN) focuses on the rarer, mainly early-onset, autosomal dominant AD (ADAD) (**http://dian-info.org/**) with known gene defects.
3. Both ADNI (U01 AG024904) and DIAN (U01 AG032438) are informing the neuroscience of AD, identifying diagnostic and prognostic markers, identifying outcome measures which can be used in clinical trials, and are helping to develop the most effective clinical trial protocols.
4. Both projects are funded by the National Institute of Aging of the National Institutes of Health. ADNI, in addition, is part funded as a public-private collaboration between academia and industry.

# ADNI and DIAN Neuropathology Core Rationale

1. To achieve the goals of ADNI and DIAN, the Neuropathology Core is essential to validate the clinical and biomarker classifications and diagnoses.
2. Nuropathologic validation of both ADNI and DIAN participants is necessary to exclude data contaminated by individuals who may not have AD, or, more commonly, co-morbidities such as vascular disease and non-AD neurodegenerative disorders.
3. A single Neuropathology Core site is necessary because different sites use different processing and staining methods, as well as different antibodies, and may interpret diagnostic criteria differently.
4. A single Neuropathology Core ensures uniformity and fidelity of staining and application of diagnostic criteria to all ADNI and DIAN participants who come to autopsy.

# ADNI and DIAN Neuropathology Core share common protocols with Knight ADRC

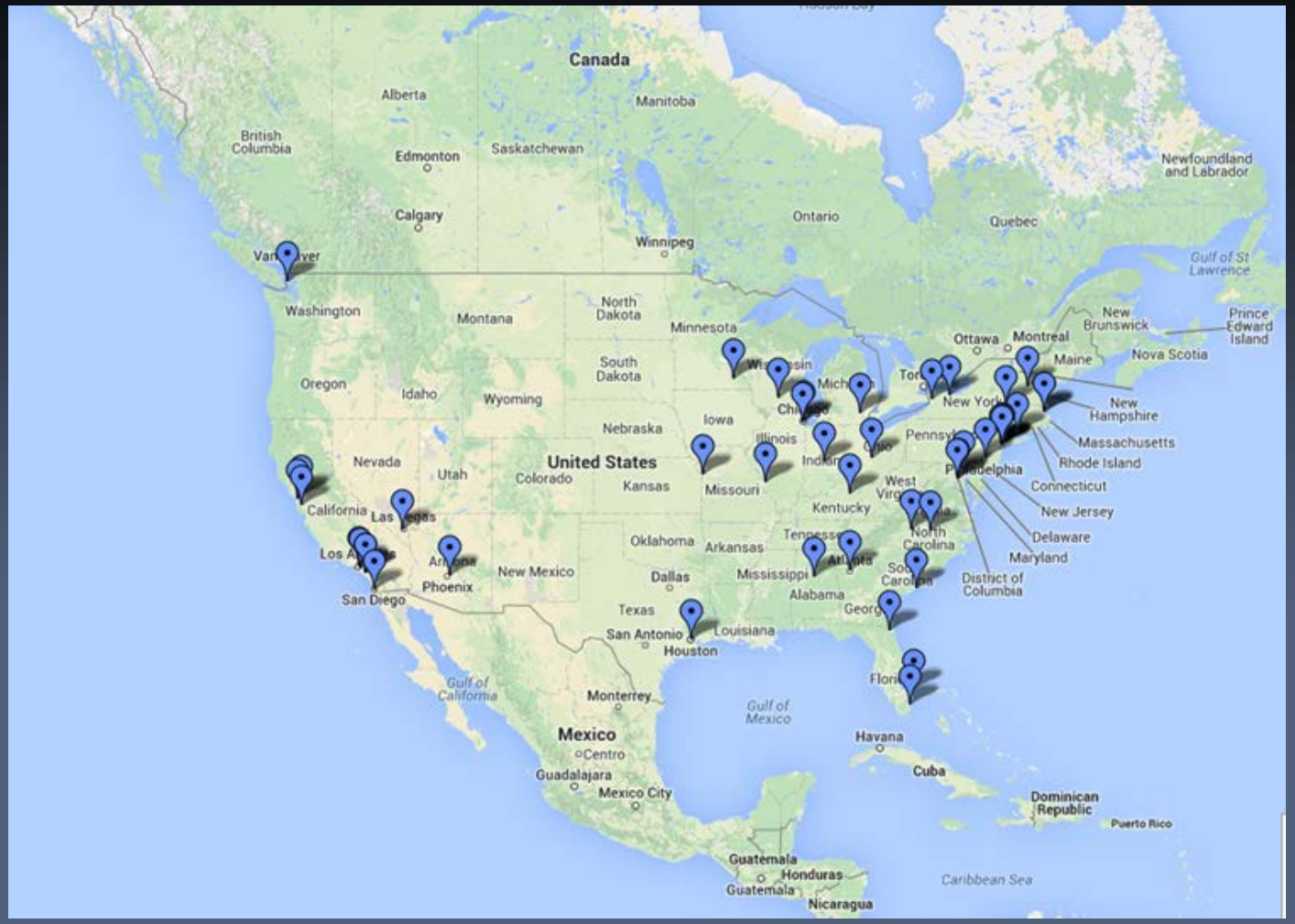
1. The ADNI and DIAN NPC capitalizes on the existing infrastructure of the Washington University Knight Alzheimer Disease Research Center (WU ADRC; P50-AG05681, JC Morris, PI), funded continuously by NIA since 1985.
2. The ADRC's Administrative (Dr. Morris) and Neuropathology (Dr. Cairns) Cores provide the framework for both the ADNI NPC and DIAN NPC.
3. Fidelity of data between ADNI, DIAN and NACC is maintained by using the same NACC Neuropathology Data Form as is used by all Alzheimer Disease Centers (ADCs) to report neuropathologic findings from autopsied cases, and is the primary data collection instrument.
4. The ADNI and DIAN NPC uses standard criteria for neuropathologic diagnoses of dementing illness and existing protocols and procedures .
5. Importantly, the ADNI and DIAN NPC does not interfere with or supersede neuropathologic activities at any ADNI or DIAN site.

# Clinical Core Accomplishments: Enrollment

- Full enrollment of all ADNI 2 Cohorts
  - Normals: n=184
  - Subjective memory concerns: n=101
  - Early MCI: n=301 (including ADNI GO)
  - Late MCI: n=160
  - Mild dementia: n=142

- Total enrollment of new participants: n=780
- Rollover participants from ADNI1 and ADNI GO: n=391
- Total for ADNI2: n=1171

# ADNI Sites in the USA
# www.adni-info.org



# Common Protocols used for ADRC, ADNI, and DIAN Participants

| Immunohistochemistry, antibodies, and antigen retrieval methods used in ADNI and DIAN protocols (n = 15 blocks) | | | | | | |
|---|---|---|---|---|---|---|
| **Antigen** | **Antibody name (Source)** | **Clone** | **Mode of staining** | **Pre-treatment** | **Dilution** | **Incubation time** |
| Aβ | 10D5 (Eli Lilly, Indianapolis, IN, USA) | 10D5 | Manual | 98% FA | 1:100,000 | 4°C overnight |
| Phospho-tau | PHF1 (Dr. P. Davies, Albert Einstein College of Medicine, NY , USA) | PHF1 | Manual | MW | 1:10,000 | 4°C overnight |
| Phospho-α-synuclein | Phospho-α-synuclein (Ser129) (Cell Applications, Inc., San Diego, CA, USA) | Rabbit polyclonal | Manual | 98% FA | 1:20,000 | 4°C overnight |
| Phospho-TDP-43 | (Cosmo Bio USA, Inc., Carlsbad, CA, USA) | pS409/410 | Manual | 98% FA | 1:40,000 | 4°C overnight |
| FA, formic acid; MW, microwave | | | | | | |

# ADNI Participants Autopsied per Funding Period

| ADNI Funding Period | ADNI-NPC | Deaths | Autopsies | Annual Autopsy Rate (%) |
|---|---|---|---|---|
| 9-1-05 to 8-31-07 | NO | 6 | 0 | 0 |
| 9-1-07 to 8-31-08 | YES | 7 | 2 | 28 |
| 9-1-08 to 8-31-09 | YES | 8 | 8 | 100 |
| 9-1-09 to 8-31-10 | YES | 4 | 1 | 25 |
| 9-1-10 to 8-31-11 | YES | 13 | 6 | 46 |
| 9-1-11 to 8-31-12 | YES | 3 | 3 | 100 |
| 9-1-12 to 8-31-13 | YES | 10 | 8 | 80 |
| 9-1-12 to 7-31-14 | YES | 14 | 13 | 93 |
| **Total (2005-2014)** | - | **65** | **41** | **63** |
| **Total since NPC established** | - | **59** | **41** | **70** |

**Note:** The ADNI-NPC was established on 9/1/2007. In the current grant cycle, there have been 40 deaths and 30 autopsies (75% autopsy rate).

# ADNI Sites and Participating ADC Neuropathology Core Leaders

*=1 case contributed.

**=more than one case contributed.

An additional 9 cases Were provided to the ADNI-NPC by ADNI sites not affiliated with an ADC.

| Site | ADC-Neuropathology Core Leader |
|---|---|
| OHSU | Randy Woltjer |
| USC | Carol A. Miller * |
| UCSD | Eliezer Masliah |
| COLUMBIA | Jean Paul Vonsattel |
| WUSTL | Nigel Cairns ** |
| MSINAI | Vahram Haroutunian |
| RUSH | Julie A. Schneider |
| HOPKINS | Juan Troncoso |
| NYU | Thomas Wisniewski |
| UPENN | John Q. Trojanowski |
| UK | Peter Nelson |
| UPITT | Julia Kofler * |
| UCI | Ronald Kim * |
| UTSW | Charles L. White III ** |
| EMORY | Martha Gearing ** |
| KANSAS | Kathy Newell ** |
| UCLA | Harry Vinters |
| MAYOJ | Dennis W. Dickson |
| IU | Bernadino Ghetti * |
| NWU | Eileen Bigio |
| UCSF | William Seeley * |
| BWH | Matthew P. Frosch |
| SHRI | Thomas G. Beach ** |
| BUSM | Ann C. McKee |
| UCD | Lee-Way Jin ** |
| UWI | Michael Hart |

| Clinical diagnosis at expiration | ADNI: Neuropathologic Diagnosis [N (%)] | | | | | | | | | | | TOTAL (%) ^ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AD | AD +DLB | AD +TDP | AD +DLB +TDP | AD+ DLB +TDP+AGD | AD +ALB+TDP | AD + AGD | AD + HS+ AGD | AD +TDP+Infarcts | AGD | Pending | |
| DAT | 14 | 10* | 1 | 1 | | | 1 | 2† | 1 | 1** | 1 | 32 (78) |
| DAT+DLB | | | | 1 | 1 | 1 | | | | | | 3 (7) |
| Pending | | | | | | | | | | | 6 | 6 (15) |
| TOTAL (%) ^ | 14 (34) | 10 (24) | 1 (2) | 2 (5) | 1 (2) | 1 (2) | 1 (2) | 2 (5) | 1 (2) | 1 (2) | 7 (29) | 41 (100) |

Note: *One case had additional AGD; †One case had additional TDP-43 proteinopathy; **One case had additional tangles in the medial temporal lobe; ^Figures are rounded and may not equal 100%. Small vessel disease (arteriolosclerosis and cerebral amyloid angiopathy) was a feature of all cases; cases with infarcts/microinfarcts are noted in the Table.

# Clinical and Multimodal Biomarker Correlates of Neuropathology in 22 ADNI Cases

JB Toledo[a]*, NJ Cairns[b]*, X Da[c], K Chen[d], D Carter[b], N Ayutyanont[d], E Householder[b], A Roontiva[d], RJ Bauer[d], LM Shaw[a], C Davatzikos[c], MW Weiner[e], E Reiman[d], JC Morris[b]** and JQ Trojanowski[a]**,

and the Alzheimer's Disease Neuroimaging Initiative

[a]Department of Pathology & Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA,

[b]Department of Neurology, Washington University School of Medicine, St. Louis, MO,

[c]Section of Biomedical Image Analysis, Department of Radiology, University of Pennsylvania, Philadelphia, PA,

[d]Banner Alzheimer's Institute, Phoenix, AZ,

[e]Center for Imaging of Neurodegenerative Diseases, Department of Radiology, San Francisco VA Medical Center/University of California San Francisco, San Francisco, CA.

*These authors contributed equally to this paper.

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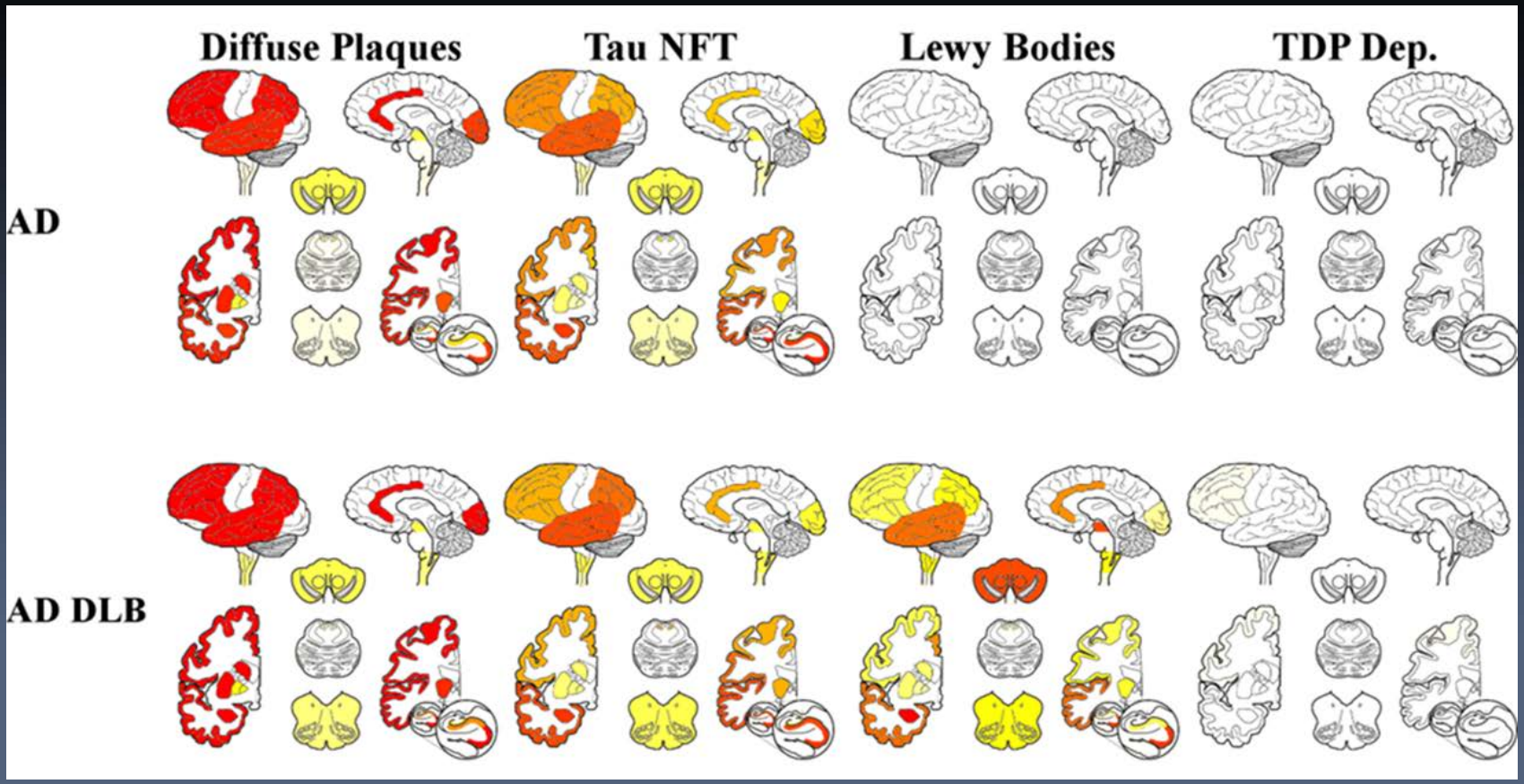
## Participant Characteristics (n = 22)

- Age = 72-88
- Gender = 77% male
- Education = 13-18 y
- *APOE e4+* = 50%
- Clinical goups at T1 assessment:
    - 1 CN
    - 11 MCI
    - 10 DAT
- A clinical Dx of DAT due to AD was supported by a pathological Dx of AD in all cases.
- Other pathologies: DLB, TDP, AGD, HS, SVD.

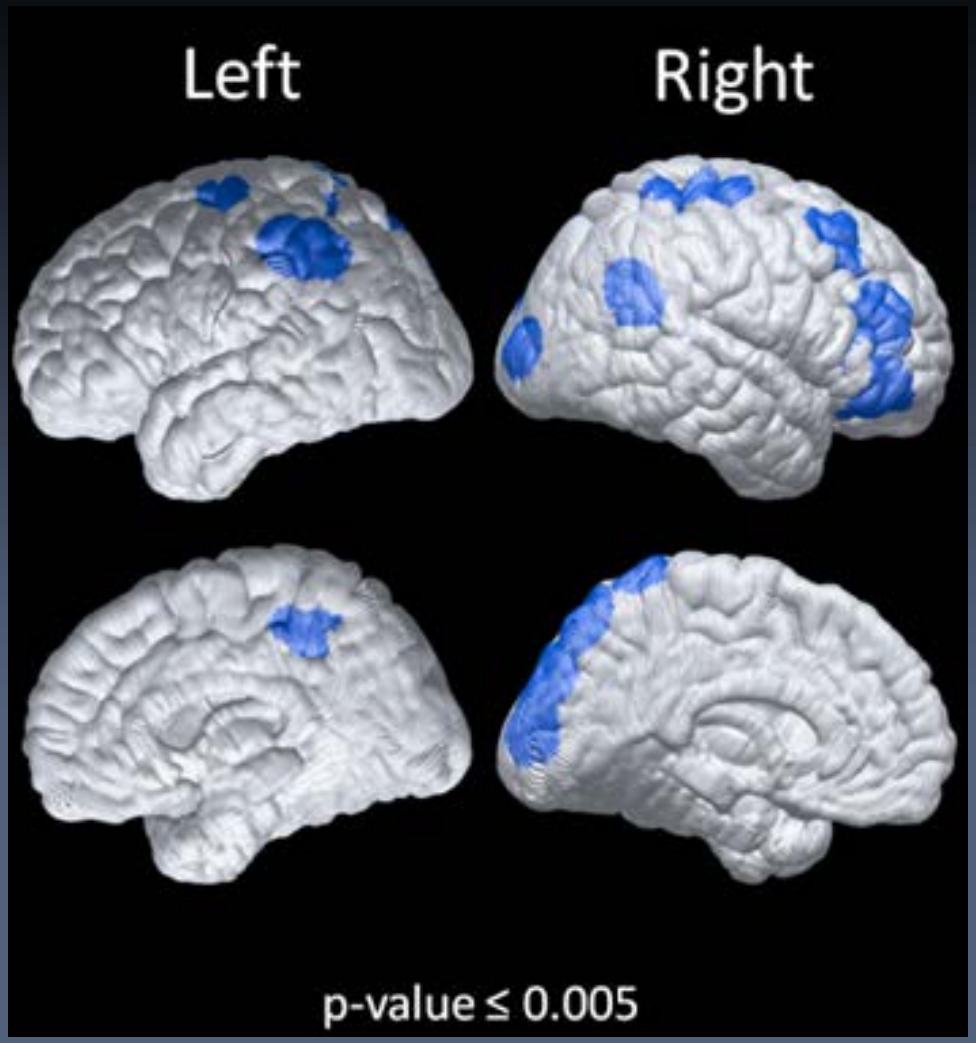
# Heatmaps of the Semiquantitative Neuropatholgic Grading of ADNI Participants




AD, Alzheimer disease; DLB, dementia with Lewy bodies. From left to right: diffuse Aβ plaques, neurofibrillary tangles (NFT), Lewy bodies, and phopho-TDP-43-immunoreactive neuronal cytoplasmic inclusions (TDP Dep.).

Toledo, Cairns *et al*. Acta Neuropathol Commun 2013;1:65

# Significant Areas of Hypometabolism (FDG-PET) in DLB




Toledo, Cairns *et al*. Acta Neuropathol Commun 2013;1:65

# ADNI Neuropathology Core: Conclusions

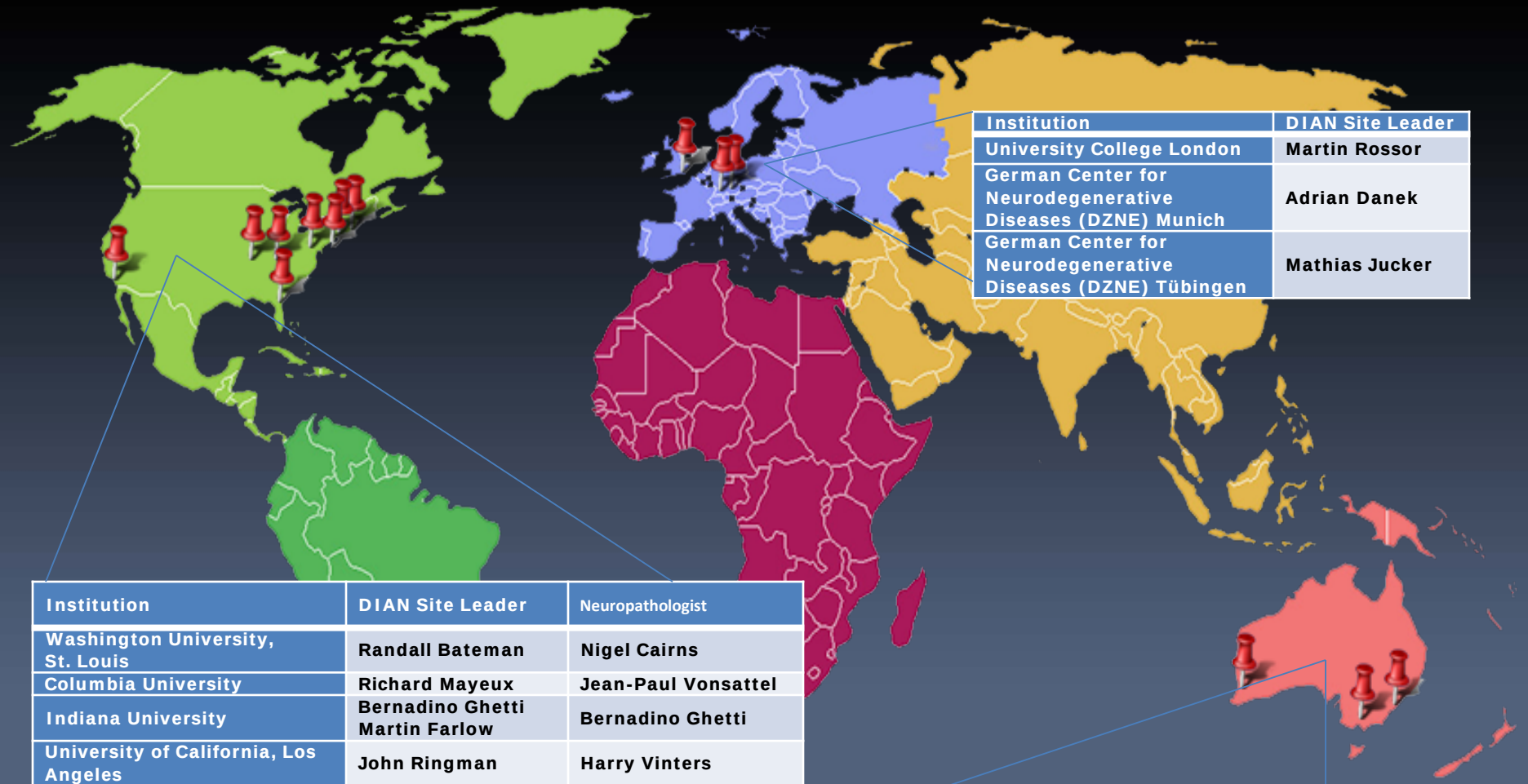
The Neuropathology Core has:

1. Implemented a protocol to solicit permission for brain autopsy in ADNI participants at all 59 sites.
2. Established procedures to send appropriate brain tissue from the decedents to the Neuropathology Core for a standardized and uniform neuropathologic assessment.
3. Co-existent pathologies, most frequently synucleinopathy with Lewy bodies, are present in the majority of autopsied cases.
4. Clinical-biomarker-neuroimaging-neuropathologic studies are being undertaken.
5. Comorbid pathology at autopsy may explain variance in ADNI data.

# Dominantly Inherited Alzheimer Network (DIAN): Aims

1. DIAN (U19 AG032438; JC Morris, PI) provides an opportunity to advance biomarker research in Alzheimer's disease (AD) both in its symptomatic and asymptomatic (preclinical) stages.
2. The DIAN study enrolls individuals from autosomal dominant (ADAD) families caused by a known deterministic mutation in the *PSEN1*, *PSEN2*, or *APP* genes.
3. Biomarker changes in asymptomatic mutation carriers (MCs) are interpreted with the certainty that these individuals are destined to become symptomatic at or about the same age as their affected parent.
4. The DIAN study is yielding the temporal ordering of AD biomarkers in asymptomatic and symptomatic MCs.
5. Neuropathology will determine the burden of AD pathology and the contribution of comorbid pathologies to biomarker changes.

# DIAN Performance Sites



| Institution | DIAN Site Leader | Neuropathologist |
|---|---|---|
| Washington University, St. Louis | Randall Bateman | Nigel Cairns |
| Columbia University | Richard Mayeux | Jean-Paul Vonsattel |
| Indiana University | Bernadino Ghetti<br>Martin Farlow | Bernadino Ghetti |
| University of California, Los Angeles | John Ringman | Harry Vinters |
| Bringham and Women's Hospital—MGH | Reisa Sperling | Matthew Frosch |
| Brown University—Butler Hospital | Stephen Salloway | Edward Stopa |
| University of Pittsburgh | Eric McDade | Julia Kofler |
| Mayo Clinic Jacksonville | Neill Graff-Radford | Dennis Dickson |

| Institution | DIAN Site Leader |
|---|---|
| University College London | Martin Rossor |
| German Center for Neurodegenerative Diseases (DZNE) Munich | Adrian Danek |
| German Center for Neurodegenerative Diseases (DZNE) Tübingen | Mathias Jucker |

| Institution | DIAN Site Leader |
|---|---|
| Neuroscience Research Australia | Peter Schofield |
| University of Melbourne | Colin Masters |
| Edith Cowan University, Perth | Ralph Martins |

## Neuropathologic Assessment of 7 DIAN Participants and 15 Family Members (total = 22)

| Mutation | P/F | PMI (h) | Brain wt. (g) | Clin. Dx.# | Npath. Dx. | A^ (Aβ) | B^ (NFT) | C^ (NP) | SYN** |
|---|---|---|---|---|---|---|---|---|---|
| PSEN1 I143T | P | 18 | 1,330 | AD | AD+DLB | 3 | 3 | 3 | 6 |
| PSEN1 M146L | P | 38 | 1,070 | AD | AD+DLB | 3 | 3 | 3 | 6 |
| PSEN1 H163R | P | 9 | 1,130 | AD | AD | 3 | 3 | 3 | 0 |
| PSEN1 H163R | F | 4.5 | 1,300 | AD | AD+ALB | 3 | 3 | 3 | ALB |
| PSEN1 H163R | F | 9 | 1,490 | AD | AD | 3 | 3 | 3 | 0 |
| PSEN1 H163R | F | 6 | 1,210 | AD | AD+DLB | 3 | 3 | 3 | 6 |
| PSEN1 G206A | F | na | na | AD | AD | 3 | 3 | 3 | 0 |
| PSEN1 G206V | P | 15 | 1,095 | AD | AD | 3 | 3 | 3 | 0 |
| PSEN1 G217R | F | 15 | 1,040 | AD | AD+DLB | 3 | 3 | 3 | 6 |
| PSEN1 L226R | F | 16 | 1,124 | AD | AD+ALB | 3 | 3 | 3 | ALB |
| PSEN1 I229F | P | 23 | 1,220 | AD | AD | 3 | 3 | 3 | 0 |
| PSEN1 I229F | P | 24.5 | 1,080 | AD | AD | 3 | 3 | 3 | 0 |
| PSEN1 S290C | F | 60 | 1,144 | AD | AD | 3 | 3 | 3 | 0 |
| PSEN1 C410Y | F | 21 | 1,224 | AD | AD | 3 | 3 | 1 | 0 |
| PSEN1 A431E | F | 5 | 720 | AD | AD+DLB | 3 | 3 | 3 | 6 |
| PSEN1 T245p | P | 6.5 | 1050 | AD | AD+DLB | 3 | 3 | 3 | 6 |
| PSEN2 A141I | F | 6 | 1,100 | AD | AD+ALB | 3 | 3 | 3 | ALB |
| APP K670N,M671L | F | 6 | 1,210 | AD | AD | 3 | 3 | 3 | 0 |
| APP V717I | F | 15 | 1,150 | AD | AD | 3 | 3 | 3 | 0 |
| APP V717I | F | 26.5 | 1,370 | AD | AD | 3 | 3 | 3 | 0 |
| APP V717I | F | 10 | 1,110 | AD | AD+ALB | 3 | 3 | 3 | ALB |
| APP V717I | F | na | 980 | AD | AD+ALB | 3 | 3 | 3 | ALB |
| Mean | 7P,15F | 16.7 | 1,150 | | AD (100%) | | | | |
| Range | | 4.5-60 | 720-1,490 | | AD+DLB/ALB (50%) | | | | |

P, participant; F, family member. ^NIA-AA stages.

## Comorbidities in AD in ADNI and DIAN Participants

| Neuropathologic diagnoses | | LOAD (ADNI) | | ADAD (DIAN) | |
|---|---|---|---|---|---|
| Primary | Comorbidities** | N* | % | N | % |
| AD | +/- Comorbidity | 33 | 100 | 22 | 100 |
| AD | None | 14 | 42.4 | 11 | 50 |
| AD | DLB/ALB | 14 | 42.4 | 11 | 50 |
| AD | TDP-43 | 7 | 21.2 | 0 | 0 |
| AD | AGD | 6 | 18.2 | 0 | 0 |
| AD | Hippocampal sclerosis | 2 | 6.1 | 0 | 0 |
| AD | Infarcts | 1 | 3.0 | 0 | 0 |
| AGD | None | 1 | 3.0 | 0 | 0 |

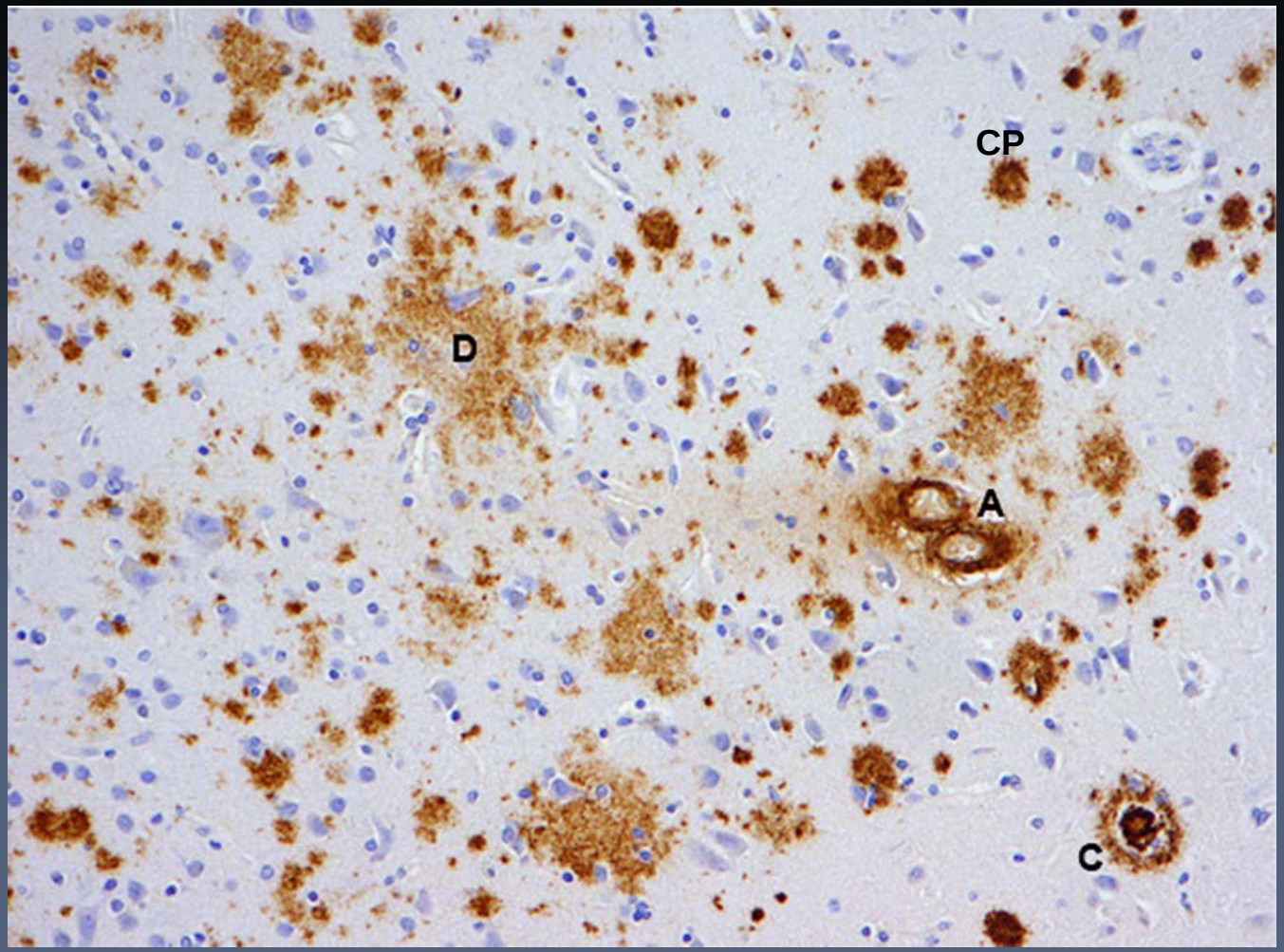
*7 cases pending; ** more than one comorbidity may be present is a single case.

# Aβ Load in ADAD and LOAD Participants

| ADAD | Mutation | APOE | Sex | Edu. (y) | Age at PiB-PET | CDR-SOB at PiB-PET | MMSE at PIB-PET | Age at death (y) | Imaging–autopsy intervals (y) | CDR | NP DX1 | NP DX 2 | NP DX 3 | CAA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *PSEN1* M146L | 44 | M | 16 | 43 | 5 | 21 | 44 | 0.67 | 3 | AD | DLB | | Moderate |
| 2 | *PSEN1* I229F | 23 | F | 12 | 38 | 5 | 16 | 39 | 1.00 | 3 | AD | | | Moderate |
| 3 | *PSEN1* N135S | 33 | M | 12 | 42 | 16 | 9 | 43 | 1.00 | 3 | AD | DLB | | Mild |
| 4 | *PSEN1* T245P | 34 | F | 14 | 46 | 6.5 | 21 | 49 | 3.25 | 3 | AD | | | Mild |
| 5 | *PSEN1* I229F | 23 | F | 12 | 42 | 10 | 12 | 44 | 2.25 | 3 | AD | | | Mild |
| 6 | *PSEN1* I143T | 33 | M | 18 | 38 | 5 | 10 | 39 | 1.75 | 3 | AD | | | Mild |
| 7 | *PSEN1* H163R | 33 | M | 12 | 50 | 10 | 13 | 51 | 1.33 | 3 | AD | | | Focal |
| LOAD | | | | | | | | | | | | | | |
| 1 | NA | 34 | M | 18 | 85 | 4 | 30 | 89 | 3.67 | 2 | AD | | | Mild |
| 2 | NA | 33 | M | 12 | 65 | 5.5 | 21 | 69 | 3.92 | 2 | AD | | | Very mild |
| 3 | NA | 34 | F | 13 | 79 | 6 | 20 | 83 | 3.83 | 3 | AD | | | Mild |
| 4 | NA | 34 | F | 13 | 68 | 2.5 | 26 | 72 | 3.83 | 3 | AD | | | Focally severe |
| 5 | NA | 34 | M | 18 | 66 | 13 | 12 | 71 | 4.75 | 3 | AD | DLB | | Mild |
| 6 | NA | 34 | F | 16 | 83 | 0 | 28 | 88 | 4.83 | 3 | AD | DLB | | Mild |
| 7 | NA | 34 | M | 20 | 76 | 4 | 25 | 80 | 4.67 | 3 | AD | DLB | TDP | Mild |

A Zhou

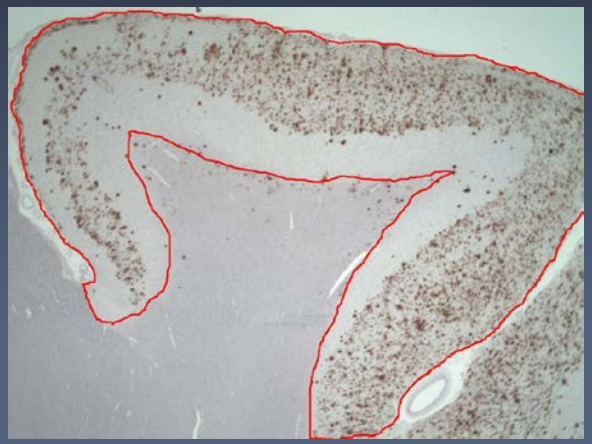
# Aβ Deposits: Morphological Heterogeneity

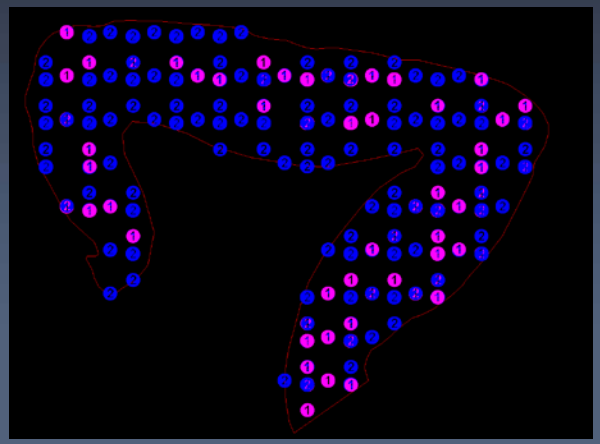


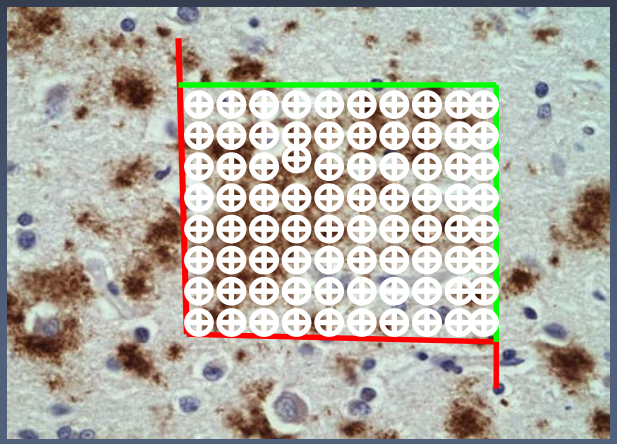

D, diffuse plaque; C, cored plaque; CP, compact plaque; A, cerebral amyloid angiopathy

## Unbiased stereology methods measure Aβ load

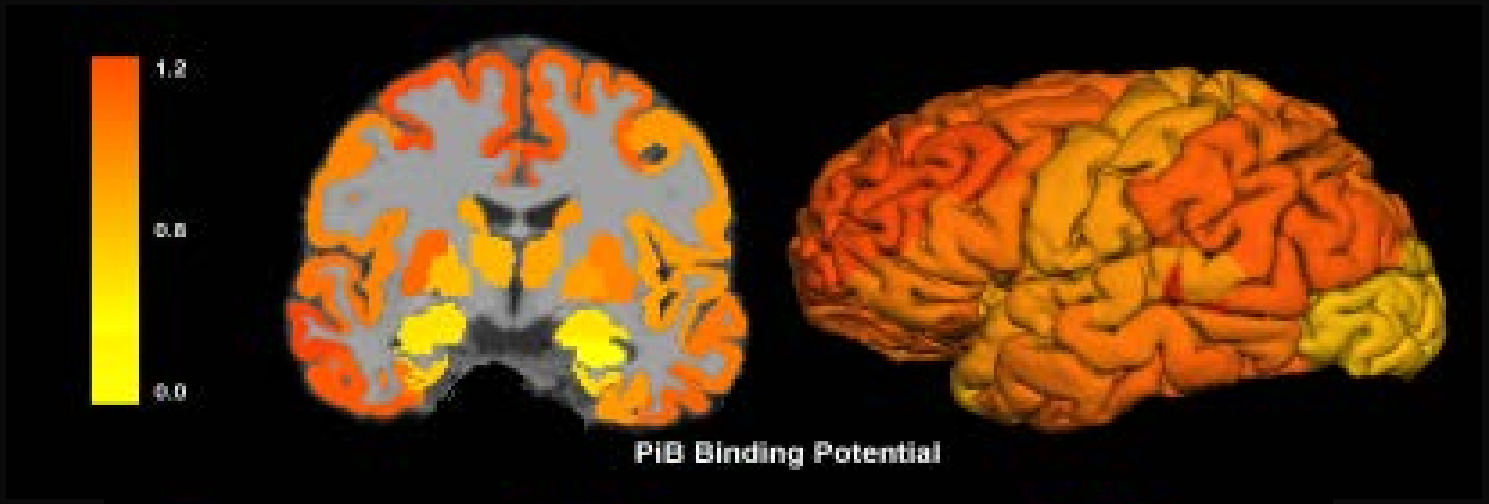
Probe: Area Fraction Fractionator (Stero Investigator, MicroBrightField, Inc.)
ROI (gyral crest and sulcal depth gray matter). Mag. X1
Aβ load: Area fraction of cortex (n=19 brain regions)

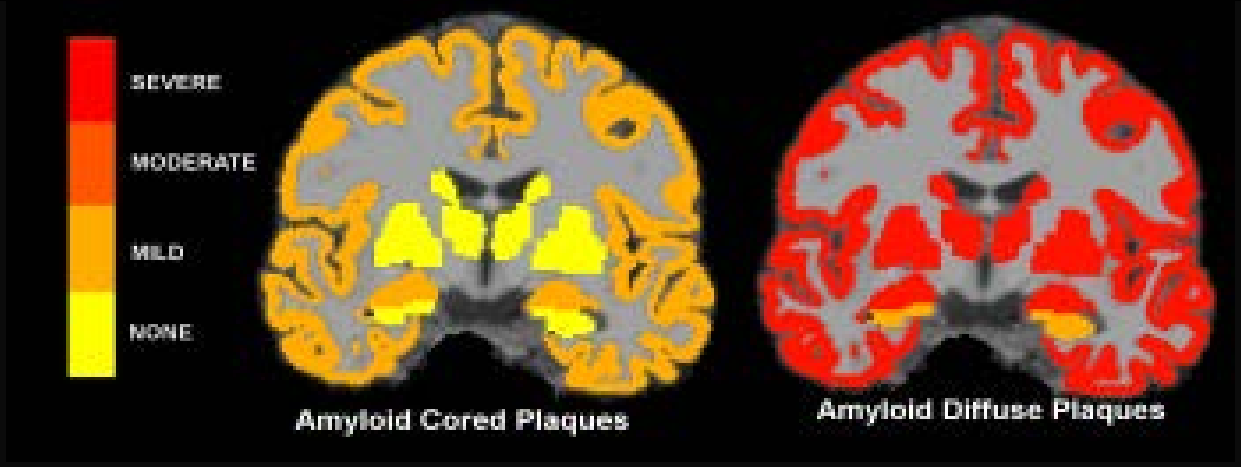






# Neuropathologic Heat Maps facilitate PET-PiB amyloid imaging in DIAN Participants

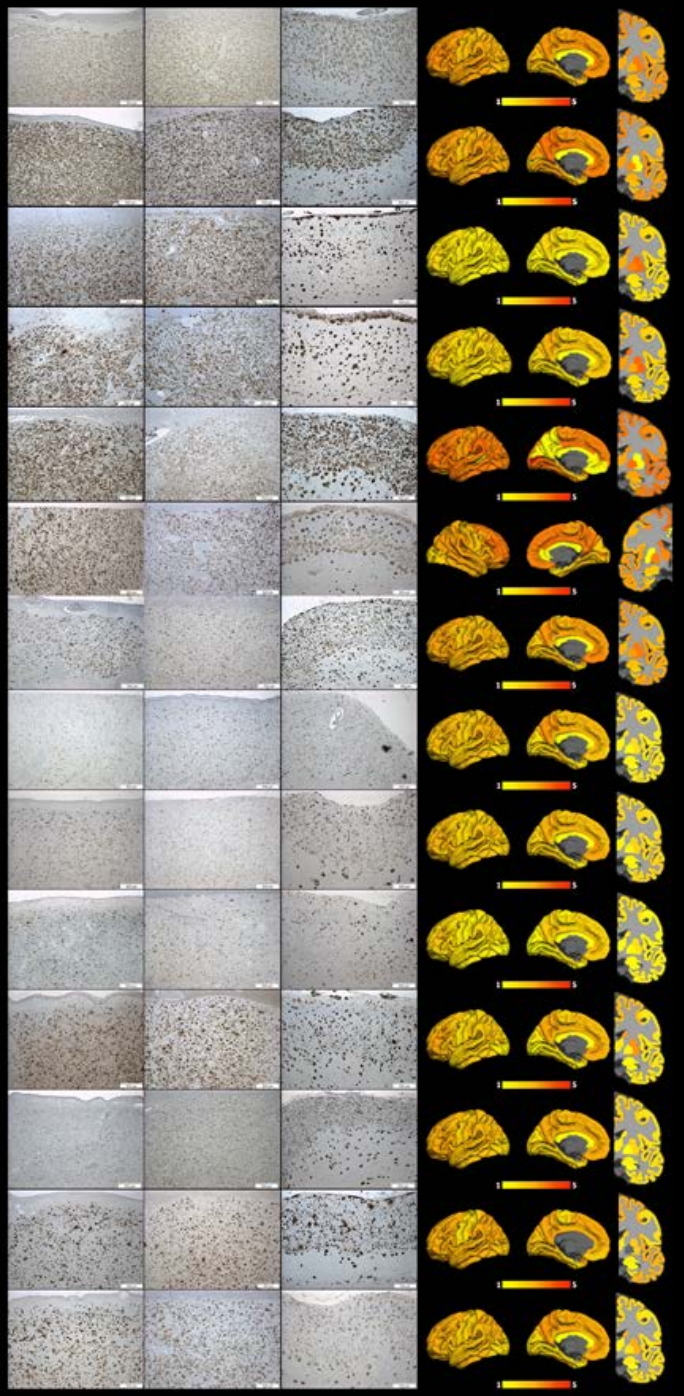



Aihong Zhou, Karl Friedrichsen
Tammie Benzinger

KnightADRC Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

# Generation of heat maps using Aβ load in LOAD and ADAD



ADAD
#1-7

LOAD
#8-14

Aβ plaques
10D5 IHC

PET-PiB

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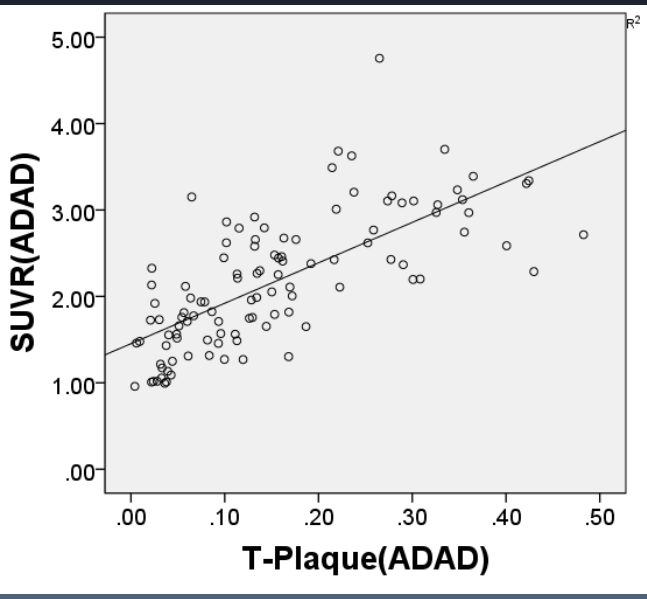
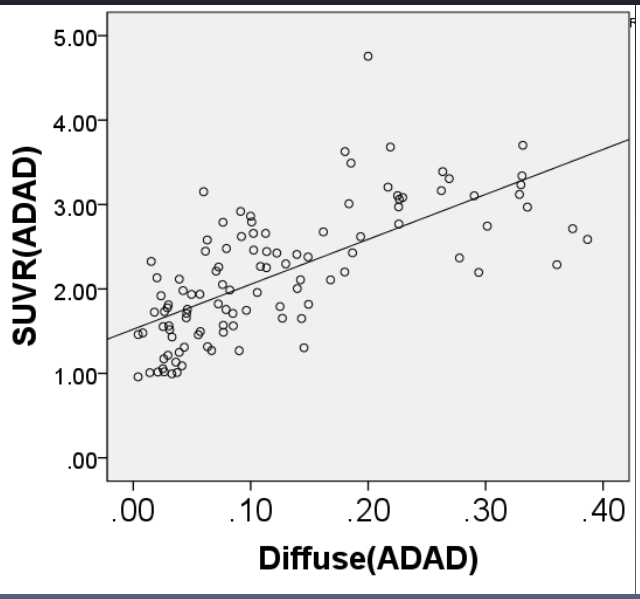
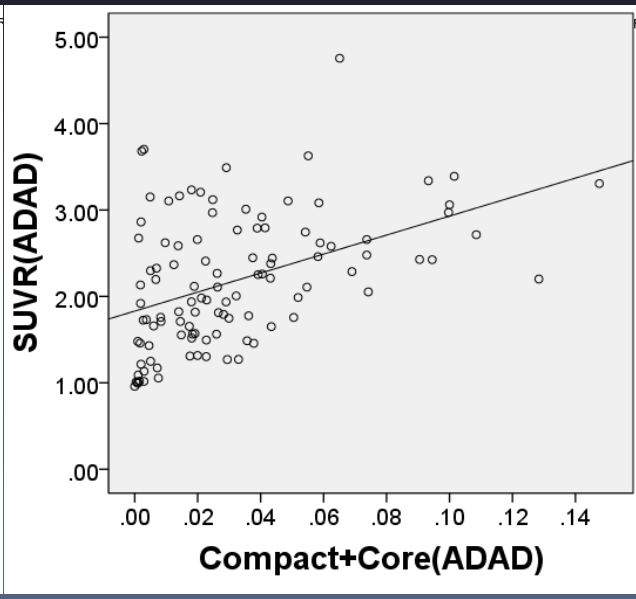
# Correlation between PiB-PET and postmortem plaques in ADAD




Total plaque burden-PiB: $r = 0.71$, $p < 0.0001$
Diffuse plaque burden-PiB: $r = 0.69$, $p < 0.0001$
Compact/cored plaque burden-PiB: $r = 0.44$, $p < 0.0001$

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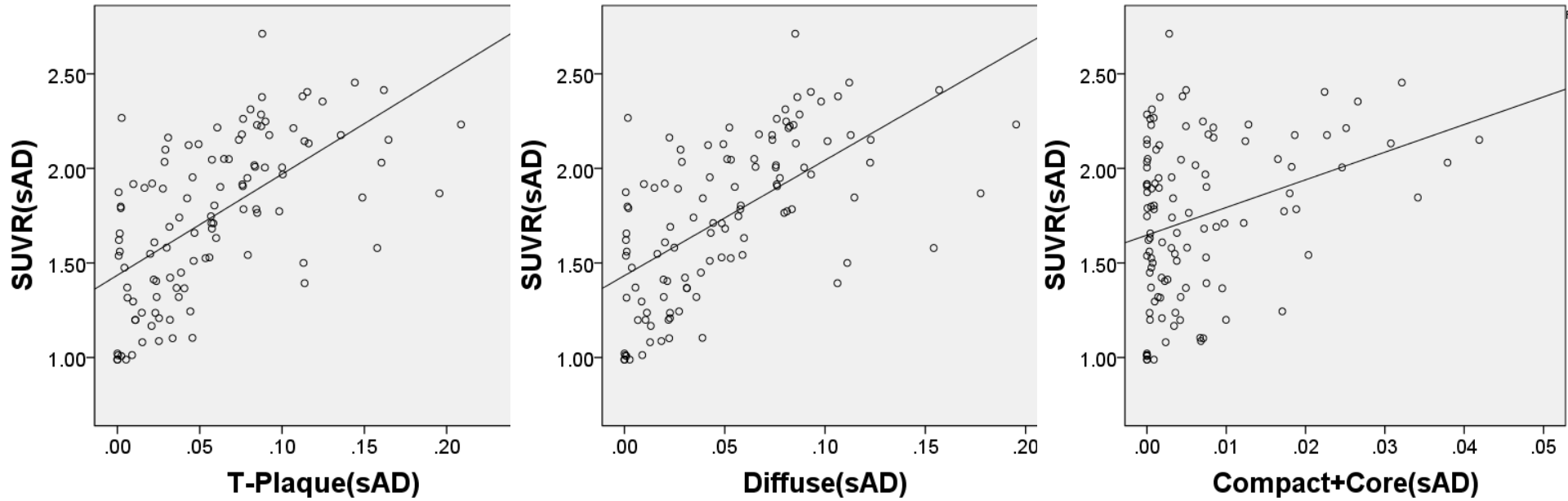
# Correlation between PiB-PET and postmortem plaques in LOAD




Total plaque burden -PiB: r = 0.60, p < 0.0001
Diffuse plaque burden -PiB: r = 0.61, p < 0.0001
Compact/cored plaque burden -PiB: r = 0.32, p < 0.001

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# Conclusions

1. ADNI and DIAN Neuropathology Core is facilitating multi-modal clinical-neuroimaging-biomarker-neuropathologic correlations.
2. PET-PiB amyloid imaging correlates well with total Aβ burden including both diffuse and compact plaques.
3. Pure AD is more frequent in ADAD than LOAD.
4. Lewy body disease is the most frequent comorbidity in both groups.
5. Comorbidities including TDP-43 proteinopathy, hippocampal sclerosis and infarcts are present in LOAD but absent in ADAD.
6. Neuropathologic differences between LOAD and ADAD cohorts may have significance in clinical trial design and interpretation.

# Acknowledgements

## The Participants

**http://www.adni-info.org/**

**http://dian-info.org/**

KnightADRC Alzheimer's Disease Research Center | WASHINGTON UNIVERSITY ST. LOUIS


**DIAN PI: John C. Morris**
**ADNI PI: Michael W. Weiner**

**DIAN Sites (14): USA, Australia, United Kingdom, Germany**
**ADNI Sites (59): USA, Canada**

**DIAN & ADNI Cores**

**Biostatistics**
**Chengjie Xiong**

**Indiana University**
**Bernardino Ghetti, Andrew Saykin**

**University of Kansas**
**Kathy Newell**

**DIAN/ADNI Neuropathology Core**
**Nigel Cairns**
**Deborah Carter**
**Erin Householder**
**Benjamin Vincent**
**Mingqiang Xie, Aihong Zhou**

**Washington University**
**Division of Neuropathology**
**Robert Schmidt**
**Joseph Corbo**
**Sonika Dahiya**
**Richard Perrin**


DIAN
Dominantly Inherited Alzheimer Network

ADNI