UNIVERSITY OF TORONTO
FACULTY OF MEDICINE

Neuropathology of neurodegenerative diseases in Toronto: Accomplishments and challenges

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Toronto Dementia Research Alliance

Human Resources

- 8.5 Neuropathologists in Toronto
  - 3 UHN
  - 1.5 Sunnybrook
  - 2 Hospital for Sick Children
  - 1Mount Sinai
  - 1 St. Michael's
- 2 Primary interest in dementia
  - L-N H, DGM

Canadian Brain Tissue Bank 1

- Established 1982
  - Initially managed by the Canadian Neurological Coalition
- 1982-1992: National scope
  - Support
    - Medical Research Council
    - Ontario Mental Health Foundation
    - Canadian Neurological Coalition
  - Budget 150K-200K/yr
  - 120 brains/yr
  - Staff:
    - 2 Office staff, 1Tissue Coordinator1Medical Director

Canadian Brain Tissue Bank 2

- 1992-2000
  - Reduced budget to 25% of prior
  - Reduced donors
  - No detailed frozen tissue dissections
- 2000-2010 (gradual)
  - No donations
  - No staff
  - Tissue stored in freezers at UHN
  - Retrievals continue as part of collaborative studies

CBTB: Ongoing international collaborations

LETTERS

nature genetics

Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions

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Frontotemporal lobar degeneration (FTLD) is the second

mutations in *GRN*. Our data implicate variants in *TMEM106B*

CBTB current status

Assets

- Collection of >300 frozen & histological brain samples of well clinically characterized patients
- Interested &dedicated neuropathologists
- Good facilities

Liabilities

- Lack of stable funding

CBTB: Potential

- Pathological confirmation of presumed diagnosis for numerous ongoing clinical studies in Toronto
  - Source of donations
- Fresh frozen tissue for basic researchers
- Further delineation of neurodegenerative diseases through clinico-pathological correlation studies
- Stable funding only missing factor

Ongoing Intra-city collaborations 1

STRUCTURAL CORRELATE OF FOCAL SIGNS IN ALZHEIMER'S DISEASE

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ORIGINAL PAPER

Argyrophilic thorny astrocyte clusters in association with Alzheimer's disease pathology in possible primary progressive aphasia

David G. Munoz · John Woulfe · Andrew Kertesz

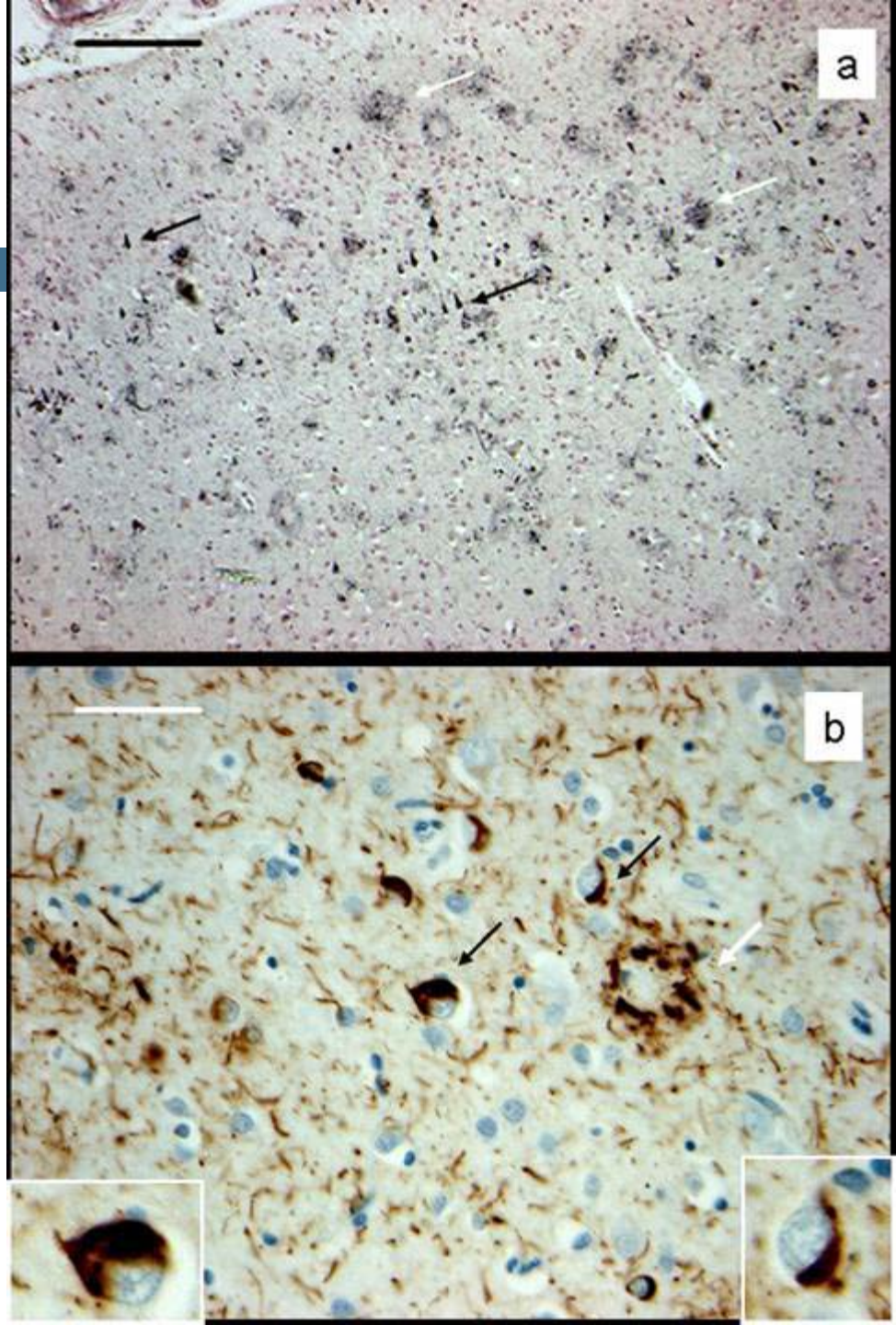
Unresolved questions

- Clinical profile of patients with PPA and AD pathology
- In cases with AD pathology, pathological differences between cases
  - with PPA symptoms
  - without PPA symptoms
- Is the focal presentation related to
  - Selective regional distribution of plaques and tangles
  - Additional presence of a different lesion

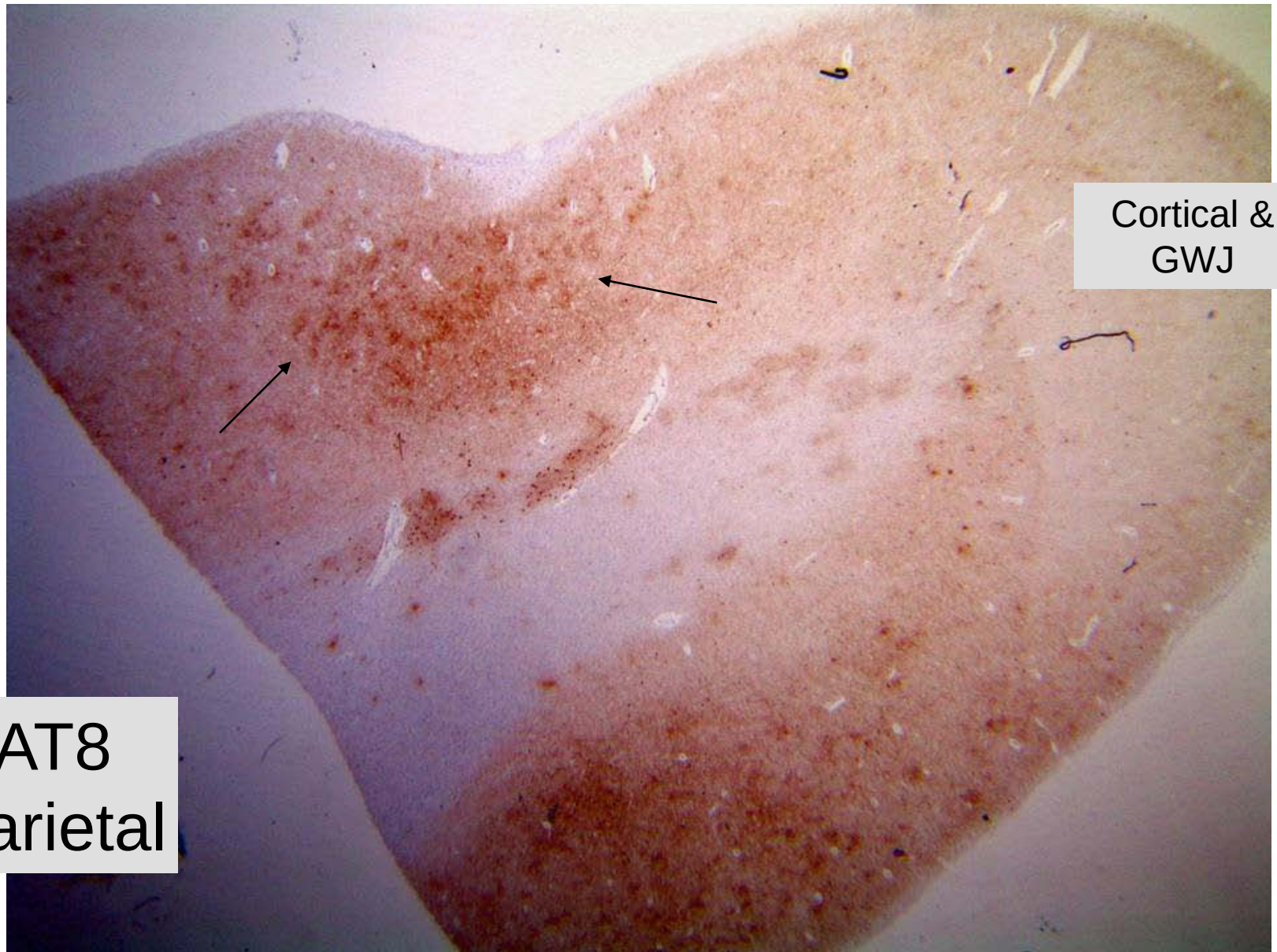
ALL CASES

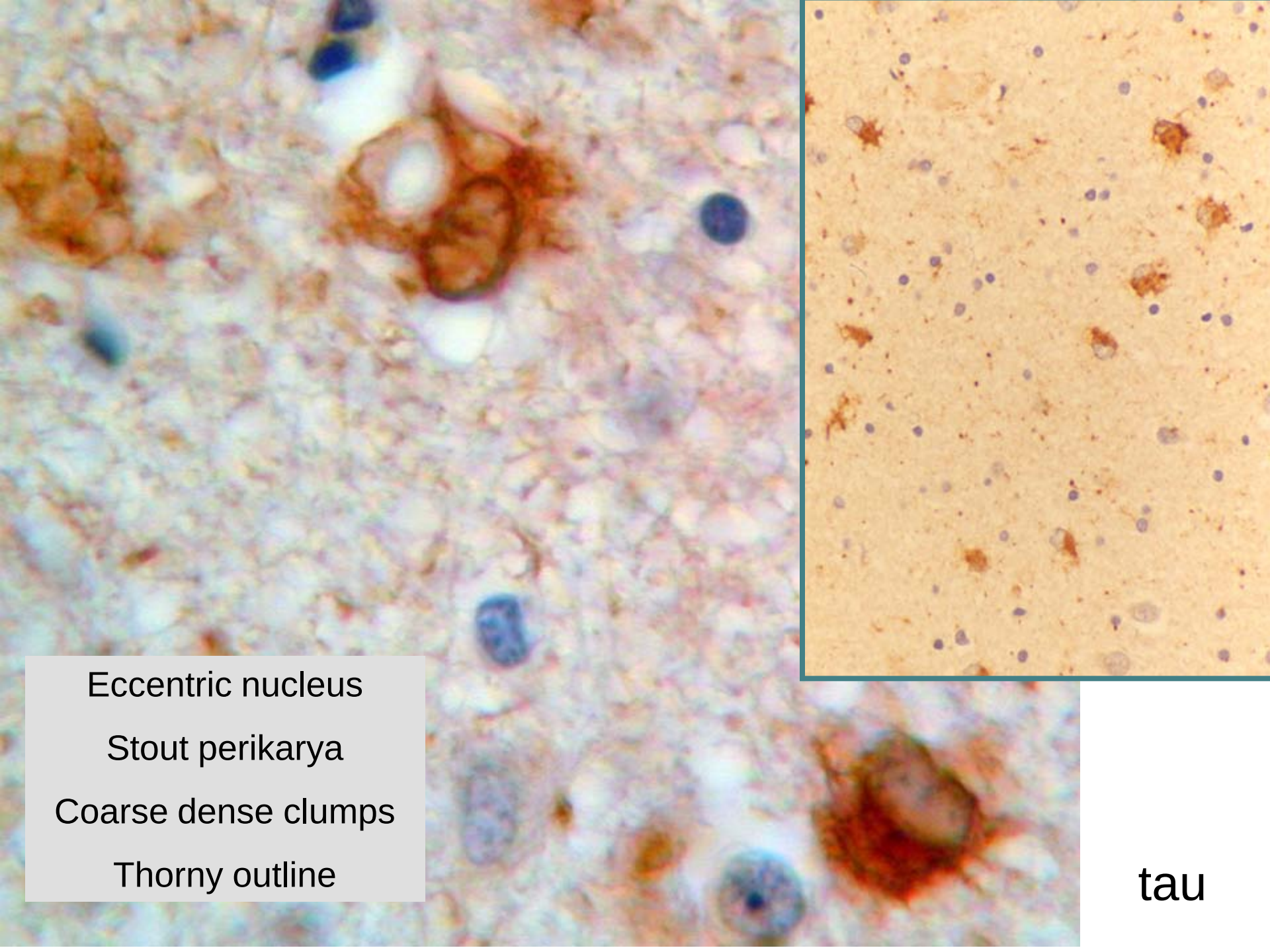
<u>Pathological Diagnosis:</u>

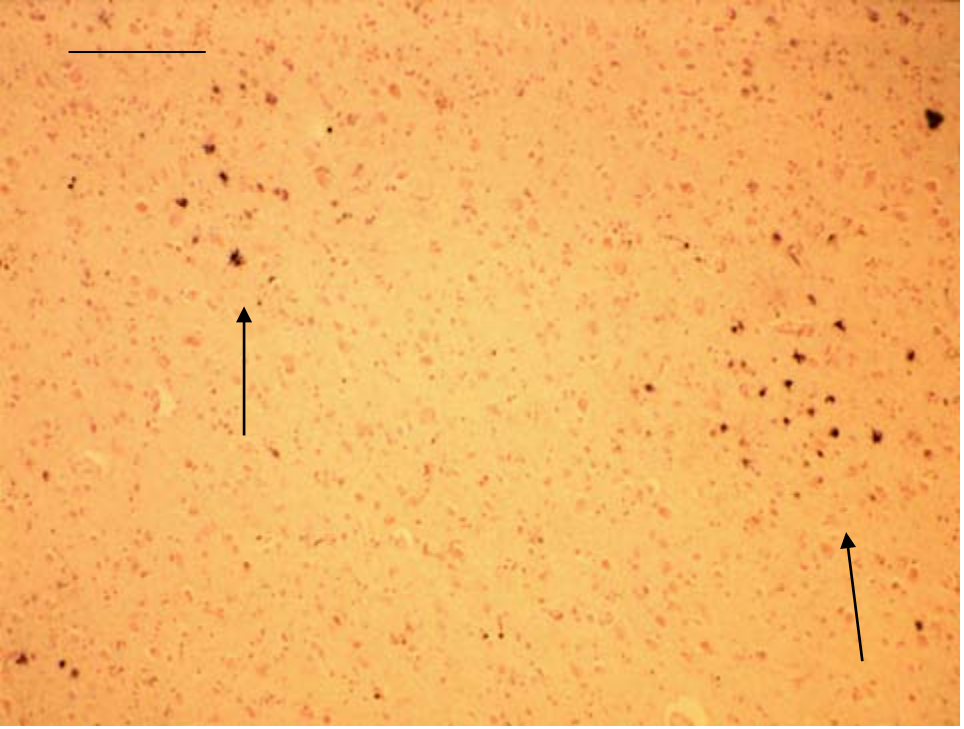
- Alzheimer´s Disease
- Abundant NP & NFT
- Braak stage V-VI
- Typical distribution

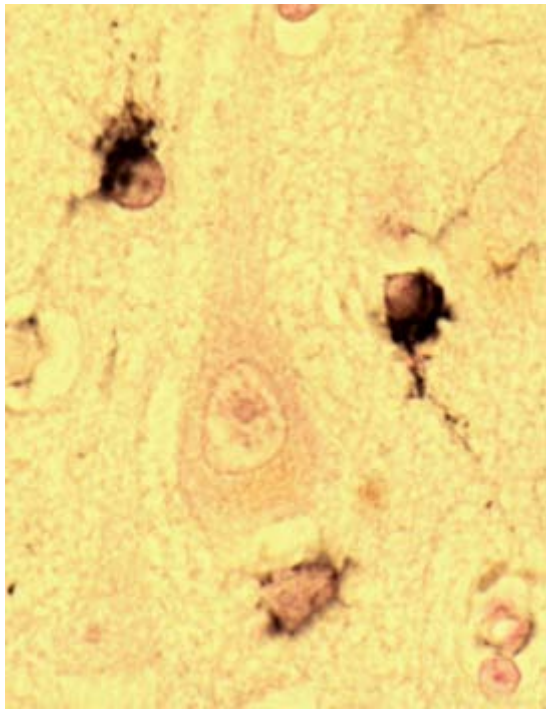


ATAC: Argyrophilic Thorny Astrocyte Clusters
7 out of 8 cases



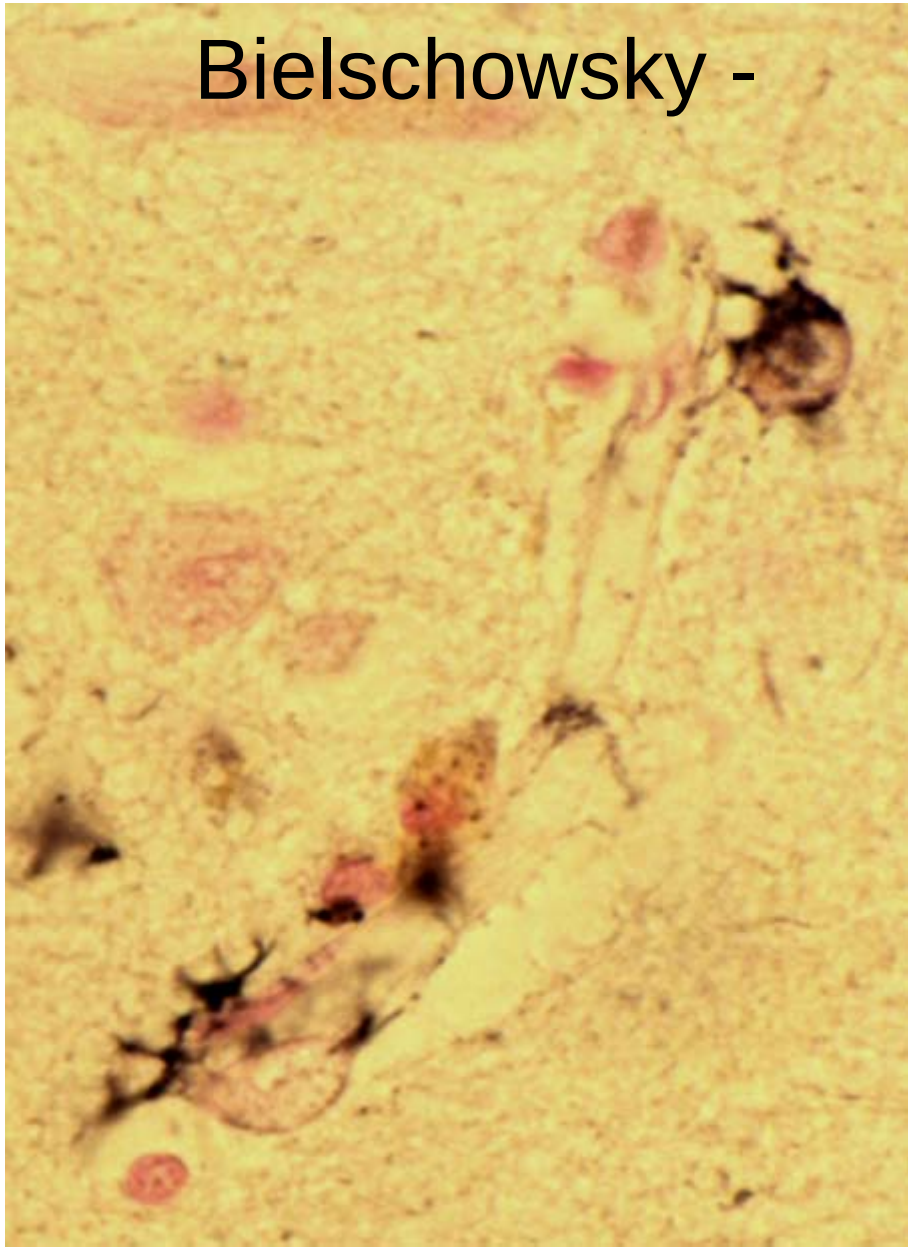

Eccentric nucleus
Stout perikarya
Coarse dense clumps
Thorny outline
tau





Gallyas +

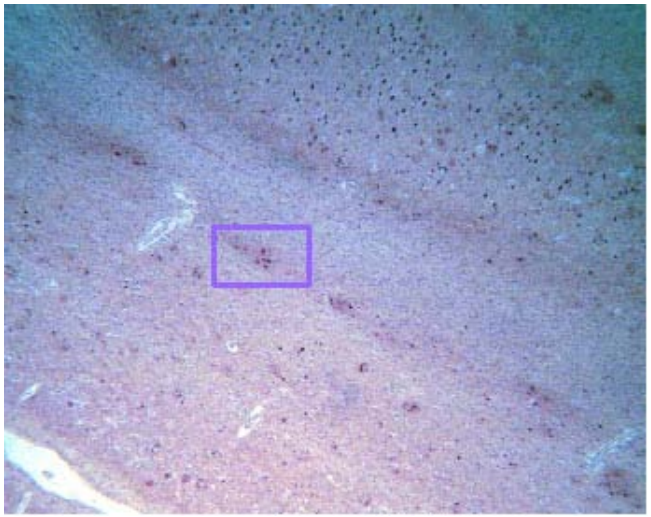
Bielschowsky -



ATAC characterization

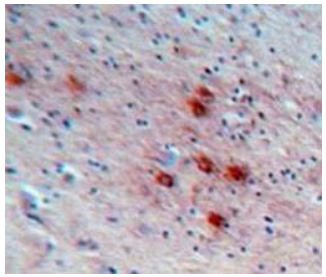
Location

- Cerebral cortex
- Subcortical WM (near GWJ)
- Absent subcortical GM



Unrelated to

- Myelin pallor (leukoaraiosis)
- Gliosis
- Infarcts
- NFT density
- Plaque density



CONCLUSIONS :ATAC

- ATAC are a common, but not universal co-substrate of PPA in AD
- ATAC differ from ATA in normal aging
  - Location, most Gallyas +
- Intensification of aging changes vs independent phenomenon
  - Neuronal NFT:
    - Aging ≈ AD
    - Aging ≠ PSP, CBD
- Hypothesis: ATAC represent a marker of a process responsible for or contributing to the prominent focal clinical manifestations in AD

External Confirmation

- Finds aphasia in AD
  - poorly related to NFT, plaque distribution.
  - ATAC in subset of cases

Alzheimer and Frontotemporal Pathology in Subsets of Primary Progressive Aphasia

Marsel Mesulam, MD,[1–3] Alissa Wicklund, PhD,[1] Nancy Johnson, PhD,[1,3] Emily Rogalski, PhD,[1]
Gabriel C. Léger, MD,[1] Alfred Rademaker, PhD,[1,4] Sandra Weintraub, PhD,[1–3] and Eileen H. Bigio, MD[1,5]

Ongoing collaboration

- Structural substrate of focal signs in AD
  - Black, Bilbao (Sunnybrook)
  - Munoz (St. Michael's)

Ongoing Intra-city collaborations 2

FUSOPATHIES

Relationship between aFTLD-U, NIFID, & BIBD

Black, Bilbao (Sunnybrook)
Munoz (St. Michael's)

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ORIGINAL PAPER

FUS pathology in basophilic inclusion body disease

David G. Munoz · Manuela Neumann · Hirofumi Kusaka · Osamu Yokota · Kenji Ishihara · Seishi Terada · Shigetoshi Kuroda · Ian R. Mackenzie

What we need

- Stable funding to support a Brain Bank
  - Strengthen clinical studies by confirming diagnosis
    - Improved QA, basic-clinical link
  - Histological studies
  - Biochemical studies
  - Imaging correlation
  - Strengthen genetic studies
- We have the capability. With funding support as an outcome of this alliance we will be in a position to re-start this program