Neuropathology And Biology Of Lewy Body Dementia

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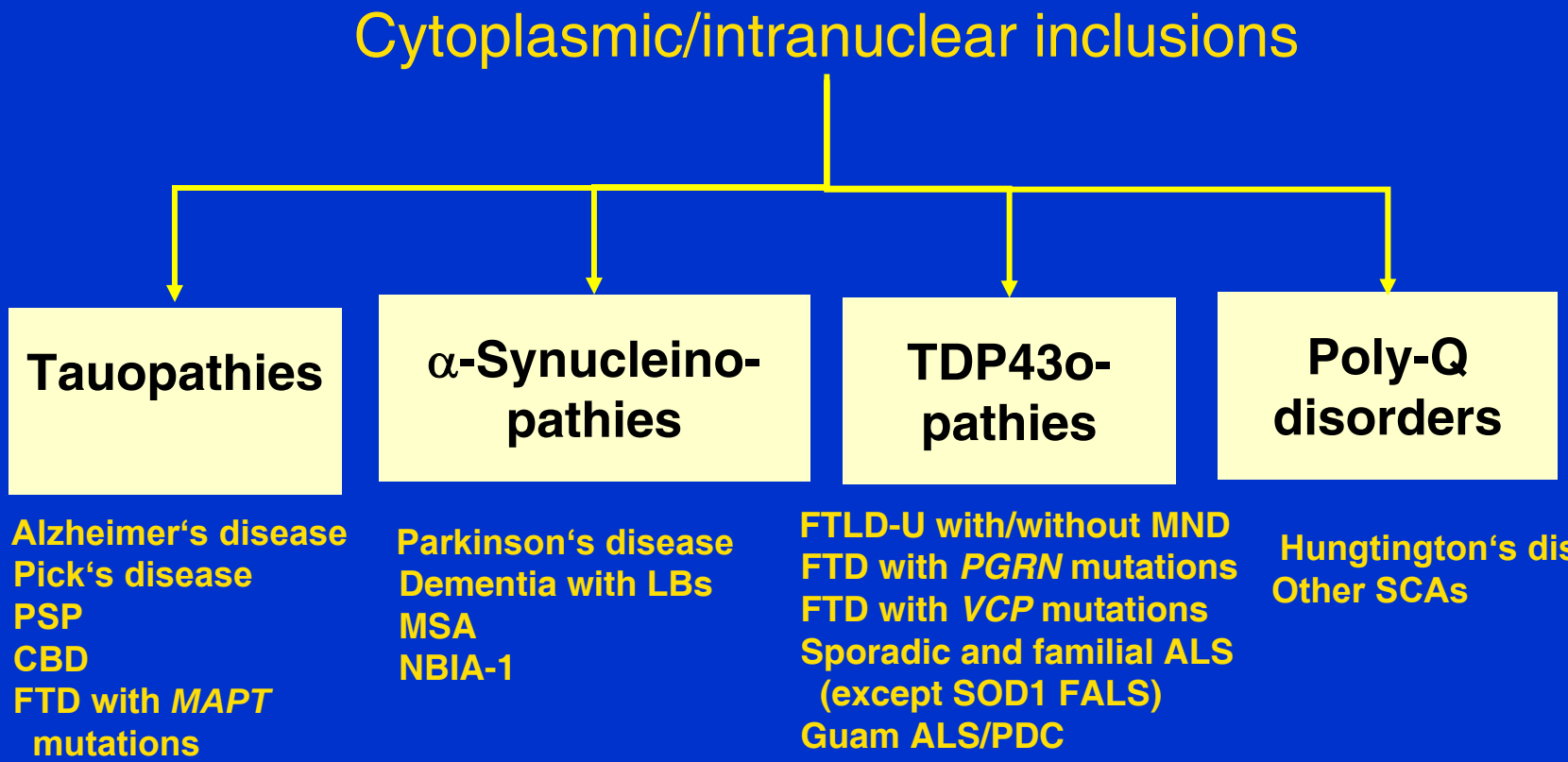
DISCLOSURE: PARTICIPATED IN 2005 DLB CONSORTIUM, CHAIRED 1997 NIA-REAGAN

Neurodegenerative Protein Misfolding Diseases: Accumulation of the same disease protein has diverse and overlapping clinical manifestgations

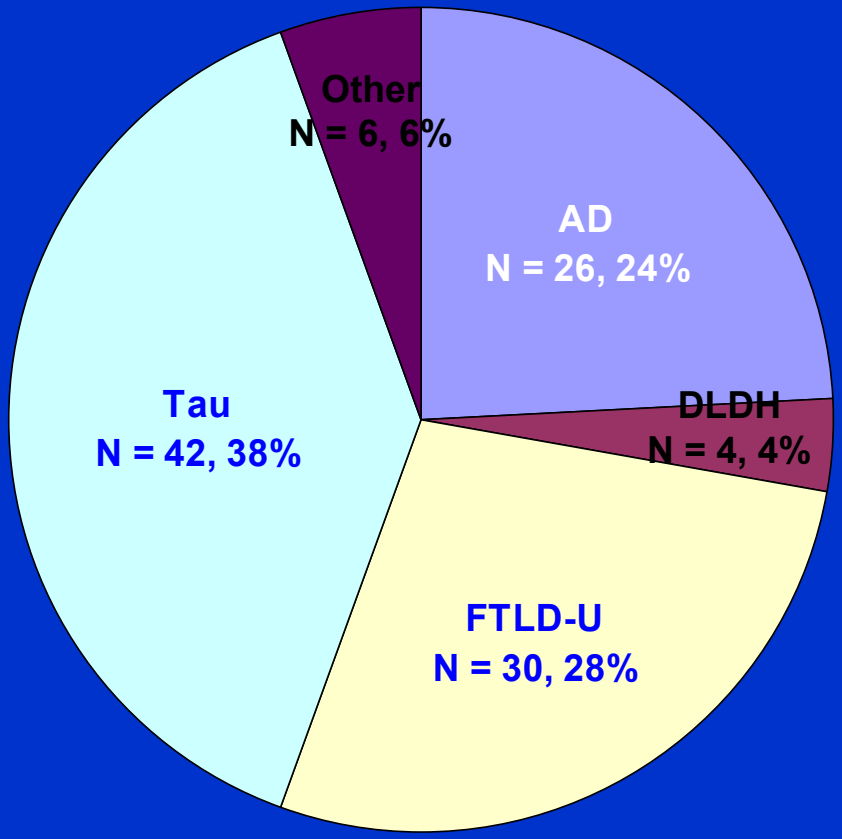


Neuman et al, Arch Neurol, 2008

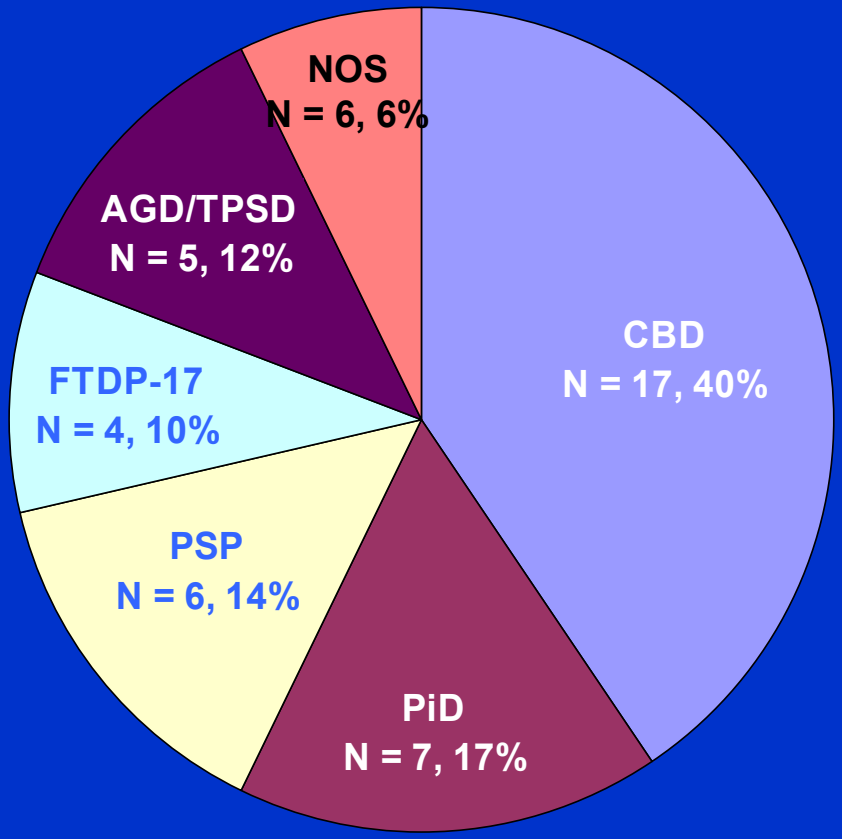
FTLD: Clinicopathological Correlations

(Forman MS, Farmer J, Johnson JK, Clark CM, Arnold SE, Coslett HB, Chatterjee A, Hurtig HI, Karlawish JH, Rosen H, Van Deerlin V, Lee VM-Y, Miller BL, Trojanowski JQ, Grossman M. Frontotemporal dementia: Clinicopathological correlations. Ann. Neurol., 59:952-962, 2006)

A. Pathology of FTD patients



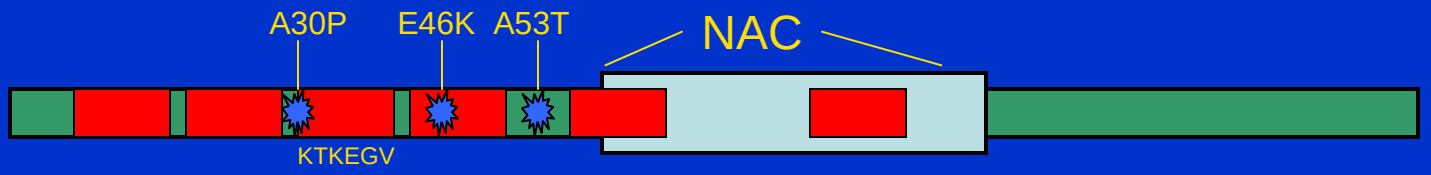
B. Tauopathies



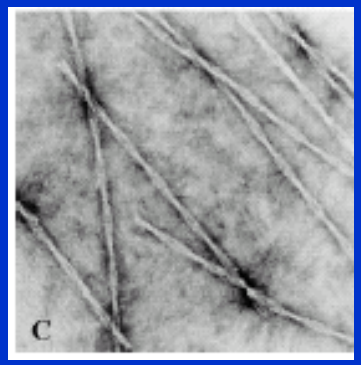
PS: First patient with clinical AD to come to autopsy in ADNI had DLB! Most clinical DLB patients in Penn ADCC have AD and DLB. Pure DLB is rare in our center.

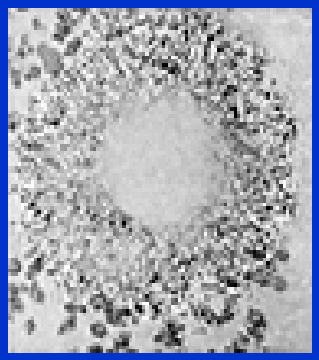
Alpha-Synuclein Genetics & Neuropathology

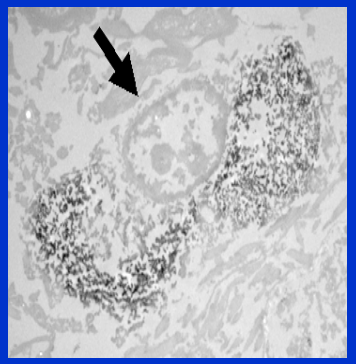
- 140 aa protein, unknown function, synaptic vesicle associated
- 3 point mutations (53T, A30P, E46K, duplication/triplication cause familial PD
- Alpha-Synuclein fibrils are main component of Lewy Bodies & Neurites

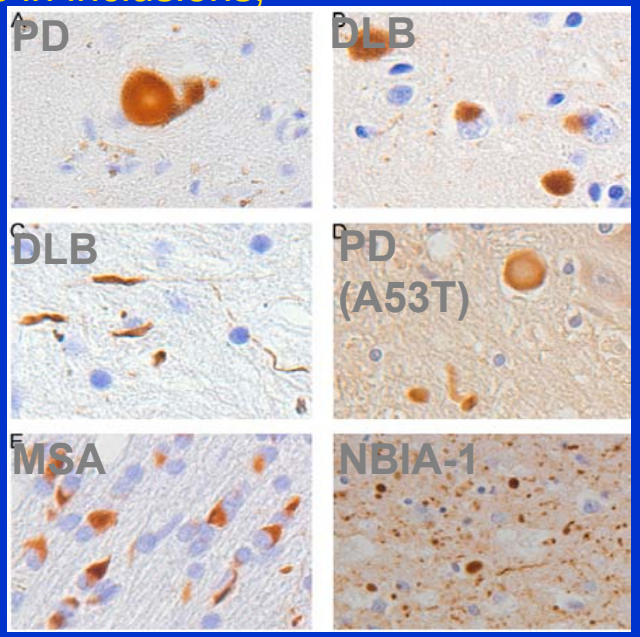


- Alpha-synuclein pathology is linked to mechanisms of neurodegeneration
  - Alpha-synuclein pathology found in PD, DLB, LBVAD, MSA, NBIA-1
  - Overexpression of alpha-synuclein in Tg mice results in inclusions, neurodegeneration & death
  - Alpha-synuclein polymerizes *in vitro*
    - Mutations, concentration increase fibrillization rate
  - But, what is the toxic or pathogenic species?









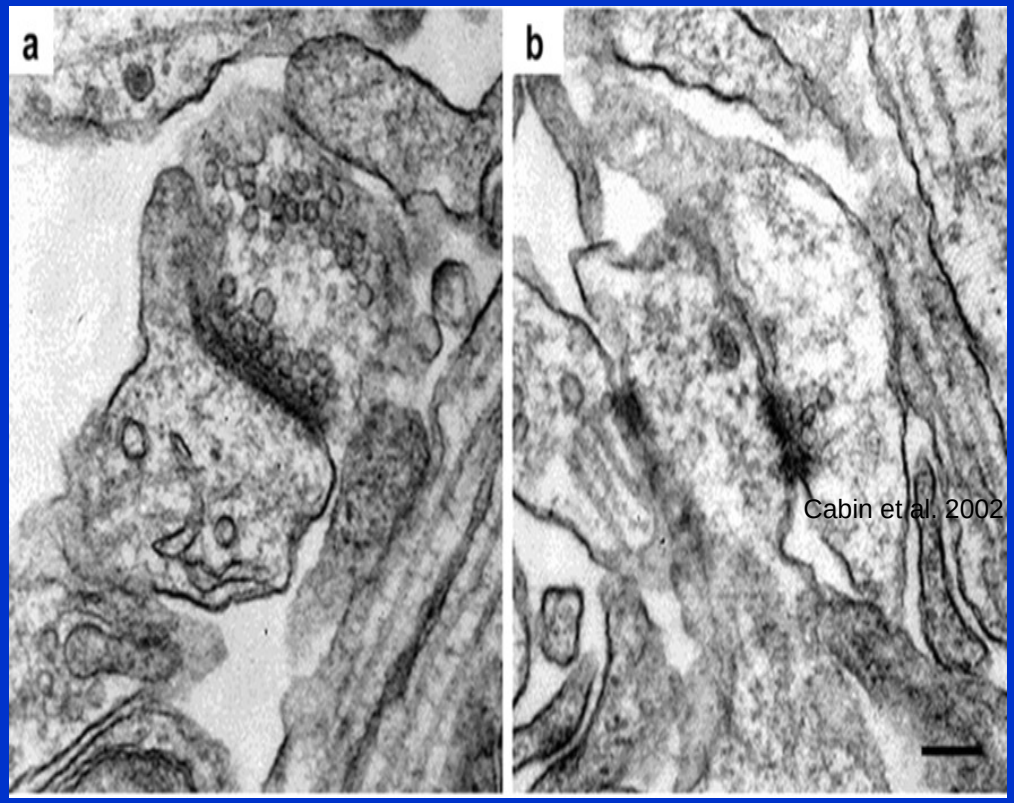
Alpha-Synuclein: Function?

•Expressed throughout brain, synaptic protein, associates with vesicles

• Alpha-synuclein knockout mice have depleted reserve, docked vesicle pool

• Alpha-synuclein overexpression in PC12 cells cause increased docked vesicles, decrease in release

• Determining alpha-synuclein function may provide insights into disease pathogenesis



Cabin et al. 2002

DLB Consensus Criteria for the Neuropathologic Diagnosis (1996)

- Sampling
  - Neocortex
    - Frontal BA8/9
    - Temporal BA21
    - Parietal BA40
  - Limbic/paralimbic
    - Anterior cingulate BA24
    - Transentorhinal BA29
  - Brain Stem
    - Substantia nigra
    - Locus ceruleus
    - Dorsal nucleus of vagus

- Scoring of neocortical and limbic regions
  - 0 LB/area 0
  - 1-5 LB/area 1
  - >5 LB/area 2

- Classification
  - LB scores are summated and final score is used to subclassify as follows:
    - 0-2 brain stem predominant
    - 3-6 limbic
    - 7-10 neocortical

***McKeith I, et al., Neurology* (1996) 47:1113**

Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium

I. G. McKeith, D. W. Dickson, J. Lowe, M. Emre, J. T. O'Brien, H. Feldman, J. Cummings, J. E. Duda, C. Lippa, E. K. Perry, D. Aarsland, H. Arai, C. G. Ballard, B. Boeve, D. J. Burn, D. Costa, T. Del Ser, B. Dubois, D. Galasko, S. Gauthier, C. G. Goetz, E. Gomez-Tortosa, G. Halliday, L. A. Hansen, J. Hardy, T. Iwatsubo, R. N. Kalaria, D. Kaufer, R. A. Kenny, A. Korczyn, K. Kosaka, V.M.Y. Lee, A. Lees, I. Litvan, E. Londos, O. L. Lopez, S. Minoshima, Y. Mizuno, J. A. Molina, E. B. Mukaetova-Ladinska, F. Pasquier, R. H. Perry, J. B. Schulz, J. Q. Trojanowski, M. Yamada and for the Consortium on DLB

Neurology 2005;65;1863-1872; originally published online Oct 19, 2005; DOI: 10.1212/01.wnl.0000187889.17253.b1

Guiding principle: The likelihood of DLB is directly related to LB Pathology and inversely related to AD pathology.

		Alzheimer pathology		
		Low AD (Braak I-II)	Intermediate AD (Braak III-IV)	High AD (Braak V-VI)
Lewy body pathology	Brainstem	Low DLB	Low DLB	Low DLB
	Transitional	High DLB	Intermediate DLB	Low DLB
	Diffuse	High DLB	High DLB	Intermediate DLB

THIRD CONSENUS MEETING: LB PATHOLOGY PATTERN

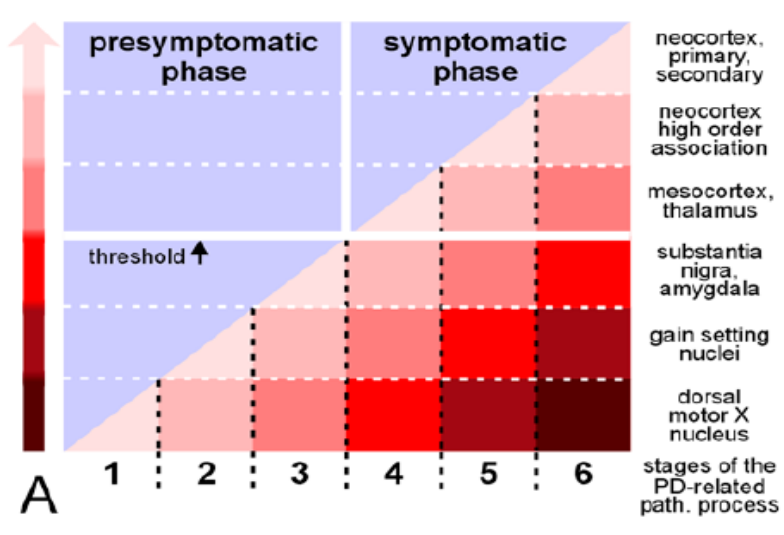
Lewy body type pathology	Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
	IX-X	LC	SN	nbM	Amygdala	Transentorhinal	Cingulate	Temporal	Frontal	Parietal
Brainstem-predominant	1-3	1-3	1-3	0-2	0-2	0-1	0-1	0	0	0
Limbic (transitional)	1-3	1-3	1-3	2-3	2-3	1-3	1-3	0-2	0-1	0
Diffuse neocortical	1-3	1-3	1-3	2-3	3-4	2-4	2-4	2-3	1-3	0-2

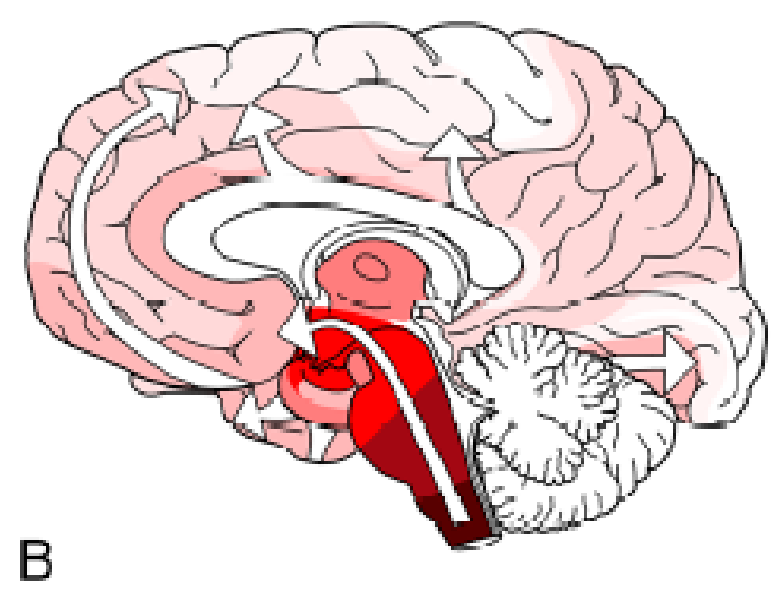
0 = None
1 = Mild (sparse LBs or LNs)
2 = Moderate (more than one LB in a low power field and sparse LNs)
3 = Severe (four or more LBs and scattered LNs in a low power field)
4 = Very severe (numerous LBs and numerous LNs)

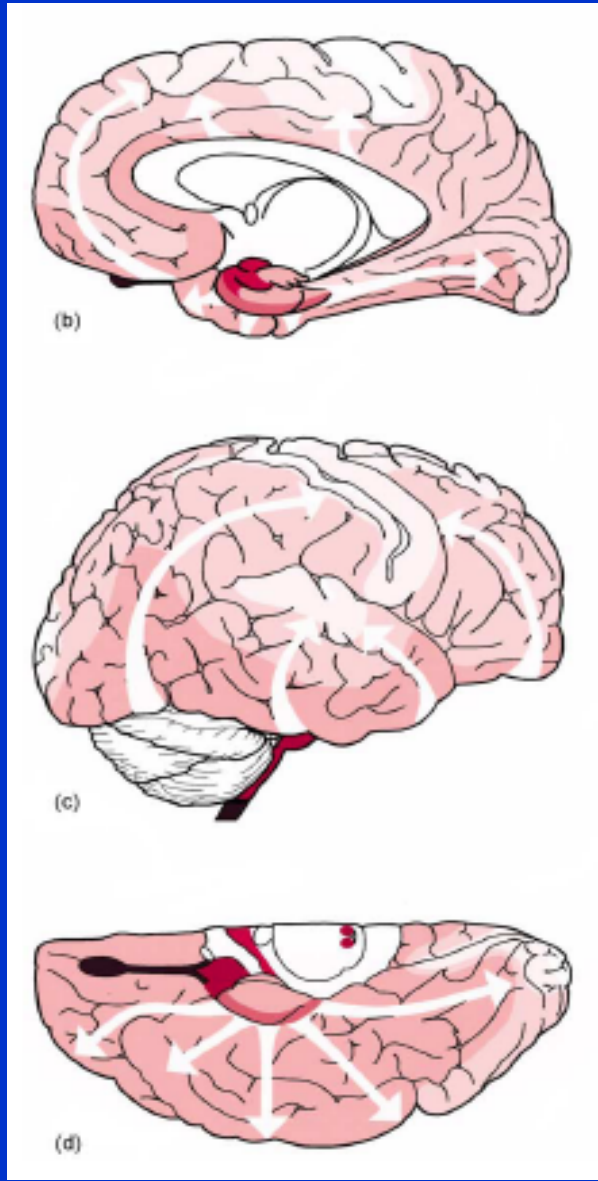
McKeith et al 2005

Braak Staging Of Lewy Body Pathology

Braak et al, 2003, 2004



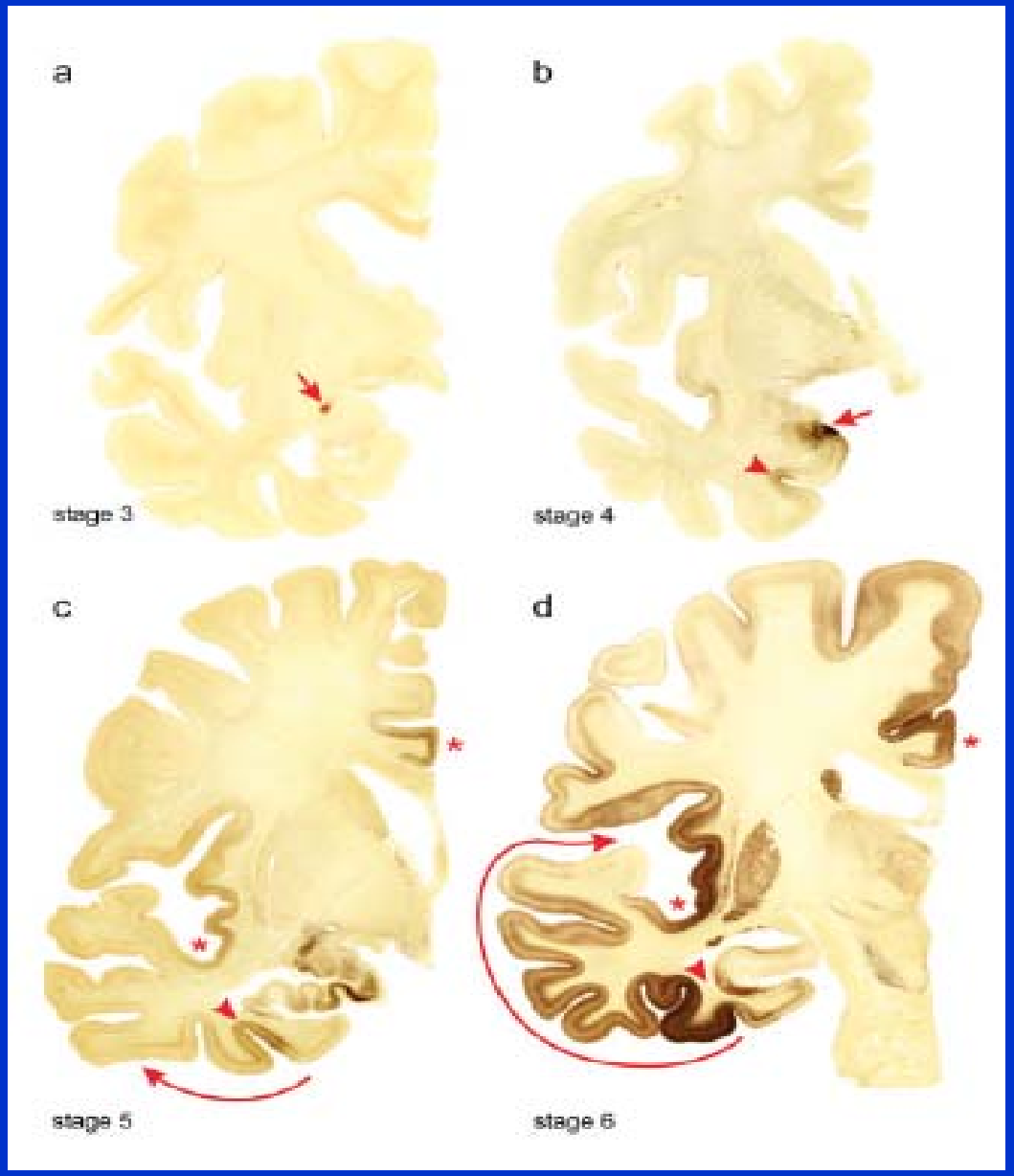




Cognitive status correlates with neuropathologic stage in Parkinson disease. Braak H, Rüb U, Jansen Steur ENH, Del Tredici K and de Vos RAI. Neurology 64:1404-1410, 2005

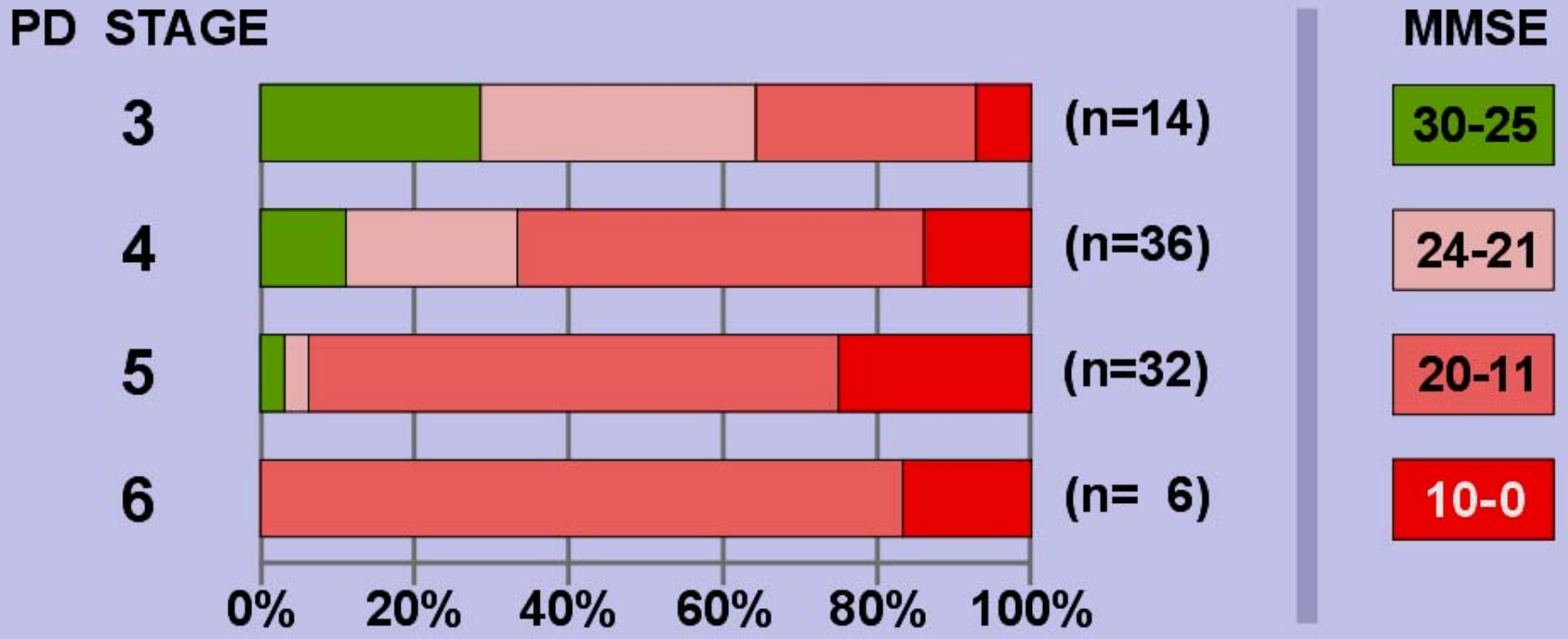
Cognitive status and Braak stages of LB pathology (LBP) were assessed in 88 PD patients based on detection of LBP by alpha-synuclein IHC. MMSE scores from the last neurological examination prior to death were used to determine cognitive status and the degree of cognitive decline. Four subgroups of MMSE scores ranging from non-significantly impaired to severely impaired cognition were analyzed. Each of the 88 cases could be assigned to one of the PD stages 3-6, and MMSE scores correlated significantly with the aforementioned stages. The median MMSE scores decreased from stages 3-6.

STAGES 3 TO 6 OF α-SYNUCLEIN PATHOLOGICAL CHANGES IN PD



Stage of Parkinson's disease neuropathology and cognitive status of individual patients

Autopsy series (N=88)



Cognitive Status

Kruskal-Wallis H-test: $H_{corr} = 15.79$; $p < 0.005$

trend test: $H_{lin} = 6.16$; $p < 0.025$

Brain Pathology ISSN 1015-6305

RESEARCH ARTICLE

Empiric Refinement of the Pathologic Assessment of Lewy-Related Pathology in the Dementia Patient

James B. Leverenz, MD[1,2,5,7]; Ronald Hamilton, MD[10]; Debby W. Tsuang, MD, MSc[1,7]; Aimee Schantz, MS[6]; Darcy Vavrek, ND, MSc[1,7]; Eric B. Larson, MD, MPH[4,8]; Walter A. Kukull, PhD[3]; Oscar Lopez, MD[9]; Douglas Galasko, MD[11]; Eliezer Masliah, MD[12]; Jeffrey Kaye, MD[13]; Randall Woltjer, MD, PhD[14]; Christopher Clark, MD[15]; John Q. Trojanowski, MD, PhD[16]; and Thomas J. Montine, MD, PhD[6,13]

[1] Departments of Veterans Affairs Northwest Network Mental Illness and [2] Parkinson's Disease Research, Education and Clinical Centers, Departments of [3] Epidemiology, [4] Medicine, [5] Neurology, [6] Pathology and [7] Psychiatry and Behavioral Sciences, University of Washington, [8] Group Health Cooperative, Seattle, Wash.
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Departments of [13] Neurology and [14] Pathology, Oregon Health & Sciences University, Portland, Ore.
Departments of [15] Neurology and [16] Pathology, University of Pennsylvania, Philadelphia, Pa.

Keywords
Lewy bodies; dementia; α-synuclein.

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doi:10.1111/j.1750-3639.2007.00117.x

Abstract

Lewy-related pathology (LRP) is a common pathologic finding at autopsy in dementia patients. Recently criteria for categorizing types of LRP in dementia patients were published, though these criteria have yet to be systematically applied to large dementia samples. We examined a large (n = 208) referral-based autopsy sample for LRP, and applied the published criteria for LRP categorization to these cases. We found almost half (49%) of LRP positive cases from this sample were not classifiable. However, modifying the published criteria by reducing the number of regions requiring examination, allowing more variability in LRP severity scores within specific brain regions, and adding an amygdala predominant category permitted classification of 97% of LRP positive cases from the referral-based sample. Application of the modified criteria to an unrelated community-based autopsy sample (n = 226) allowed classification of 96% of LRP positive cases. Modest modifications in the published criteria permit a significantly greater number of dementia cases with LRP to be classified. In addition, this modification allows for more limited sampling of brain regions for classification of LRP. We propose that these modified criteria for the categorization of LRP be utilized in patients with a history of dementia.

Cases evaluated from the referral-based Lewy body Associated Dementia Research Study (LADRS) sample and the community-based Alzheimer's Disease Patient Registry (ADPR) sample.

	TABLE OF LADRS & ADPR CASES		
Autopsies (n)		LADRS	ADPR
	Available cases with dementia diagnosis[1]	324	260
	& with sufficient tissue sampling	208	226
	& with LRP in any region	125	126
	& with LRP in amygdala, SN, or medulla	125	126
Age[2]	at onset (mean ± SD)	68 ± 9	76 ± 6
	at death (mean ± SD)	78 ± 8	84 ± 6
M:F (n)[2]		68:57	52:74
CERAD Neuritic Plaque Score (n)[2]	None	4	3
	Sparse	2	9
	Intermediate	16	20
	Frequent	103	94
Braak Stage (n)[2]	0	0	0
	I or II	10	23
	III or IV	38	36
	V or VI	77	67

[1]Probable or possible AD, DLB, or dementia of type unknown (LADRS) or DSM-III R criteria for any dementia (ADPR). [2]Age, gender, plaque score, and Braak stage refer to those autopsies that had any LPR.
Abbreviations: Alzheimer's disease (AD), Dementia with Lewy Bodies (DLB), Lewy-related pathology (LRP), Consortium to Establish a Registry for AD (CERAD).

Table 2. LRP categorization in LRP positive LADRS cases using all nine regions recommended by the published criteria[1] or using a subset of five regions.

Lewy body type pathology	Nine regions assessed[1] N (%)	Five regions assessed[2] N (%)
Brainstem-predominant	**0 (0%)**	**1 (1%)**
Limbic (transitional)	**3 (2%)**	**10 (8%)**
Diffuse neocortical	**61 (49%)**	**67 (54%)**
Unclassifiable	**61 (49%)**	**47 (38%)**

[1] reference 16
[2] medulla, SN, amygdala, cingulate gyrus, frontal cortex

Proposed modified criteria for categorization of Lewy-related pathology (LRP) in patients with dementia.

Results from two autopsy series

Predominant region	LRP severity scoring with proposed criteria				Results	
	SN or medulla	Amyg-dala	Cingulate gyrus	Frontal cortex	LADRS n (%)	ADPR n (%)
Brainstem	1+ in either	0–2	0–1	0	5 (*4*)	20 (*16*)
Amygdala	0–1 in both	1+	0–1	0	23 (*18*)	24 (*19*)
Limbic	1+ in either	2+	1–3	0–1	26 (*21*)	22 (*18*)
Neocortical	1+ in either	2+	2+	2+	67 (*54*)	55 (*44*)
Mixed	Cases not classifiable by modified criteria				4 (*3*)	5 (*4*)

LADRS = Lewy Body-Associated Dementia Research Study; ADPR = Alzheimer's Disease Patient Registry

Leverenz et al, Brain Pathol 2008

J Neuropathol Exp Neurol

Vol. 67, No. 7
July 2008
pp. 649–656

ORIGINAL ARTICLE

Validation of the Neuropathologic Criteria of the Third Consortium for Dementia With Lewy Bodies for Prospectively Diagnosed Cases

Hiroshige Fujishiro, MD, PhD, Tanis J. Ferman, PhD, Bradley F. Boeve, MD, Glenn E. Smith, PhD, Neill R. Graff-Radford, MBBCh, FRCP, Ryan J. Uitti, MD, Zbigniew K. Wszolek, MD, David S. Knopman, MD, Ronald C. Petersen, MD, Joseph E. Parisi, MD, and Dennis W. Dickson, MD

Clinico-pathological study of prospectively follow patients:
43 probable DLB, 9 possible DLB, 24 probable AD

Prospective cohort study

95% have high or intermediate likelihood DLB and most have diffuse cortical LBs.

Number of clinically probable DLB cases per category

	Low AD	Intermediate AD	High AD
Brainstem LBs	0	0	0
Transitional LBs	2	2	2
Diffuse LBs	6	20	10

High likelihood DLB
Intermediate likelihood DLB
Low likelihood DLB

Possible changes in CDLB neuropathologic criteria based upon prospective clinically probable DLB & AD

Ratio: clinically probable DLB / total with this pathologic profile

	Braak NFT 0-II	Braak NFT III-IV	Braak NFT V	Braak NFT VI
No LBs	0	0/9	0/3	1/7
Amygdala LBs	0	0	0	0/2
Brainstem LBs	0	0	0	0/1
Transitional LBs	2/2	2/2	0/1	2/4
Diffuse LBS	6/6	20/21	9/10	1/5

High likelihood DLB

Intermediate likelihood DLB

Low likelihood DLB

Fujishiro et al. J Neuropathol Exp Neurol 67:649-56, 2008.

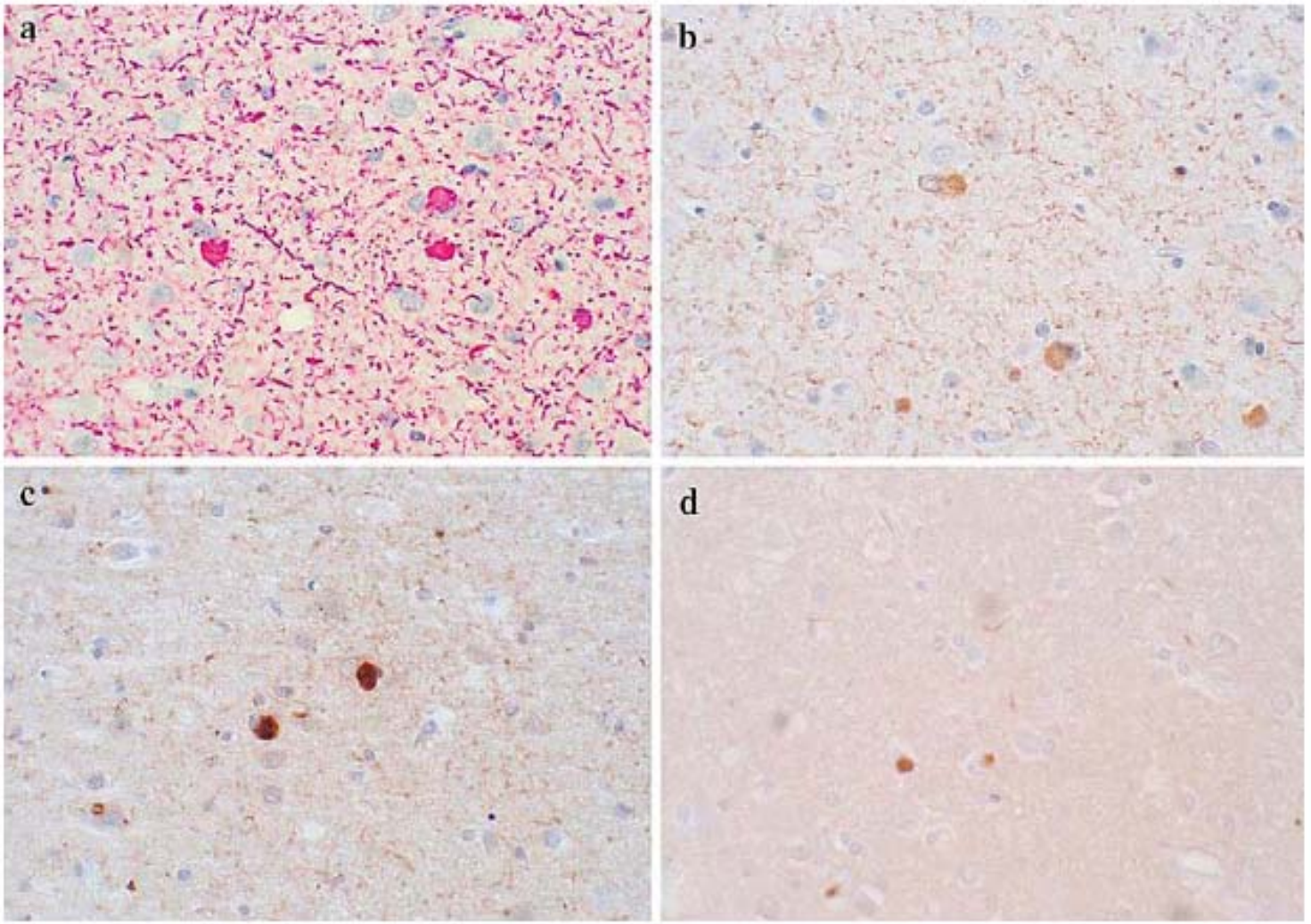
- **Evaluation of alpha-synuclein immunohistochemical methods used by invited experts. Acta Neuropathol. 2008; 116:277-88.**

  - **Beach TG, White CL, Hamilton RL, Duda JE, Iwatsubo T, Dickson DW, Leverenz JB, Roncaroli F, Buttini M, Hladeik C, Sue LI, Noorigian JN Adler CH**

  - **The use of alpha-synuclein immunohistochemistry has altered our concepts of the cellular pathology, anatomical distribution and prevalence of LB disorders, but use of different methods between laboratories has led to inconsistent results. Eight different IHC methods for demonstrating alpha-synuclein pathology, developed in eight separate expert laboratories, were evaluated for detecting Lb pathology. Identical test sets of formalin-fixed, paraffin-embedded sections from subjects with/without LB disorders were stained and graded. The methods did not differ significantly in terms of LB counts, but varied considerably in their ability to reveal neuropil pathology. One method was superior for revealing these neuropil elements and the critical factor contributing to its high sensitivity was the use of proteinase K for epitope retrieval. Some methods, however, achieved relatively high sensitivities with optimized formic acid protocols combined with a hydrolytic step. One method was developed that allows high sensitivity with commercially available reagents.**

Beach et al., Acta Neuropathol. 2008; 116:277-88.

Figure 3



What next? Collaborations Between NIA ADCs & NINDS Morris K. Udall Parkinson's Disease Research Centers May Yield Insights Into Mechanisms Underlying PDD/DLB

Now there 14 centers across the US (12 are at institutions with an ADC):

- Harvard U, Brigham and Women's Hospital, Boston, MA
- Columbia U, NYC
- Duke U, Durham, NC
- Harvard U, /McLean Hospital, Belmont, MA
- Johns Hopkins U, Baltimore, MD
- Harvard U/MIT Massachusetts General Hospital, Boston, MA
- Mayo Clinic, Jacksonville, FL
- Northwestern University, Evanston, IL
- UCLA, Los Angeles, CA
- U of Kentucky Medical Center, Lexington, KY
- U of Virginia, Charlottesville, VA
- U of Pittsburgh, Pittsburgh, PA
- U of Rochester – Parkinson's Disease Data Organizing Center, Rochester, NY
- University of Pennsylvania, Philadelphia, PA

The new Penn Udall Center addresses unresolved questions about the pathobiology and underlying mechanisms of dementia in PD

Focus of the Penn Udall Research Center:

- Elucidate mechanisms of cognitive impairments and brain degeneration in patients with Parkinson's disease (PD) and dementia (PDD) in patient oriented studies and studies of in vivo model systems.

TDP-43 Pathology Occurs In Synucleinopathies

DLB+AD = 25/80 (31%); PD = 5/69 (7%); PDD = 4/21 (19%);controls = 1/33 (3%); DLB 0/10 (0%)

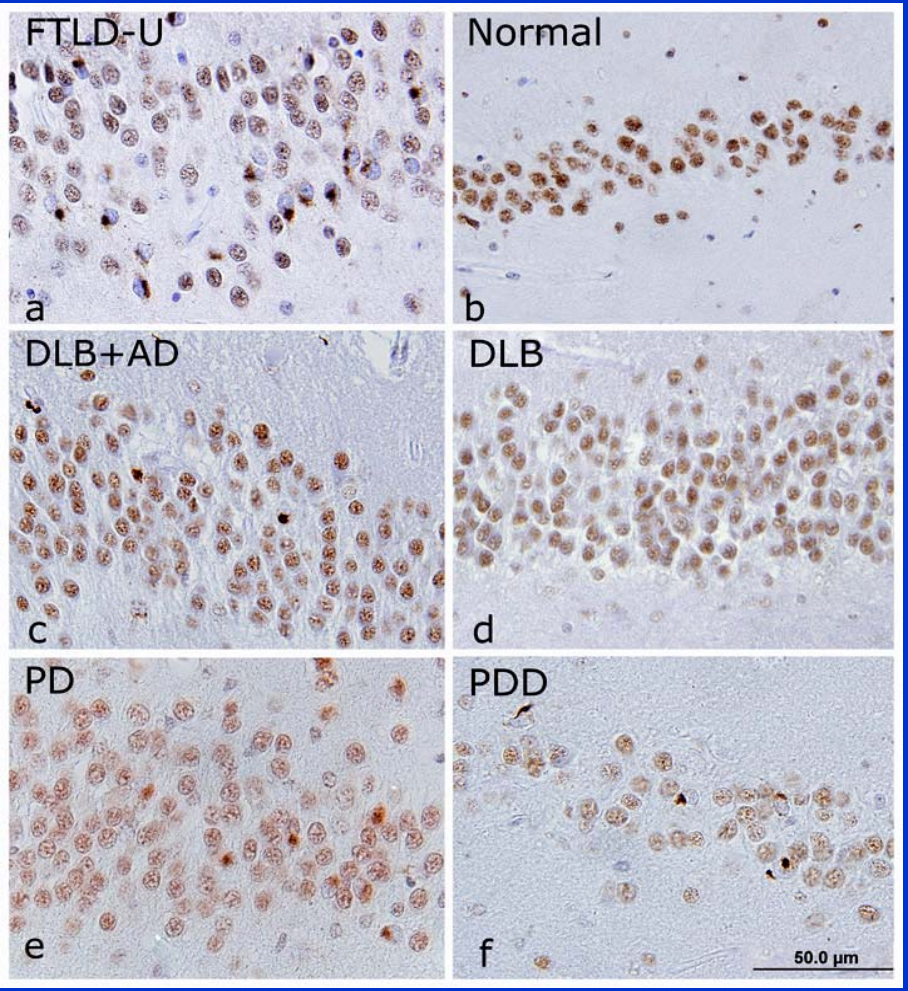
Nakashima-Yasuda H, Uryu K, Robinson J, Xie SX, Hurtig H, Duda J, Leverenz JB, Lopez O, Hamilton R, Tsuang DW, Galasko D, Masliah E, Kaye J, Woltjer R, Clark CM, Montine TJ, Lee VM –Y, Trojanowski, J.Q. Co-morbidity of TDP-43 Proteinopathy in Lewy body diseases. Acta Neuropath, 114:221-229, 2007.

Neumann M, Sampathu DM, Kwong LK, Traux A, Miscenyi M, Chou TT, Bruce J, Schuck T, Grossman M, Clark C, McKluskey L, Miller BL, Masliah E, Mackenzie IR, Feldman H, Feiden W, Kretzschmar HA, Trojanowski JQ, Lee VM-Y. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science, 314:130-133, 2006.

100%

31%

7%

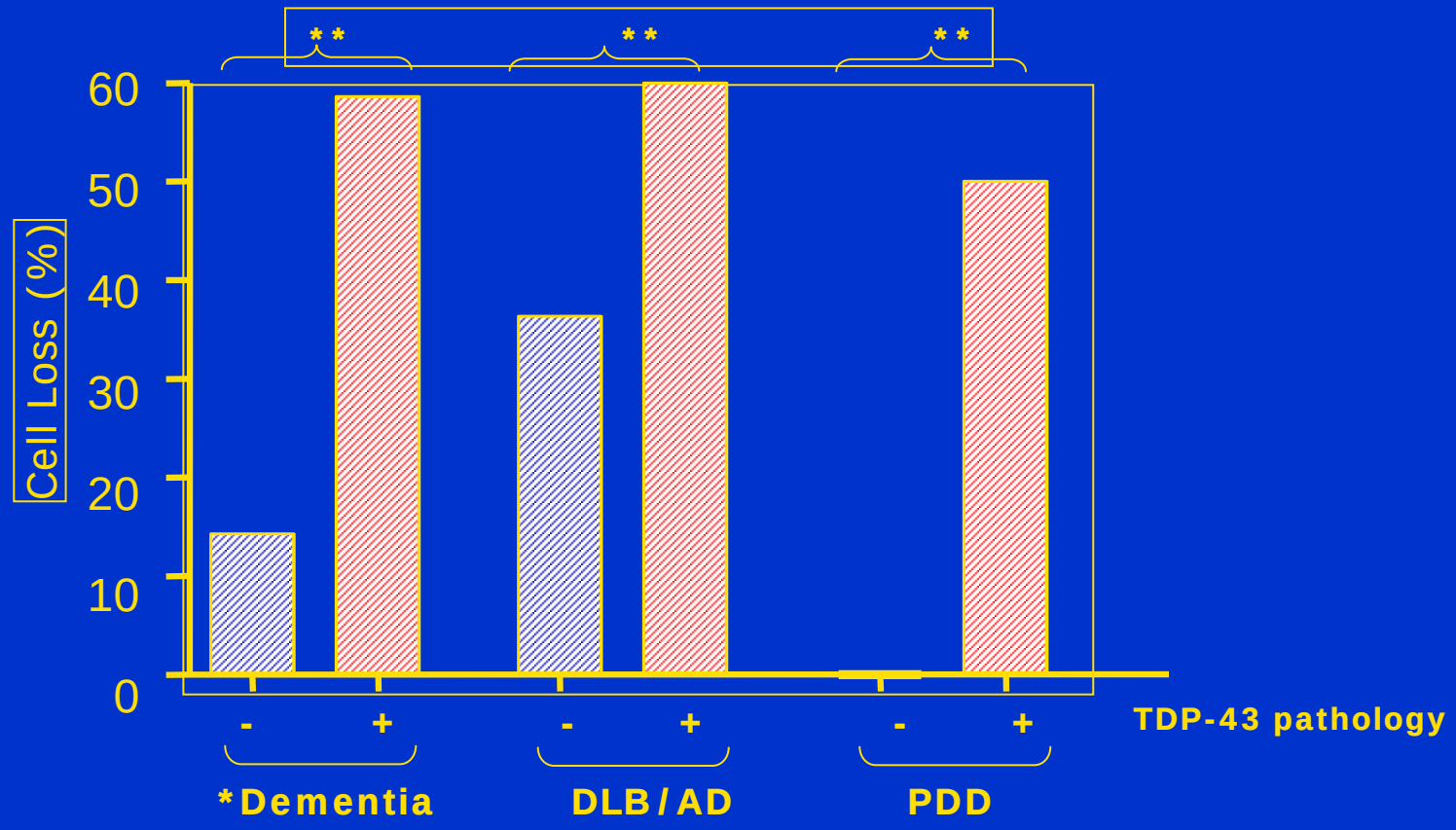


0%

0%

19%

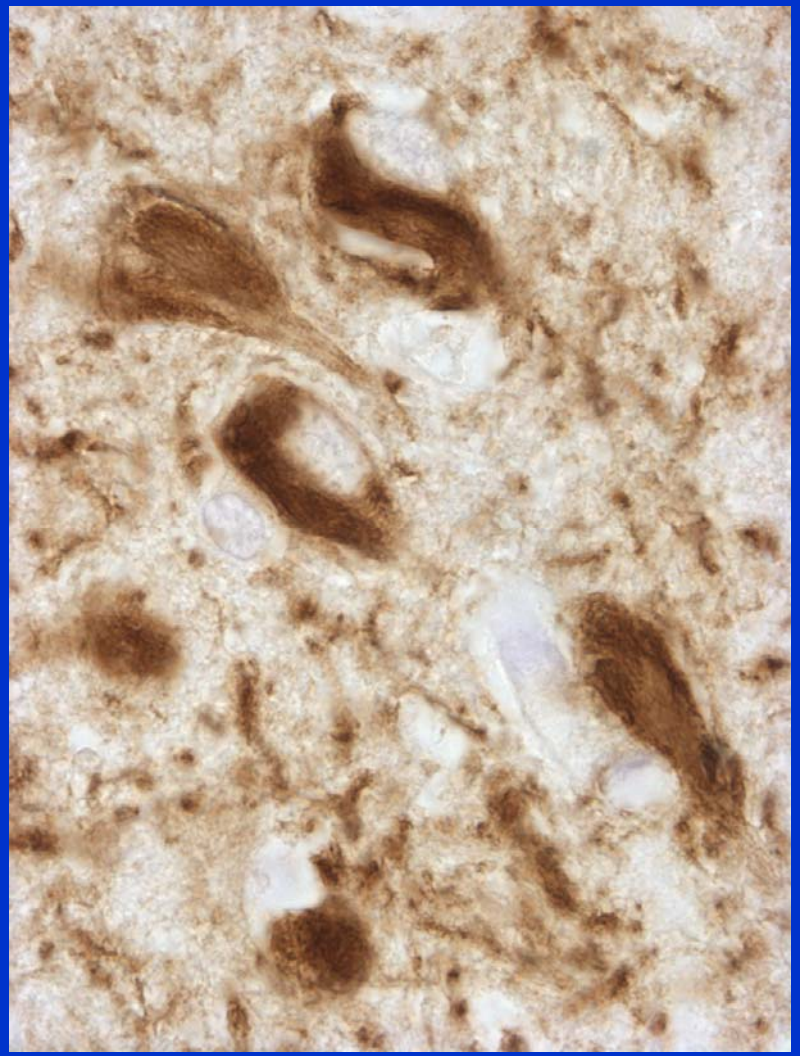
Core C: A subset of TDP-43 positive cases show significant CA1/subiculum neuron loss



*Dementia represents all patients from DLB+AD, DLB, PDD

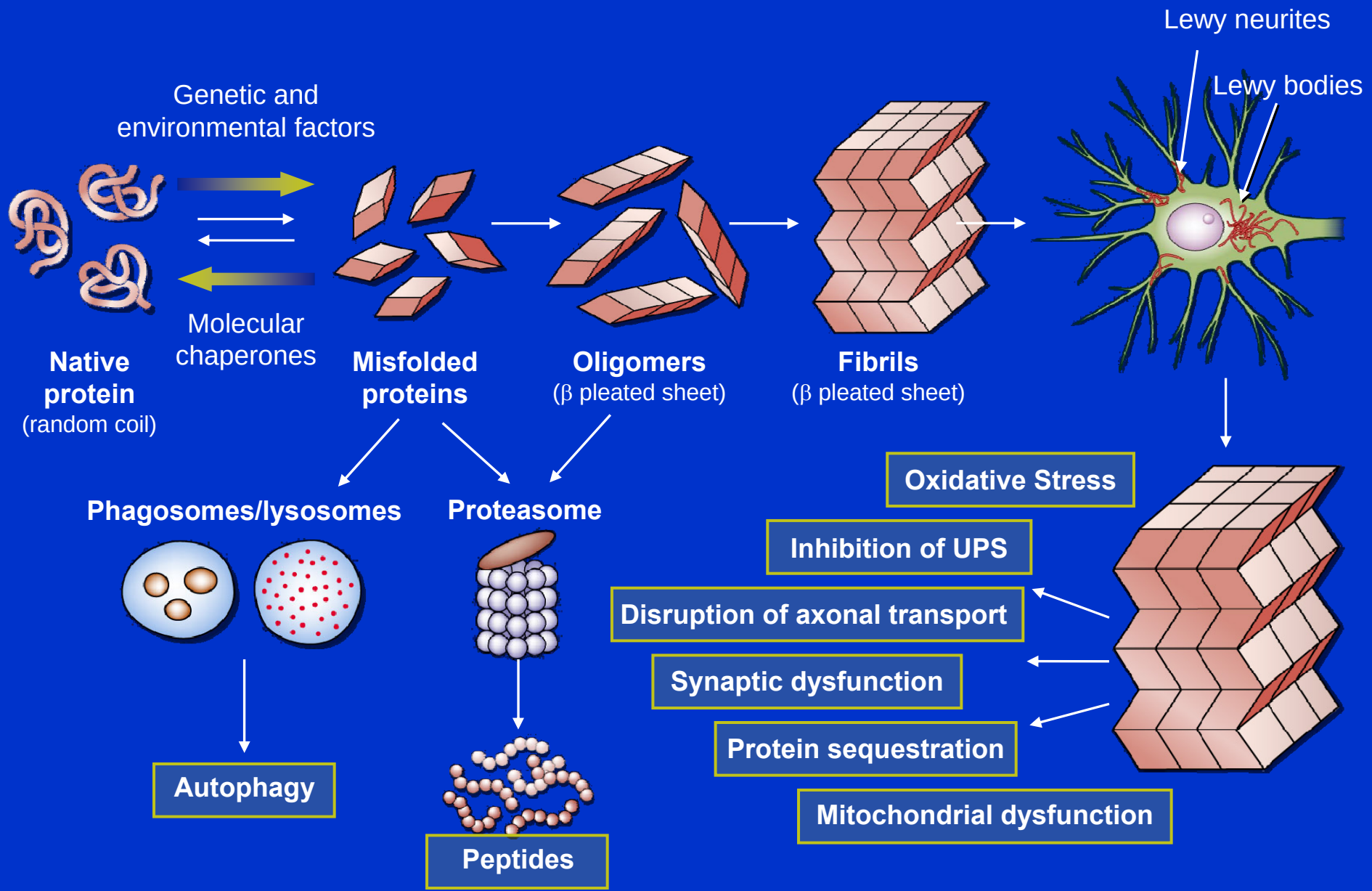
** significant differences ($p < 0.05$)

Lessons From AD & Tau Stained Tangles & Neurites

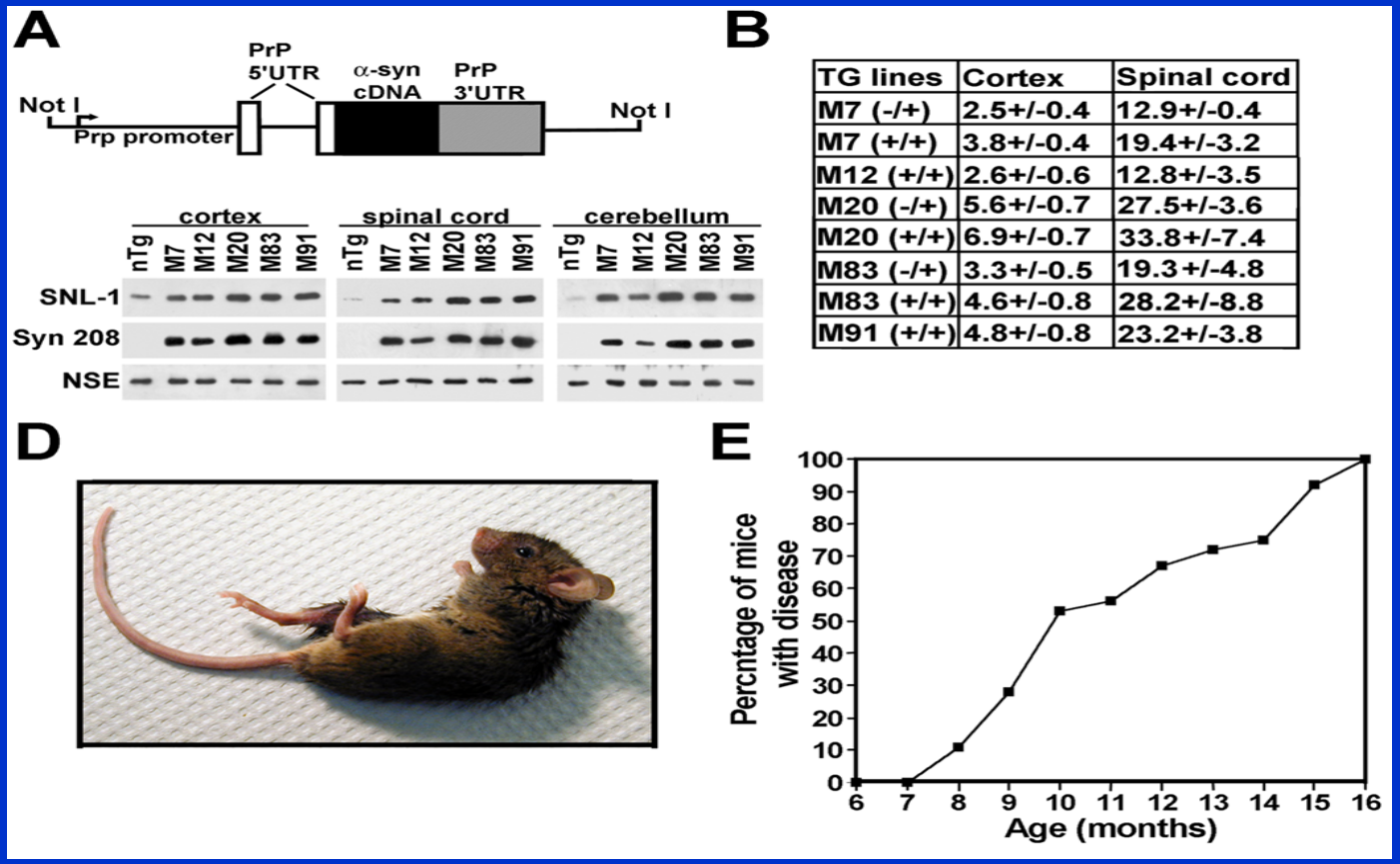


- ~95% of tau pathology is in dystrophic neurites (Mitchell TW, Nissanov J, Han LY, Mufson EJ, Schneider JA, Cochran EJ, Bennett DA, Lee VM-Y, Trojanowski JQ, Arnold SE. Novel method to quantify neuropil threads in brains from elders with and without cognitive impairment. J Histochem Cytochem, 48:1627-1638, 2000)
- Alpha-synuclein neuritic pathology may explain behavioral impairments in PDD/DLB but if they are eliminated with disease progression they may be difficult to correlate with these impairments

Mechanisms of Alpha-synuclein Mediated Neurodegeneration In Parkinson's Disease



There is a need for α-Synuclein Tg Mice with cognitive impairment and no motor impairments to elucidate mechanisms of dementia due to LBs and for drug discovery research



Giasson BI, Duda JE, Quinn SM, Zhang B, Trojanowski JQ, Lee VM-Y. Neuronal alpha-synucleinopathy with severe movement disorder in mice expressing A53T human alpha-synuclein. Neuron, 34:521-533, 2002.

Transgenic mice overexpressing tyrosine-to-cysteine mutant human alpha-synuclein: a progressive neurodegenerative model of diffuse Lewy body disease.

Zhou W, Milder JB, Freed CR

This group showed that tyrosine-to-cysteine mutation Y39C enhanced alpha-synuclein (AS) fibril formation and neurotoxicity. Here, they generated Tg mice expressing Y39C mutant human AS gene controlled by the mouse Thy1 promoter. Mutant human AS was 150% overexpressed and at 9-12 months, Tg mice began to display motor dysfunction in rotarod testing. At 21-24 months, AS aggregates were accompanied by severe behavioral deficits. At this age, Tg developed Lewy body-like AS and ubiquitin-positive inclusions. In summary, Y39C human AS Tg mice show age-dependent, progressive neuronal degeneration with motor and cognitive deficits similar to diffuse Lewy body disease.

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But, More Rapid Progress Is Needed Now! To Put Things in Perspective……..

- The US will spend $1 Trillion on banking/mortgage crisis caused by lacks regulation.
- The US spends $53 Billion/year on anti-aging balms, salves, lotions, etc. with no proven efficacy.
- The US spends $2.6 Billion/year on Viagra and Cialis and probably far more on breast implants.
- The US spends $2 Billion/year on popcorn.
- French President Sarkozy recently unveiled a plan to spend $480 Million per year – or $558 per person – for 5 years to fight AD which afflicts 860,000 people in France.
- And in the US, the NIH spends only $644 Million/year – or $129 per person - for research on AD which afflicts 5,000,000 US citizens.
- We can do more to solve the epidemic of AD, PD, DLB, FTLD, etc. which will bankrupt our economy by 2050 if not earlier.

PENN Neurodegenerative Disease Research
- Solving the Puzzle!