



Published in final edited form as:

*Acta Neuropathol.* 2014 December ; 128(6): 755–766. doi:10.1007/s00401-014-1349-0.

## Primary age-related tauopathy (PART): a common pathology associated with human aging

John F. Crary<sup>1,\*</sup>, John Q. Trojanowski<sup>2</sup>, Julie A. Schneider<sup>3</sup>, Jose F. Abisambra<sup>4</sup>, Erin L. Abner<sup>5</sup>, Irina Alafuzoff<sup>6</sup>, Steven E. Arnold<sup>7</sup>, Johannes Attems<sup>8</sup>, Thomas G. Beach<sup>9</sup>, Eileen H. Bigio<sup>10</sup>, Nigel J. Cairns<sup>11</sup>, Dennis W. Dickson<sup>12</sup>, Marla Gearing<sup>13</sup>, Lea T. Grinberg<sup>14</sup>, Patrick R. Hof<sup>15</sup>, Bradley T. Hyman<sup>16</sup>, Kurt Jellinger<sup>17</sup>, Gregory A. Jicha<sup>18</sup>, Gabor G. Kovacs<sup>19</sup>, David S. Knopman<sup>20</sup>, Julia Kofler<sup>21</sup>, Walter A. Kukull<sup>22</sup>, Ian R. Mackenzie<sup>23</sup>, Eliezer Masliah<sup>24</sup>, Ann McKee<sup>25</sup>, Thomas J. Montine<sup>26</sup>, Melissa E. Murray<sup>27</sup>, Janna H. Neltner<sup>28</sup>, Ismael Santa-Maria<sup>29</sup>, William W. Seeley<sup>30</sup>, Alberto Serrano-Pozo<sup>31</sup>, Michael L. Shelanski<sup>32</sup>, Thor Stein<sup>33</sup>, Masaki Takao<sup>34</sup>, Dietmar R. Thal<sup>35</sup>, Jonathan B. Toledo<sup>36</sup>, Juan C. Troncoso<sup>37</sup>, Jean Paul Vonsattel<sup>38</sup>, Charles L. White 3rd<sup>39</sup>, Thomas Wisniewski<sup>40</sup>, Randall L. Woltjer<sup>41</sup>, Masahito Yamada<sup>42</sup>, and Peter T. Nelson<sup>43,\*</sup>

<sup>1</sup>Department of Pathology & Cell Biology and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, 10032 USA

<sup>2</sup>Department of Pathology, Division of Neuropathology, University of Pennsylvania, Philadelphia PA 19104 USA

<sup>3</sup>Departments of Pathology (Neuropathology) and Neurological Sciences, Rush University Medical Center, Chicago IL 60612, USA

<sup>4</sup>Department of Physiology and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, 40536, USA

<sup>5</sup>Department of Public Health and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, 40536, USA

<sup>6</sup>Department of Immunology, Genetics and Pathology, Uppsala University 751 85 Uppsala, Sweden

<sup>7</sup>Departments of Psychiatry and Neurology, University of Pennsylvania, Philadelphia PA 19104, USA

<sup>8</sup>Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

<sup>9</sup>Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, AZ 85351, USA

<sup>10</sup>Department of Pathology (Neuropathology), Northwestern Cognitive Neurology and Alzheimer Disease Center, Northwestern University Feinberg School of Medicine, Chicago, IL, 60611, USA

<sup>11</sup>Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO, 63110, USA

---

\*-Co-corresponding authors.

<sup>12</sup>Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL, 32224, USA

<sup>13</sup>Department of Pathology and Laboratory Medicine (Neuropathology) Emory University School of Medicine, Atlanta, GA 30322, USA

<sup>14</sup>Departments of Neurology and Pathology, UC San Francisco, CA 94110, USA, and Department of Pathology, University of Sao Paulo, Brazil

<sup>15</sup>Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

<sup>16</sup>Department of Neurology, Harvard Medical School and Massachusetts General Hospital, Charlestown, MA 02129, USA

<sup>17</sup>Institute of Clinical Neurobiology A-1070 Vienna Austria

<sup>18</sup>Department of Neurology and the Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA

<sup>19</sup>Institute of Neurology, Medical University Vienna, A-1090 Vienna, Austria

<sup>20</sup>Department of Neurology, Mayo Clinic, Rochester MN 55905, USA

<sup>21</sup>Department of Pathology (Neuropathology), University of Pittsburgh Medical Center, Pittsburgh PA 15213, USA

<sup>22</sup>Department of Epidemiology, University of Washington, Seattle, WA 98104, USA

<sup>23</sup>Department of Pathology, University of British Columbia, 855 West 12th Avenue, Vancouver, British Columbia V5Z 1M9, Canada

<sup>24</sup>Departments of Neurosciences and Pathology, University of California, San Diego, La Jolla, CA 92093, USA

<sup>25</sup>Department of Pathology (Neuropathology), Boston University, Boston MA 02118, USA

<sup>26</sup>Department of Pathology, University of Washington, Seattle, WA 98104, USA

<sup>27</sup>Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL, 32224, USA

<sup>28</sup>Department of Pathology, University of Kentucky, Lexington, KY, 40536, USA

<sup>29</sup>Department of Pathology & Cell Biology and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, 10032 USA

<sup>30</sup>Departments of Neurology and Pathology, University of California, San Francisco, CA 94143, USA

<sup>31</sup>Department of Neurology, University of Iowa Hospitals & Clinics, Iowa city, IA 52242, USA

<sup>32</sup>Department of Pathology & Cell Biology and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, 10032 USA

<sup>33</sup>Department of Pathology (Neuropathology), VA Medical Center & Boston University School of Medicine, Boston, MA 02118, USA

<sup>34</sup>Department of Neuropathology, Tokyo Metropolitan Geriatric Hospital, Tokyo, 173-0015, Japan

<sup>35</sup>Laboratory of Neuropathology, University of Ulm, D-89081 Ulm, Germany

<sup>36</sup>Department of Pathology, Division of Neuropathology, University of Pennsylvania, Philadelphia, PA 19104, USA

<sup>37</sup>Department of Pathology & Laboratory Medicine, Institute on Aging, Center for Neurodegenerative Disease Research, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA

<sup>38</sup>Department of Pathology & Cell Biology and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, 10032 USA

<sup>39</sup>Department of Pathology (Neuropathology), University of Texas Southwestern Medical School, Dallas, TX 75390, USA

<sup>40</sup>Departments of Neurology, Pathology and Psychiatry, New York University School of Medicine, New York, NY 10016, USA

<sup>41</sup>Department of Pathology L113, Oregon Health Sciences University, Portland, OR 97239, USA

<sup>42</sup>Departments of Neurology & Neurobiology of Aging, Kanazawa University Graduate School of Medical Sciences, Kanazawa 920-8640, Japan

<sup>43</sup>Department of Pathology (Neuropathology) and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, 40536, USA

## Abstract

We recommend a new term, “primary age-related tauopathy” (PART), to describe a pathology that is commonly observed in the brains of aged individuals. Many autopsy studies have reported brains with neurofibrillary tangles (NFT) that are indistinguishable from those of Alzheimer's disease (AD), in the absence of amyloid (A $\beta$ ) plaques. For these “NFT+/A $\beta$ -” brains, for which formal criteria for AD neuropathologic changes are not met, the NFT are mostly restricted to structures in the medial temporal lobe, basal forebrain, brainstem, and olfactory areas (bulb and cortex). Symptoms in persons with PART usually range from normal to amnesic cognitive changes, with only a minority exhibiting profound impairment. Because cognitive impairment is often mild, existing clinicopathologic designations, such as “tangle-only dementia” and “tangle-predominant senile dementia”, are imprecise and not appropriate for most subjects. PART is almost universally detectable at autopsy among elderly individuals, yet this pathological process cannot be specifically identified pre-mortem at the present time. Improved biomarkers and tau imaging may enable diagnosis of PART in clinical settings in the future. Indeed, recent studies have identified a common biomarker profile consisting of temporal lobe atrophy and tauopathy without evidence of A $\beta$  accumulation. For both researchers and clinicians, a revised nomenclature will raise awareness of this extremely common pathologic change while providing a conceptual foundation for future studies. Prior reports that have elucidated features of the pathologic entity we refer to as PART are discussed, and working neuropathological diagnostic criteria are proposed.

## Keywords

TSPD; TOD; Braak; Neuropathology; consensus

## Introduction

We propose a new term, “primary age-related tauopathy” (PART), to describe a pathologic continuum ranging from focally-distributed neurofibrillary tangles (NFT) observed in cognitively normal aged individuals, through the pathology observed in persons with dementing illnesses that have been referred to as “tangle-predominant senile dementia” (TPSD), “tangle-only dementia”, “preferential development of NFT without senile plaques”, and “senile dementia of the neurofibrillary tangle type” (SD-NFT), among other names. Here we explain the need for introducing this term, reviewing the relevant studies in the clinical and pathologic literature. We conclude with new proposed working guidelines for the neuropathological classification of subjects with PART.

The main reasons for proposing this new terminology are to provide a conceptual framework for studying PART, to facilitate communication among pathologists, clinicians, and researchers, and to draw attention to this entity, which is often overlooked. Another motivation, as with the recent National Institute on Aging-Alzheimer's Association diagnostic criteria for Alzheimer's disease (AD) [64, 102], is to “disentangle” pathologic classification from clinical diagnosis for a given patient. In the case of PART, the separation of clinical information from the pathological diagnosis is especially necessary, as the term “dementia”, as in “tangle-only dementia”, implies a multi-domain cognitive impairment with a profound decrease in the ability to perform activities of daily living, both of which are absent in the majority of persons with PART [65, 66, 107, 125, 142]. Practicing neuropathologists will benefit from the revised terminology because many are reluctant to apply the clinical term “dementia” to a pathologic diagnosis when dementia was not documented clinically or when knowledge of the clinical history is limited. Also, there have been recommendations to lessen the use of labels such as “dementia” and “senile” partly due to pejorative implications [139] and because the terms are considered to be imprecise [24].

Patients with mild-to-moderate AD-type neurofibrillary degeneration in the medial temporal lobe, but lacking A $\beta$  plaques, have been described in European, Japanese, North and South American cohorts [2, 3, 14, 51, 52, 58, 69, 72, 79, 81, 82, 126, 142, 147, 149, 151]. NFT are practically universal in older persons' brains [22, 30, 108, 132], and are also observed in a more limited distribution in many younger individuals [30, 32, 42]. Cases at the more severe end of the pathologic spectrum (Braak stages III-IV) lacking A $\beta$  plaques were observed in 2-10% of brains in large autopsy series that included community-based sampling [89, 94, 107, 125]. These pathologic changes were more prevalent in a few autopsy series drawing from memory disorder clinics [128, 129]. The theoretical and practical implications of these findings remain controversial [9, 15, 29, 107]. Differences in nomenclature, study design, including cohort recruitment methods, variable sensitivity in detecting pathologic changes, and conceptual interpretations have fueled uncertainty. A more specific and ultimately useful term for neuropathologic diagnoses is required, drawing from an expanding research corpus.

## Clinical features

Published data indicate that severe PART can be associated with memory loss in aging [66, 107]. However, the high prevalence of comorbid brain diseases in elderly individuals make clinicopathological correlations challenging in this population [76, 80, 108, 109, 117, 125], and the entire clinical-pathological spectrum of PART has yet to be systematically characterized. Most relevant prior studies have either focused on the most severe cases with TPSD or have investigated the associations between medial temporal lobe or brainstem tau pathology related to AD [5, 6, 11, 12, 19, 48, 49, 55, 56, 79, 133, 134, 144]. A subset of patients with PART (previously referred to as SD-NFT, TPSD, etc.) display marked clinical impairment in the absence of any other recognizable substrate for dementia [14, 21, 39, 60, 66, 72, 99, 142]. The average age of death is generally higher for these patients than those with AD pathology [37, 79, 107]. Whereas cognitively impaired subjects with PART often carry a clinical diagnosis of possible or probable AD [115], the coexistence of PART and AD in aging is an inevitable complicating factor [153]. A recent analysis of the National Alzheimer's Coordinating Center (NACC) autopsy database [16] found that ~14% of subjects clinically diagnosed with mild-to-moderate probable AD had no or sparse neuritic plaques [128]. Here we provide additional data from the NACC database that underscore characteristics of PART: the pathology is common and Braak stage "0" is relatively unusual in older individuals; there is an absence of an association between PART and *APOE* genotype; and, the more severe PART pathology is associated with a higher age of death and lower scores on cognitive tests (Table 1).

The application of imaging and CSF biomarkers has given a novel perspective on the prevalence and associated clinical features of neurodegenerative processes that undoubtedly include PART. Biomarker-based clinical research supports the claim, initially made based on the autopsy studies of putatively cognitively intact people [36, 88] and of persons with mild cognitive impairment (MCI) [83, 93, 113], that tauopathy in the absence of A $\beta$ -type amyloidosis is common. Reported biomarkers include CSF A $\beta$ (1–42) or positron emission tomography (PET) imaging for A $\beta$  pathology and CSF tau or phospho-tau, structural MRI, and PET (including fluorodeoxyglucose PET) for neurodegeneration. The abnormalities of the neurodegeneration biomarkers have generally been defined relative to levels seen in AD. It appears that roughly a quarter of cognitively normal elderly individuals have abnormal neurodegeneration biomarkers in the absence of abnormal brain amyloidosis [86, 87, 143, 145]. This clinical cohort's status has been termed "suspected non-Alzheimer pathophysiology" (SNAP) to distinguish it from persons with A $\beta$ -type amyloidosis [75, 87]. In persons with amnesic MCI, remarkably, about the same proportion of SNAP cases is found [112, 114]. Although autopsy experience is limited so far in cases with biomarker-defined SNAP, the prominent involvement of the medial temporal lobe in reported SNAP cases suggests that PART-type pathologic changes may underlie at least a subset of persons with the SNAP biomarker profile in the broader population. A more specific diagnostic classification enables terminology that parallels the recently adopted nomenclature for AD, with a biomarker-positive presymptomatic stage and a symptomatic stage where both biomarkers and clinical phenotype are present [74]. There are ongoing and potential future clinical trials that target either A $\beta$ - or tau-related pathogenic mechanisms. PART and AD

may well respond differently to those therapeutic interventions [23], which underscores the importance of harmonizing clinical decisions with data that were previously obtained in high-quality autopsy series.

## Neuropathologic changes

Gross examination of the brain of subjects with PART may show no obvious differences from those deemed “normal for age”. In other individuals with PART, there may be mild to moderate diffuse atrophy of the neocortex, and medial temporal lobe atrophy may be pronounced in persons with dementia (Fig. 1) [110, 122]. Immunohistochemistry reveals telencephalic NFT emerging most consistently in the medial temporal lobe, particularly the hippocampal formation and adjacent regions (Fig. 1b-d). Abnormal tau-immunoreactive inclusions are most prominent in neurons (Fig. 2). Subcortical NFT can be observed even in teenage years in the locus coeruleus [9, 30, 41, 42, 131], so this process is not necessarily limited to individuals of advanced age. NFT may also be seen in the amygdala, nucleus basalis of Meynert, nucleus accumbens, hypothalamus, thalamus, olfactory system (bulb and cortex), dorsal raphé nucleus, and medulla oblongata [7, 8, 53, 107, 141]. While NFT at all stages of evolution can be seen in PART, individuals with cognitive impairment often have abundant extracellular, so-called “ghost”, tangles [110, 122].

The only existing grading system that applies to PART is Braak neurofibrillary staging [26, 28, 32]. The pathologic continuum of PART includes pretangle or cortical pretangle (up to Stage Ib), entorhinal (I-II), or limbic (III-IV) Braak stages [25, 27, 28]. Theoretically, given experimental findings that tau pathology might be propagated trans-synaptically [34, 35, 38, 46, 47, 57, 91], it is notable that PART-type pathology generally does not progress to the isocortical Braak stages (i.e., V-VI), remaining relatively restricted neuroanatomically even in the oldest-old subjects with limited extension beyond the temporal neocortex to other neocortical regions [73, 148].

The neurofibrillary changes in PART resemble those in AD brains (Fig. 3). Immunohistochemical and biochemical studies have found that NFT in PART, as in AD, contain accumulation of both 3-repeat (3R) and 4-repeat (4R) tau isoforms (Fig. 3a-c) [70, 79, 122, 130]. In AD, electron microscopy has revealed predominantly paired helical filaments (PHF), which are considered a disease hallmark [85, 119, 146]. The tau fibrils in brains with PART pathology also display a typical PHF morphology (Fig. 3d) [67, 72, 122]. These observations are not unique to PART and the pathologic overlap requires further consideration.

## Differentiating PART from other neurodegenerative diseases

A synthesis of previously reported observations exposes an apparent paradox: NFT are one of two defining pathological hallmarks of AD, the other is the A $\beta$  plaque. However, AD-type NFT are almost ubiquitously observed in older persons' brains, even in the absence of A $\beta$  plaques or features of other classifiable tauopathies. Because there are pathologic features in common with AD, some investigators may consider PART a subset of AD or an early stage of AD. Indeed, NFT in the brainstem of younger adults show features in common with the pathological processes of AD [31]. Yet the pathologic overlap may exist despite

clinically and pathologically salient features that are different. In comparison to AD, current data suggest that PART typically has a far more limited impact on cognition and develops in persons without A $\beta$  plaques or biochemical evidence of elevated A $\beta$  [122]. A diagnosis of AD neuropathologic changes requires at least a minimum threshold level of A $\beta$  deposition [64, 102]. This criterion is supported by extensive genetic and clinicopathologic observations [108]. There is an accumulating body of evidence suggesting that medial temporal lobe NFT are involved in at least two common processes, an AD-related process, and a non-AD aging-related process [103, 107]. Supportive evidence comes from genetic studies that show an association between PART and the microtubule-associated protein tau gene (*MAPT*) H1 haplotype [76, 122], whereas there is an absence of an association between PART and the strongest risk factor for AD, the *APOE*  $\epsilon$ 4 allele [13, 67, 70, 122, 150, 151].

PART cases have likely been reported in autopsy series of SD-NFT, TPSD, tangle-predominant dementia or tangle-only dementia [10, 14, 17, 43, 79, 98, 106, 110, 122]. These proposed pathologic entities may have included some cases that would now be considered frontotemporal lobar degeneration (FTLD). TPSD has previously been grouped among FTLD subtypes [33] and there are presumably FTLD-tau subtypes that may overlap with the spectrum of PART even if the pathogenesis is distinct. For example, individuals with germ line *MAPT* R406W mutation may present with a temporal lobe predominant tauopathy with similar features to TPSD [63], but the presence of NFT in the globus pallidus, subthalamic nucleus, substantia nigra, and pons in such cases are reminiscent of PSP. The pattern of tau isoform accumulation associated with PART pathology can also be seen in other tauopathies, including amyotrophic lateral sclerosis/Parkinsonism dementia complex of Guam [61, 111, 123, 124], which, like AD, may also show  $\alpha$ -synuclein and TDP-43 pathology [50, 140]. By contrast, PSP and CBD display a predominance of 4-repeat tau isoforms, and Pick disease show predominantly 3-repeat tau isoforms [4, 44, 79, 90, 138, 152]. Also commonly seen in brains from individuals of advanced age are tau-immunoreactive argyrophilic grains. However, argyrophilic grain disease is a 4R tauopathy featuring CA2 pretangles and dentate granule cell involvement, all acetylated tau-negative, none of these features are seen in AD/PART [54, 71, 84, 107, 120, 136, 138].

## Future studies and unanswered questions

Additional studies are necessary to refine our understanding of PART in the complicated context of the aged human brain. Most fundamentally, the exact clinicopathologic spectrum of PART remains to be definitively characterized. Additional topical questions relate to the “boundary zone” between PART and other tauopathies, especially AD. The precise threshold of A $\beta$  deposition below which a diagnosis of definite PART is appropriate, and the relative importance of diffuse amyloid and neuritic plaques, require further study. Additionally, there is a growing appreciation, not yet incorporated into consensus-based guidelines, that the neuropathology of AD is heterogeneous [2, 18, 20, 59, 62, 76-78, 92, 104, 105, 118, 151]. It is possible that brains with hypothesized hippocampal “localized” [100, 101] or “limbic-predominant” [76, 104, 105, 151] AD subtypes are along a common continuum with PART [76, 79, 105]. The rationale for including extracortical tau pathology in PART is that the pathologies commonly coexist and that brainstem NFT, if they represent the same process, appear to occur even earlier in human aging [30-32, 53]. In this context, it

is also not known whether spinal cord tauopathy is related to PART [40]. More studies will be needed to determine whether there are distinct subtypes of extracortical tauopathy and how these changes relate to AD as well as PART. There are other conditions besides AD that overlap pathologically with PART. For example, it is notable that chronic traumatic encephalopathy generally presents pathologically as a non-A $\beta$  tauopathy with features that overlap pathologically with PART [95], and in the future markers may be developed to better discriminate between disorders in which NFT develop in similar brain areas. Tau-immunoreactive glial pathology is also frequently seen in advanced old age [1, 44, 65, 68, 89, 90, 127]. It is unknown whether the age-related glial tauopathy is associated with mechanisms that also cause PART pathology, but PART appears to be a predominantly neuronal pathology. To enable future studies aimed at addressing the extant unresolved questions, a working diagnostic guideline is required.

## Neuropathological criteria for PART

New criteria are proposed to classify patients with PART for research and potential future clinical purposes (Table 2). PART is defined by AD-type neurofibrillary changes without, or with few, A $\beta$  plaques as described below. PART can be designated as “Definite” or “Possible” depending on the presence of coexisting neuropathology and many cases will not be gradable due to comorbid pathology. Specifically, neurofibrillary changes may correspond to subcortical pretangle or cortical pretangle (up to Ib), entorhinal (I-II), or limbic (III-IV) Braak stages [25, 27, 28]. In keeping with the current guidelines for AD [64, 102], mild A $\beta$  plaques defined using the Thal grading system [116, 135, 137], consistent with low AD neuropathologic changes, preclude the diagnosis of “Definite” PART. Some pathologists may prefer the CERAD system for grading neuritic plaque density [96], but the method used must be indicated as it would alter the classification of some subjects. Possible wording for the pathologic diagnoses are provided (Table 2). If both early AD pathology and “Possible” PART pathology are observed, both may be reported diagnostically. The presence of few or moderate argyrophilic grains as assessed with established staging methods [45, 121] does not rule out PART. We emphasize that a pathologic diagnosis of PART does not necessarily indicate that a functional deficit was detected clinically. We also note that Braak stage IV pathology without A $\beta$  plaques is unusual and in these cases the possibility of a FTLT-tau condition should be considered.

## Summary

PART is a common brain pathology relevant to researchers, clinicians, and the broader public. Despite the high prevalence in published brain autopsy series, PART has been difficult to categorize because of the absence of a well-accepted nosology. We expect that the study of tau biomarkers will broaden the recognition of PART, and improve our understanding of a condition currently known mostly from neuropathologic studies. More studies are needed to better understand the pathogenesis of PART, its relation to other neurodegenerative disorders, and the full clinical spectrum of this common brain disease of aging.



## Acknowledgments

We are extremely grateful to the patients, clinicians, and fellow researchers that made this effort possible. We also acknowledge the following funding sources: the Society for Supporting Research in Experimental Neurology, Vienna, Austria, National Institutes of Health grants P50AG08702, R01 AG037212, P01AG07232, P30 AG028383, P50 AG005138, P50 AG016574, U01 AG006786, R01 AG041851, R01 AG011378, P30 AG028383, P50 AG016574, P01 AG003949, P30 AG012300, P50 AG005146, P50 AG005136, P50 AG025688, P50 AG005138, P01 AG002219, P50 AG005133, P50 AG005681, P01 AG003991, R01 AG038651, P30 AG019610, P30 AG013854, P30 AG036453, P30 AG010124, AG005131, AG184440, AG008051, Medical Research Council (MRC, G0400074), National Institute for Health Research (NIHR, R:CH/ML/0712), the Dunhill Medical Trust (R173/1110), Alzheimer's Research UK (ARUK), and the Alzheimer's Society (AS-PG-2013-011), Louis V. Gerstner, Jr., Foundation, Alzheimer's Association (NIRG-11-204450), FP7 EU Project Develage (No. 278486), Comprehensive brain research network, Grant-in-Aid for Scientific Research (C; 26430060), and Daiwa Health Science Foundation, BrightFocus Foundation, Alzheimer's Association NIRGD-12-242642, Alzheimer Forschung Initiative (AFI # 13803) (DRT); German Ministry for Research and Education (BMBF) FTLD-Net, Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation

## References cited

1. Ahmed Z, Bigio EH, Budka H, et al. Globular glial tauopathies (GGT): consensus recommendations. *Acta Neuropathol.* 2013; 126:537–544.10.1007/s00401-013-1171-0 [PubMed: 23995422]
2. Alafuzoff I. Alzheimer's disease-related lesions. *J Alzheimers Dis.* 2013; 33(Suppl 1):S173–179.10.3233/JAD-2012-129024 [PubMed: 22695621]
3. Andrade-Moraes CH, Oliveira-Pinto AV, Castro-Fonseca E, et al. Cell number changes in Alzheimer's disease relate to dementia, not to plaques and tangles. *Brain.* 2013; 136:3738–3752.10.1093/brain/awt273 [PubMed: 24136825]
4. Arai T, Ikeda K, Akiyama H, et al. Distinct isoforms of tau aggregated in neurons and glial cells in brains of patients with Pick's disease, corticobasal degeneration and progressive supranuclear palsy. *Acta Neuropathol.* 2001; 101:167–173. doi. [PubMed: 11271372]
5. Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cerebral Cortex.* 1991; 1:103–116. doi. [PubMed: 1822725]
6. Arriagada PV, Marzloff K, Hyman BT. Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease. *Neurology.* 1992; 42:1681–1688. doi. [PubMed: 1307688]
7. Attems J, Jellinger KA. Olfactory tau pathology in Alzheimer disease and mild cognitive impairment. *Clin Neuropathol.* 2006; 25:265–271. doi. [PubMed: 17140156]
8. Attems J, Lintner F, Jellinger KA. Olfactory involvement in aging and Alzheimer's disease: an autopsy study. *J Alzheimers Dis.* 2005; 7:149–157. discussion 173-180. doi. [PubMed: 15851853]
9. Attems J, Thal DR, Jellinger KA. The relationship between subcortical tau pathology and Alzheimer's disease. *Biochemical Society Trans.* 2012; 40:711–715.10.1042/BST20120034
10. Baborie A, Griffiths TD, Jaros E, et al. Frontotemporal dementia in elderly individuals. *Arch Neurol.* 2012; 69:1052–1060.10.1001/archneurol.2011.3323 [PubMed: 22529248]
11. Ball MJ. Topographic distribution of neurofibrillary tangles and granulovacuolar degeneration in hippocampal cortex of aging and demented patients. A quantitative study. *Acta Neuropathol.* 1978; 42:73–80. [PubMed: 654888]
12. Ball MJ, Nuttall K. Topography of neurofibrillary tangles and granulovacuoles in hippocampi of patients with Down's syndrome: quantitative comparison with normal ageing and Alzheimer's disease. *Neuropathol Appl Neurobiol.* 1981; 7:13–20. doi. [PubMed: 6453301]
13. Baner C, Egensperger R, Kosel S, Jellinger K, Graeber MB. Low prevalence of apolipoprotein E epsilon 4 allele in the neurofibrillary tangle predominant form of senile dementia. *Acta Neuropathol.* 1997; 94:403–409. doi. [PubMed: 9386771]
14. Baner C, Jellinger KA. Neurofibrillary tangle predominant form of senile dementia of Alzheimer type: a rare subtype in very old subjects. *Acta Neuropathol.* 1994; 88:565–570. doi. [PubMed: 7879604]

15. Bancher C, Paulus W, Paukner K, Jellinger K. Neuropathologic diagnosis of Alzheimer disease: consensus between practicing neuropathologists? *Alzheimer disease and Associated Disorders*. 1997; 11:207–219. doi. [PubMed: 9437438]
16. Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. *Alzheimer disease and associated disorders*. 2007; 21:249–258.10.1097/WAD.0b013e318142774e [PubMed: 17804958]
17. Berg L, McKeel DW Jr, Miller JP, et al. Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. *Arch Neurol*. 1998; 55:326–335. doi. [PubMed: 9520006]
18. Bondareff W, Mountjoy CQ, Roth M, et al. Age and histopathologic heterogeneity in Alzheimer's disease. Evidence for subtypes. *Archives of general psychiatry*. 1987; 44:412–417. doi. [PubMed: 2883954]
19. Bondareff W, Mountjoy CQ, Roth M, et al. Neuronal degeneration in locus ceruleus and cortical correlates of Alzheimer disease. *Alzheimer disease and associated disorders*. 1987; 1:256–262. doi. [PubMed: 3453748]
20. Bondareff W, Mountjoy CQ, Wischik CM, et al. Evidence of subtypes of Alzheimer's disease and implications for etiology. *Archives of general psychiatry*. 1993; 50:350–356. doi. [PubMed: 8489324]
21. Bouras C, Hof PR, Giannakopoulos P, Michel JP, Morrison JH. Regional distribution of neurofibrillary tangles and senile plaques in the cerebral cortex of elderly patients: a quantitative evaluation of a one-year autopsy population from a geriatric hospital. *Cerebral cortex*. 1994; 4:138–150. doi. [PubMed: 8038565]
22. Bouras C, Hof PR, Morrison JH. Neurofibrillary tangle densities in the hippocampal formation in a non-demented population define subgroups of patients with differential early pathologic changes. *Neurosci Lett*. 1993; 153:131–135. doi. [PubMed: 8327187]
23. Boutajangout A, Wisniewski T. Tau-Based Therapeutic Approaches for Alzheimer's Disease - A Mini-Review. *Gerontology*. 2014.10.1159/000358875
24. Bowler JV, Hachinski V. Vascular cognitive impairment: a new approach to vascular dementia. *Bailliere's Clinical Neurology*. 1995; 4:357–376. doi.
25. Braak H, Alafuzoff I, Arzberger T, Kretschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol*. 2006; 112:389–404.10.1007/s00401-006-0127-z [PubMed: 16906426]
26. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991; 82:239–259. doi. [PubMed: 1759558]
27. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging*. 1995; 16:271–278. discussion 278–284. doi. [PubMed: 7566337]
28. Braak H, Braak E, Bohl J. Staging of Alzheimer-related cortical destruction. *European Neurology*. 1993; 33:403–408. doi. [PubMed: 8307060]
29. Braak H, Del Tredici K. Alzheimer's disease: intraneuronal alterations precede insoluble amyloid-beta formation. *Neurobiol Aging*. 2004; 25:713–718. discussion 743–716. doi:10.1016/j.neurobiolaging.2003.12.015 S0197458004000831 [pii]. [PubMed: 15165692]
30. Braak H, Del Tredici K. The pathological process underlying Alzheimer's disease in individuals under thirty. *Acta Neuropathol*. 2011; 121:171–181.10.1007/s00401-010-0789-4 [PubMed: 21170538]
31. Braak H, Del Tredici K. Where, when, and in what form does sporadic Alzheimer's disease begin? *Current opinion in neurology*. 2012; 25:708–714.10.1097/WCO.0b013e3182835a3432 [PubMed: 23160422]
32. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *Journal of neuropathology and experimental neurology*. 2011; 70:960–969.10.1097/NEN.0b013e318232a379 [PubMed: 22002422]
33. Cairns NJ, Bigio EH, Mackenzie IR, et al. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta Neuropathol (Berl)*. 2007; 114:5–22. doi. [PubMed: 17579875]

34. Clavaguera F, Akatsu H, Fraser G, et al. Brain homogenates from human tauopathies induce tau inclusions in mouse brain. *Proc Natl Acad Sci U S A*. 2013; 110:9535–9540. doi:10.1073/pnas.1301175110 [PubMed: 23690619]
35. Clavaguera F, Bolmont T, Crowther RA, et al. Transmission and spreading of tauopathy in transgenic mouse brain. *Nature cell biology*. 2009; 11:909–913. doi:ncb1901 [pii] 10.1038/ncb1901.
36. Davis DG, Schmitt FA, Wekstein DR, Markesbery WR. Alzheimer neuropathologic alterations in aged cognitively normal subjects. *J Neuropathol Exp Neurol*. 1999; 58:376–388. [PubMed: 10218633]
37. Dawe RJ, Bennett DA, Schneider JA, Arfanakis K. Neuropathologic correlates of hippocampal atrophy in the elderly: a clinical, pathologic, postmortem MRI study. *PLoS one*. 2011; 6:e26286. doi:10.1371/journal.pone.0026286 PONE-D-11-13485 [pii]. [PubMed: 22043314]
38. de Calignon A, Polydoro M, Suarez-Calvet M, et al. Propagation of tau pathology in a model of early Alzheimer's disease. *Neuron*. 2012; 73:685–697. doi:10.1016/j.neuron.2011.11.033 [PubMed: 22365544]
39. Dickson DW, Kouri N, Murray ME, Josephs KA. Neuropathology of Frontotemporal Lobar Degeneration-tau (FTLD-tau). *Journal of Molecular Neurosci*. 2011; 45(3):384–9. doi:10.1007/s12031-011-9589-0
40. Dugger BN, Hidalgo JA, Chiarolanza G, et al. The distribution of phosphorylated tau in spinal cords of Alzheimer's disease and non-demented individuals. *J Alzheimers Dis*. 2013; 34:529–536. doi:10.3233/JAD-121864 [PubMed: 23246918]
41. Dugger BN, Tu M, Murray ME, Dickson DW. Disease specificity and pathologic progression of tau pathology in brainstem nuclei of Alzheimer's disease and progressive supranuclear palsy. *Neurosci Lett*. 2011 doi:S0304-3940(11)00024-3 [pii] 10.1016/j.neulet.2011.01.020.
42. Elobeid A, Soininen H, Alafuzoff I. Hyperphosphorylated tau in young and middle-aged subjects. *Acta Neuropathol*. 2012; 123:97–104. doi:10.1007/s00401-011-0906-z [PubMed: 22160320]
43. Feany MB, Dickson DW. Neurodegenerative disorders with extensive tau pathology: a comparative study and review. *Ann Neurol*. 1996; 40:139–148. doi:10.1002/ana.410400204 [PubMed: 8773594]
44. Ferrer I, Lopez-Gonzalez I, Carmona M, et al. Glial and neuronal tau pathology in tauopathies: characterization of disease-specific phenotypes and tau pathology progression. *J Neuropathol Exp Neurol*. 2014; 73:81–97. doi:10.1097/NEN.0000000000000030 [PubMed: 24335532]
45. Ferrer I, Santpere G, van Leeuwen FW. Argyrophilic grain disease. *Brain*. 2008; 131:1416–1432. doi:10.1093/brain/awm305 [PubMed: 18234698]
46. Frost B, Diamond MI. Prion-like mechanisms in neurodegenerative diseases. *Nature reviews Neuroscience*. 2010; 11:155–159. doi:nrn2786 [pii] 10.1038/nrn2786.
47. Frost B, Jacks RL, Diamond MI. Propagation of tau misfolding from the outside to the inside of a cell. *J Biol Chem*. 2009; 284:12845–12852. doi:M808759200 [pii] 10.1074/jbc.M808759200. [PubMed: 19282288]
48. Fukutani Y, Kobayashi K, Nakamura I, et al. Neurons, intracellular and extracellular neurofibrillary tangles in subdivisions of the hippocampal cortex in normal ageing and Alzheimer's disease. *Neurosci Lett*. 1995; 200:57–60. doi:0304-3940(95)12083-G [pii]. [PubMed: 8584267]
49. Garcia-Sierra F, Hauw JJ, Duyckaerts C, et al. The extent of neurofibrillary pathology in perforant pathway neurons is the key determinant of dementia in the very old. *Acta Neuropathol*. 2000; 100:29–35. doi: [PubMed: 10912917]
50. Geser F, Winton MJ, Kwong LK, et al. Pathological TDP-43 in parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam. *Acta Neuropathol*. 2008; 115:133–145. doi:10.1007/s00401-007-0257-y [PubMed: 17713769]
51. Giannakopoulos P, Hof PR, Mottier S, Michel JP, Bouras C. Neuropathological changes in the cerebral cortex of 1258 cases from a geriatric hospital: retrospective clinicopathological evaluation of a 10-year autopsy population. *Acta Neuropathol*. 1994; 87:456–468. doi: [PubMed: 8059598]
52. Goodman L. Alzheimer's disease: A clinico-pathologic analysis of twenty-three cases with a theory on pathogenesis. *J Nerv Ment Dis*. 1953; 117:97–130. doi: [PubMed: 13109530]

53. Grinberg LT, Rub U, Ferretti RE, et al. The dorsal raphe nucleus shows phospho-tau neurofibrillary changes before the transentorhinal region in Alzheimer's disease. A precocious onset? *Neuropathol Appl Neurobiol*. 2009; 35:406–416.10.1111/j.1365-2990.2009.00997.x [PubMed: 19508444]
54. Grinberg LT, Wang X, Wang C, et al. Argyrophilic grain disease differs from other tauopathies by lacking tau acetylation. *Acta Neuropathol*. 2013; 125:581–593.10.1007/s00401-013-1080-2 [PubMed: 23371364]
55. Grudzien A, Shaw P, Weintraub S, et al. Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease. *Neurobiol Aging*. 2007; 28:327–335. doi:S0197-4580(06)00045-5 [pii] 10.1016/j.neurobiolaging.2006.02.007. [PubMed: 16574280]
56. Guillozet AL, Weintraub S, Mash DC, Mesulam MM. Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. *Arch Neurol*. 2003; 60:729–736. doi. [PubMed: 12756137]
57. Guo JL, Lee VM. Seeding of normal tau by pathological tau conformers drives pathogenesis of Alzheimer-like tangles. *J Biol Chem*. 2011 doi:M110.209296 [pii] 10.1074/jbc.M110.209296.
58. Hauw JJ, Vignolo P, Duyckaerts C, et al. Neuropathological study of 12 centenarians: the incidence of Alzheimer type senile dementia is not particularly increased in this group of very old patients. *Revue neurologique*. 1986; 142:107–115. doi. [PubMed: 3726387]
59. Hof PR, Archin N, Osmand AP, et al. Posterior cortical atrophy in Alzheimer's disease: analysis of a new case and re-evaluation of a historical report. *Acta Neuropathol*. 1993; 86:215–223. doi. [PubMed: 8213079]
60. Hof PR, Bouras C, Buée L, et al. Differential distribution of neurofibrillary tangles in the cerebral cortex of dementia pugilistica and Alzheimer's disease cases. *Acta Neuropathol*. 1992; 85:23–30. doi. [PubMed: 1285493]
61. Hof PR, Perl DP, Loerzel AJ, Morrison JH. Neurofibrillary tangle distribution in the cerebral cortex of parkinsonism-dementia cases from Guam: differences with Alzheimer's disease. *Brain Res*. 1991; 564:306–313. doi:0006-8993(91)91467-F [pii]. [PubMed: 1810629]
62. Hof PR, Vogt BA, Bouras C, Morrison JH. Atypical form of Alzheimer's disease with prominent posterior cortical atrophy: a review of lesion distribution and circuit disconnection in cortical visual pathways. *Vision Res*. 1997; 37:3609–3625. doi:S0042-6989(96)00240-4 [pii] 10.1016/S0042-6989(96)00240-4. [PubMed: 9425534]
63. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature*. 1998; 393:702–705.10.1038/31508 [PubMed: 9641683]
64. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement*. 2012; 8:1–13.10.1016/j.jalz.2011.10.007 [PubMed: 22265587]
65. Ikeda K, Akiyama H, Arai T, Nishimura T. Glial tau pathology in neurodegenerative diseases: their nature and comparison with neuronal tangles. *Neurobiol Aging*. 1998; 19:S85–91. doi. [PubMed: 9562475]
66. Ikeda K, Akiyama H, Arai T, et al. Clinical aspects of 'senile dementia of the tangle type'-- a subset of dementia in the senium separable from late-onset Alzheimer's disease. *Dement Geriatr Cogn Disord*. 1999; 10:6–11. doi. [PubMed: 9844032]
67. Ikeda K, Akiyama H, Arai T, et al. A subset of senile dementia with high incidence of the apolipoprotein E epsilon2 allele. *Ann Neurol*. 1997; 41:693–695.10.1002/ana.410410522 [PubMed: 9153535]
68. Ikeda K, Akiyama H, Kondo H, et al. Thorn-shaped astrocytes: possibly secondarily induced tau-positive glial fibrillary tangles. *Acta Neuropathol*. 1995; 90:620–625. doi. [PubMed: 8615083]
69. Ikeda K, Kondo H, Fujishima T, Kase K, Mizutani Y. A case of atypical senile dementia of Alzheimer type. *No To Shinkei = Brain and nerve*. 1993; 45:455–460. doi. [PubMed: 8343297]
70. Iseki E, Tsunoda S, Suzuki K, et al. Regional quantitative analysis of NFT in brains of non-demented elderly persons: comparisons with findings in brains of late-onset Alzheimer's disease and limbic NFT dementia. *Neuropathology*. 2002; 22:34–39. doi. [PubMed: 12030413]

71. Ishizawa T, Ko LW, Cookson N, et al. Selective neurofibrillary degeneration of the hippocampal CA2 sector is associated with four-repeat tauopathies. *J Neuropathol Exp Neurol*. 2002; 61:1040–1047. doi. [PubMed: 12484566]
72. Itoh, Yamada M, Yoshida R, et al. Dementia characterized by abundant neurofibrillary tangles and scarce senile plaques: a quantitative pathological study. *European neurology*. 1996; 36:94–97. doi. [PubMed: 8654493]
73. Itoh Y, Yamada M, Suematsu N, Matsushita M, Otomo E. An immunohistochemical study of centenarian brains: a comparison. *J Neurol Sci*. 1998; 157:73–81. doi. [PubMed: 9600680]
74. Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7:257–262. doi:S1552-5260(11)00100-2 [pii] 10.1016/j.jalz.2011.03.004. [PubMed: 21514247]
75. Jack CR Jr, Knopman DS, Weigand SD, et al. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Ann Neurol*. 2012; 71:765–775.10.1002/ana.22628 [PubMed: 22488240]
76. Janocko NJ, Brodersen KA, Soto-Ortolaza AI, et al. Neuropathologically defined subtypes of Alzheimer's disease differ significantly from neurofibrillary tangle-predominant dementia. *Acta Neuropathol*. 2012; 124:681–692.10.1007/s00401-012-1044-y [PubMed: 22968369]
77. Jellinger KA. Challenges in the Neuropathological Diagnosis of Dementias. *International Journal of Neuropathology*. 2013; 1:44.
78. Jellinger KA. Neuropathological subtypes of Alzheimer's disease. *Acta Neuropathol*. 2012; 123:153–154.10.1007/s00401-011-0889-9 [PubMed: 22009303]
79. Jellinger KA, Attems J. Neurofibrillary tangle-predominant dementia: comparison with classical Alzheimer disease. *Acta Neuropathol*. 2007; 113:107–117.10.1007/s00401-006-0156-7 [PubMed: 17089134]
80. Jellinger KA, Attems J. Prevalence and pathology of vascular dementia in the oldest-old. *J Alzheimers Dis*. 2010; 21:1283–1293. doi. [PubMed: 21504129]
81. Jellinger KA, Bancher C. Senile dementia with tangles (tangle predominant form of senile dementia). *Brain Pathol*. 1998; 8:367–376. doi. [PubMed: 9546293]
82. Jicha GA, Abner EL, Schmitt FA, et al. Preclinical AD Workgroup staging: pathological correlates and potential challenges. *Neurobiol Aging*. 2012; 33:622 e621–622 e616.10.1016/j.neurobiolaging.2011.02.018 [PubMed: 21507528]
83. Jicha GA, Parisi JE, Dickson DW, et al. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Arch Neurol*. 2006; 63:674–681. doi. [PubMed: 16682537]
84. Josephs KA, Whitwell JL, Parisi JE, et al. Argyrophilic grains: a distinct disease or an additive pathology? *Neurobiol Aging*. 2008; 29:566–573.10.1016/j.neurobiolaging.2006.10.032 [PubMed: 17188783]
85. Kidd M. Paired helical filaments in electron microscopy of Alzheimer's disease. *Nature*. 1963; 197:192–193. [PubMed: 14032480]
86. Knopman DS, Caselli RJ. Appraisal of cognition in preclinical Alzheimer's disease: a conceptual review. *Neurodegenerative Dis Manag*. 2012; 2:183–195.10.2217/NMT.12.5
87. Knopman DS, Jack CR Jr, Wiste HJ, et al. Brain injury biomarkers are not dependent on beta-amyloid in normal elderly. *Ann Neurol*. 2013; 73:472–480.10.1002/ana.23816 [PubMed: 23424032]
88. Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. *J Neuropathol Exp Neurol*. 2003; 62:1087–1095. [PubMed: 14656067]
89. Kovacs GG, Milenkovic I, Wohrer A, et al. Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series. *Acta Neuropathol*. 2013; 126:365–384.10.1007/s00401-013-1157-y [PubMed: 23900711]
90. Kovacs GG, Molnar K, Laszlo L, et al. A peculiar constellation of tau pathology defines a subset of dementia in the elderly. *Acta Neuropathol*. 2011; 122:205–222.10.1007/s00401-011-0819-x [PubMed: 21437732]

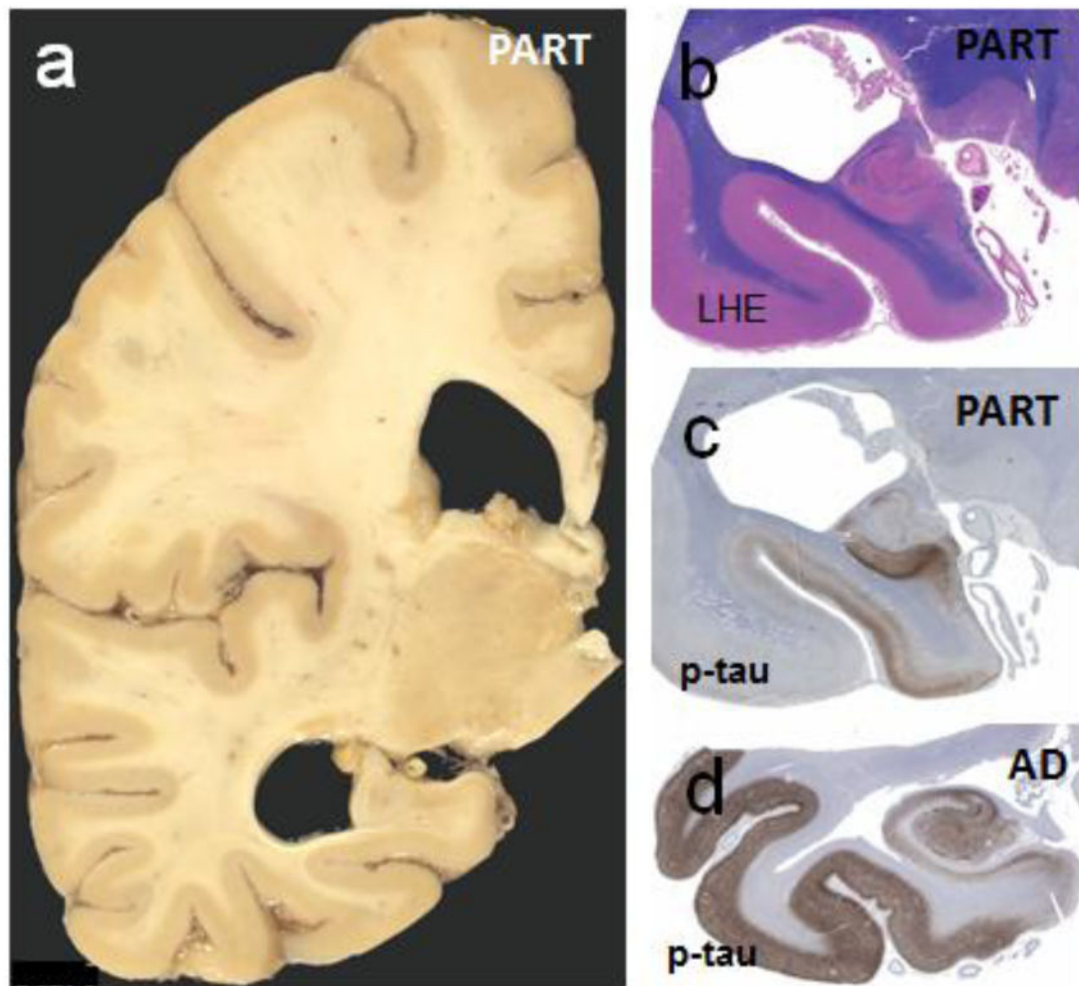
91. Liu L, Drouet V, Wu JW, et al. Trans-synaptic spread of tau pathology in vivo. *PLoS one*. 2012; 7:e31302.10.1371/journal.pone.0031302 [PubMed: 22312444]
92. Malkani RG, Dickson DW, Simuni T. Hippocampal-sparing Alzheimer's disease presenting as corticobasal syndrome. *Parkinsonism Relat Disord*. 2012; 18:683–685.10.1016/j.parkreldis.2011.11.022 [PubMed: 22172552]
93. Markesbery WR, Schmitt FA, Kryscio RJ, et al. Neuropathologic substrate of mild cognitive impairment. *Arch Neurol*. 2006; 63:38–46. [PubMed: 16401735]
94. Matsui Y, Tanizaki Y, Arima H, et al. Incidence and survival of dementia in a general population of Japanese elderly: the Hisayama study. *J Neurol Neurosurg Psychiatry*. 2009; 80:366–370.10.1136/jnnp.2008.155481 [PubMed: 18977814]
95. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol*. 2009; 68:709–735.10.1097/NEN.0b013e3181a9d503 [PubMed: 19535999]
96. Mirra SS. The CERAD neuropathology protocol and consensus recommendations for the postmortem diagnosis of Alzheimer's disease: a commentary. *Neurobiol Aging*. 1997; 18:S91–94. [PubMed: 9330994]
97. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology*. 1991; 41:479–486. [PubMed: 2011243]
98. Mitchell TW, Mufson EJ, Schneider JA, et al. Parahippocampal tau pathology in healthy aging, mild cognitive impairment, and early Alzheimer's disease. *Ann Neurol*. 2002; 51:182–189. [PubMed: 11835374]
99. Mizutani T, Kasahara M, Yamada S, Mukai M, Amano N. Study on the neuropathological diagnosis of senile dementia of the Alzheimer type. *No To Shinkei = Brain and nerve*. 1993; 45:333–342. [PubMed: 8334018]
100. Mizutani T, Shimada H. Neuropathological background of twenty-seven centenarian brains. *J Neurol Sci*. 1992; 108:168–177. [PubMed: 1517748]
101. Mizutani T, Shimada H. Quantitative study of neurofibrillary tangles in subdivisions of the hippocampus. CA2 as a special area in normal aging and senile dementia of the Alzheimer type. *Acta Pathologica Japonica*. 1991; 41:597–603. [PubMed: 1750357]
102. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol*. 2012; 123:1–11.10.1007/s00401-011-0910-3 [PubMed: 22101365]
103. Mungas D, Tractenberg R, Schneider JA, Crane PK, Bennett DA. A 2-process model for neuropathology of Alzheimer's disease. *Neurobiol Aging*. 2014; 35:301–308.10.1016/j.neurobiolaging.2013.08.007 [PubMed: 24080173]
104. Murray ME, Cannon A, Graff-Radford NR, et al. Differential clinicopathologic and genetic features of late-onset amnesic dementias. *Acta Neuropathol*. 2014.10.1007/s00401-014-1302-2
105. Murray ME, Graff-Radford NR, Ross OA, et al. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet neurology*. 2011; 10:785–796. doi:S1474-4422(11)70156-9 [pii] 10.1016/S1474-4422(11)70156-9.
106. Nakaya H, Miki T, Seino S, et al. Molecular and functional diversity of ATP-sensitive K<sup>+</sup> channels: the pathophysiological roles and potential drug targets. *Nihon yakurigaku zasshi Folia pharmacologica Japonica*. 2003; 122:243–250. [PubMed: 12939542]
107. Nelson PT, Abner EL, Schmitt FA, et al. Brains with medial temporal lobe neurofibrillary tangles but no neuritic amyloid plaques are a diagnostic dilemma but may have pathogenetic aspects distinct from Alzheimer disease. *J Neuropathol Exp Neurol*. 2009; 68:774–784.10.1097/NEN.0b013e3181a9d503 [PubMed: 19535994]
108. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J Neuropathol Exp Neurol*. 2012; 71:362–381.10.1097/NEN.0b013e31825018f7 [PubMed: 22487856]
109. Nelson PT, Jicha GA, Schmitt FA, et al. Clinicopathologic correlations in a large Alzheimer disease center autopsy cohort: neuritic plaques and neurofibrillary tangles “do count” when staging disease severity. *J Neuropathol Exp Neurol*. 2007; 66:1136–1146. [PubMed: 18090922]

110. Noda K, Sasaki K, Fujimi K, et al. Quantitative analysis of neurofibrillary pathology in a general population to reappraise neuropathological criteria for senile dementia of the neurofibrillary tangle type (tangle-only dementia): the Hisayama Study. *Neuropathology*. 2006; 26:508–518. [PubMed: 17203586]
111. Perl DP, Hof PR, Purohit DP, Loerzel AJ, Kakulas BA. Hippocampal and entorhinal cortex neurofibrillary tangle formation in Guamanian Chamorros free of overt neurologic dysfunction. *J Neuropathol Exp Neurol*. 2003; 62:381–388. [PubMed: 12722830]
112. Petersen RC, Aisen P, Boeve BF, et al. Criteria for mild cognitive impairment due to Alzheimer's disease in the community. *Ann Neurol*. 2013;10.1002/ana.23931
113. Petersen RC, Parisi JE, Dickson DW, et al. Neuropathologic features of amnesic mild cognitive impairment. *Arch Neurol*. 2006; 63:665–672. doi:63/5/665 [pii] 10.1001/archneur.63.5.665. [PubMed: 16682536]
114. Prestia A, Caroli A, van der Flier WM, et al. Prediction of dementia in MCI patients based on core diagnostic markers for Alzheimer disease. *Neurology*. 2013; 80:1048–1056.10.1212/WNL.0b013e3182872830 [PubMed: 23390179]
115. Ranginwala NA, Hynan LS, Weiner MF, White CL 3rd. Clinical criteria for the diagnosis of Alzheimer disease: still good after all these years. *Am J Geriatr Psychiatry*. 2008; 16:384–388.10.1097/JGP.0b013e3181629971 [PubMed: 18448850]
116. Rijal Upadhaya A, Kosterin I, Kumar S, et al. Biochemical stages of amyloid-beta peptide aggregation and accumulation in the human brain and their association with symptomatic and pathologically preclinical Alzheimer's disease. *Brain*. 2014; 137:887–903.10.1093/brain/awt362 [PubMed: 24519982]
117. Robinson JL, Geser F, Corrada MM, et al. Neocortical and hippocampal amyloid-beta and tau measures associate with dementia in the oldest-old. *Brain*. 2011; 134:3708–3715.10.1093/brain/awr308 [PubMed: 22120149]
118. Rohrer JD, Schott JM. Primary progressive aphasia - defining genetic and pathological subtypes. *Curr Alzheimer Res*. 2011; 8:266–272. doi:BSP/CAR/0119 [pii]. [PubMed: 21222598]
119. Ruben GC, Wang JZ, Iqbal K, Grundke-Iqbal I. Paired helical filaments (PHFs) are a family of single filament structures with a common helical turn period: negatively stained PHF imaged by TEM and measured before and after sonication, deglycosylation, and dephosphorylation. *Microscopy research and technique*. 2005; 67:175–195.10.1002/jemt.20197 [PubMed: 16104003]
120. Sabbagh MN, Sandhu SS, Farlow MR, et al. Correlation of clinical features with argyrophilic grains at autopsy. *Alzheimer Disease Assoc Disord*. 2009; 23:229–233. doi:10.1097/WAD.0b013e318199d83300002093-200907000-00009 [pii].
121. Saito Y, Ruberu NN, Sawabe M, et al. Staging of argyrophilic grains: an age-associated tauopathy. *Journal of neuropathology and experimental neurology*. 2004; 63:911–918. doi. [PubMed: 15453090]
122. Santa-Maria I, Haggiagi A, Liu X, et al. The MAPT H1 haplotype is associated with tangle-predominant dementia. *Acta Neuropathol*. 2012; 124:693–704.10.1007/s00401-012-1017-1 [PubMed: 22802095]
123. Schmidt ML, Garruto R, Chen J, Lee VM, Trojanowski JQ. Tau epitopes in spinal cord neurofibrillary lesions in Chamorros of Guam. *Neuroreport*. 2000; 11:3427–3430. [PubMed: 11095492]
124. Schmidt ML, Zhukareva V, Perl DP, et al. Spinal cord neurofibrillary pathology in Alzheimer disease and Guam Parkinsonism-dementia complex. *J Neuropathol Exp Neurol*. 2001; 60:1075–1086. [PubMed: 11706937]
125. Schneider JA, Aggarwal NT, Barnes L, Boyle P, Bennett DA. The neuropathology of older persons with and without dementia from community versus clinic cohorts. *J Alzheimers Dis*. 2009; 18:691–701. doi:D646027568658127 [pii] 10.3233/JAD-2009-1227. [PubMed: 19749406]
126. Schnitzler JG. Zur Abgrenzung der sogenannten Alzheimerschen Erkrankung. *Z ges Neurol Psychiat*. 1911; 7:34–57. doi.

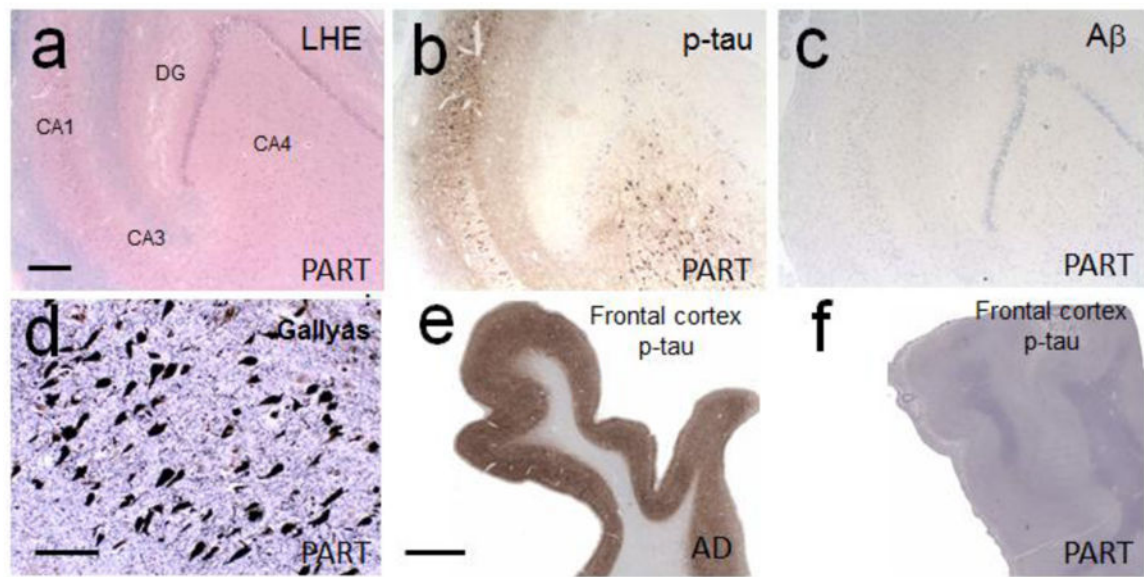
127. Schultz C, Ghebremedhin E, Del Tredici K, Rüb U, Braak H. High prevalence of thorn-shaped astrocytes in the aged human medial temporal lobe. *Neurobiol Aging*. 2004; 25:397–405.10.1016/S0197-4580(03)00113-1 [PubMed: 15123344]
128. Serrano-Pozo A, Qian J, Monsell SE, et al. Mild to moderate Alzheimer dementia with insufficient neuropathological changes. *Ann Neurol*. 2014; 75:597–601.10.1002/ana.24125 [PubMed: 24585367]
129. Serrano-Pozo A, Qian J, Monsell SE, et al. Examination of the clinicopathologic continuum of Alzheimer disease in the autopsy cohort of the National Alzheimer Coordinating Center. *J Neuropathol Exp Neurol*. 2013; 72:1182–1192.10.1097/NEN.000000000000016 [PubMed: 24226270]
130. Shiarli AM, Jennings R, Shi J, et al. Comparison of extent of tau pathology in patients with frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration with Pick bodies and early onset Alzheimer's disease. *Neuropathol Appl Neurobiol*. 2006; 32:374–387. doi:NAN736 [pii] 10.1111/j.1365-2990.2006.00736.x. [PubMed: 16866983]
131. Simic G, Stanic G, Mladinov M, et al. Does Alzheimer's disease begin in the brainstem? *Neuropathol Appl Neurobiol*. 2009; 35:532–554. doi:NAN1038 [pii] 10.1111/j.1365-2990.2009.01038.x. [PubMed: 19682326]
132. Sonnen JA, Santa Cruz K, Hemmy LS, et al. Ecology of the aging human brain. *Arch Neurol*. 2011; 68:1049–1056. doi:68/8/1049 [pii] 10.1001/archneurol.2011.157. [PubMed: 21825242]
133. Syed A, Chatfield M, Matthews F, et al. Depression in the elderly: pathological study of raphe and locus ceruleus. *Neuropathol Appl Neurobiol*. 2005; 31:405–413. doi:NAN662 [pii] 10.1111/j.1365-2990.2005.00662.x. [PubMed: 16008824]
134. Takahashi J, Shibata T, Sasaki M, et al. Detection of changes in the locus coeruleus in patients with mild cognitive impairment and Alzheimer's disease: High-resolution fast spin-echo T1-weighted imaging. *Geriatrics & gerontology international*. 2014;10.1111/ggi.12280
135. Thal DR, Capetillo-Zarate E, Del Tredici K, Braak H. The development of amyloid beta protein deposits in the aged brain. *Sci Aging Knowledge Environ*. 2006; 2006:re1. doi:2006/6/re1 [pii] 10.1126/sageke.2006.6.re1. [PubMed: 16525193]
136. Thal DR, Schultz C, Botez G, et al. The impact of argyrophilic grain disease on the development of dementia and its relationship to concurrent Alzheimer's disease-related pathology. *Neuropathol Appl Neurobiol*. 2005; 31:270–279. doi:NAN635 [pii] 10.1111/j.1365-2990.2005.00635.x. [PubMed: 15885064]
137. Thal DR, von Arnim C, Griffin WS, et al. Pathology of clinical and preclinical Alzheimer's disease. *European archives of psychiatry and clinical neuroscience*. 2013; 263(Suppl 2):S137–145.10.1007/s00406-013-0449-5 [PubMed: 24077890]
138. Togo T, Sahara N, Yen SH, et al. Argyrophilic grain disease is a sporadic 4-repeat tauopathy. *Journal of neuropathology and experimental neurology*. 2002; 61:547–556. doi. [PubMed: 12071638]
139. Trachtenberg DI, Trojanowski JQ. Dementia: a word to be forgotten. *Arch Neurol*. 2008; 65:593–595.10.1001/archneur.65.5.593 [PubMed: 18474733]
140. Trojanowski JQ, Ishihara T, Higuchi M, et al. Amyotrophic lateral sclerosis/parkinsonism dementia complex: transgenic mice provide insights into mechanisms underlying a common tauopathy in an ethnic minority on Guam. *Exp Neurol*. 2002; 176:1–11. [PubMed: 12093078]
141. Tsuboi Y, Wszolek ZK, Graff-Radford NR, Cookson N, Dickson DW. Tau pathology in the olfactory bulb correlates with Braak stage, Lewy body pathology and apolipoprotein epsilon4. *Neuropathol Appl Neurobiol*. 2003; 29:503–510. [PubMed: 14507342]
142. Ulrich J, Spillantini MG, Goedert M, Dukas L, Staehelin HB. Abundant neurofibrillary tangles without senile plaques in a subset of patients with senile dementia. *Neurodegeneration*. 1992;257–284.
143. Vos SJ, Xiong C, Visser PJ, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet neurology*. 2013; 12:957–965.10.1016/S1474-4422(13)70194-7



144. West MJ, Coleman PD, Flood DG, Troncoso JC. Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. *Lancet*. 1994; 344:769–772. [PubMed: 7916070]
145. Wirth M, Villeneuve S, Haase CM, et al. Associations between Alzheimer disease biomarkers, neurodegeneration, and cognition in cognitively normal older people. *JAMA neurology*. 2013; 70:1512–1519.10.1001/jamaneurol.2013.4013 [PubMed: 24166579]
146. Wisniewski HM, Narang HK, Terry RD. Neurofibrillary tangles of paired helical filaments. *J Neurol Sci*. 1976; 27:173–181. [PubMed: 129541]
147. Yamada M. Senile dementia of the neurofibrillary tangle type (tangle-only dementia): neuropathological criteria and clinical guidelines for diagnosis. *Neuropathology*. 2003; 23:311–317. [PubMed: 14719548]
148. Yamada M, Itoh Y, Sodeyama N, et al. Aging of the human limbic system: Observations of centenarian brains and analyses of genetic risk factors for senile changes. *Neuropathology*. 1998; 18:228–234.
149. Yamada M, Itoh Y, Sodeyama N, et al. Senile dementia of the neurofibrillary tangle type: a comparison with Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2001; 12:117–126. doi: 51245. [PubMed: 11173884]
150. Yamada M, Itoh Y, Suematsu N, Otomo E, Matsushita M. Apolipoprotein E genotype in elderly nondemented subjects without senile changes in the brain. *Ann Neurol*. 1996; 40:243–245.10.1002/ana.410400217 [PubMed: 8773607]
151. Yamada M, Itoh Y, Yohinori I, et al. Dementia of the Alzheimer type and related dementias in the aged: DAT subgroups and senile dementia of the neurofibrillary tangle type. *Neuropathology*. 1996; 16:89–98.
152. Yoshida M. Cellular tau pathology and immunohistochemical study of tau isoforms in sporadic tauopathies. *Neuropathology*. 2006; 26:457–470. doi. [PubMed: 17080726]
153. Yu L, Boyle PA, Leurgans S, Schneider JA, Bennett DA. Disentangling the effects of age and APOE on neuropathology and late life cognitive decline. *Neurobiol Aging*. 2014; 35:819–826.10.1016/j.neurobiolaging.2013.10.074 [PubMed: 24199961]

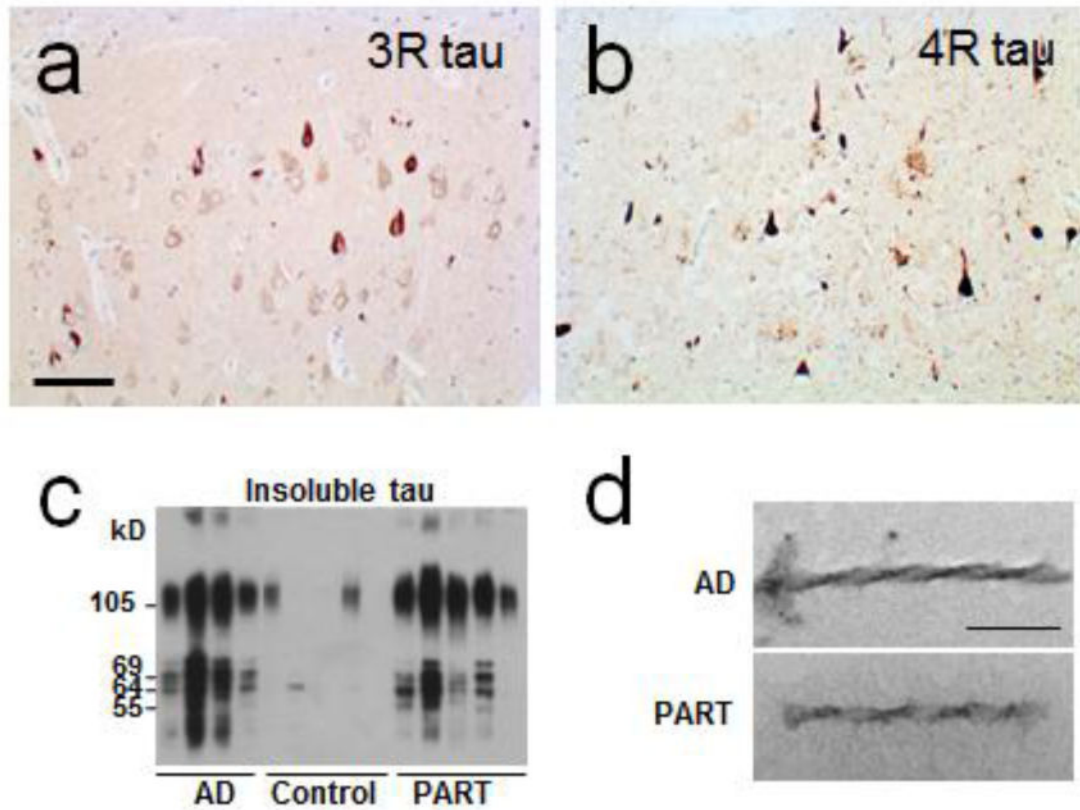


**Fig. 1.** Primary age-related tauopathy (PART): gross pathology and low-power photomicrographs. (a) A formalin-fixed left hemisphere from a 103-year-old woman reveals enlargement of the inferior horn of lateral ventricle and severe medial temporal atrophy. Only mild neocortical atrophy is present. (b) A Luxol fast blue-counterstained hematoxylin-eosin section (LHE) shows atrophy of the medial temporal lobe. (c) Phospho-tau (p-tau; AT8)-immunolabeled sections highlight marked tauopathic changes predominantly in the hippocampus and entorhinal cortex. (d) For comparison, a case with advanced AD demonstrates a more severe tauopathy extending into the temporal neocortex.



**Fig. 2.**

Primary age-related tauopathy (PART): histopathology. The neuropathology corresponds to Braak stages I-IV, with involvement of the hippocampal formation (a-c are nearly serial sections from the hippocampus of the same patient) as shown with Luxol Fast Blue-counterstained hematoxylin-eosin (LHE) (a), and p-tau (AT8) immunohistochemistry (b). However, unlike cases with AD, A $\beta$  immunohistochemistry (c) shows minimal or no staining. Gallyas silver impregnation reveals many “ghost tangles” in the hippocampal formation (d), here without amyloid plaques. A key difference between AD and PART pathology is that, by definition, advanced AD (e) shows extensive hyperphosphorylated tau (p-tau) in neocortical areas such as the prefrontal cortex (Brodmann area 9), whereas PART pathology spares the neocortex (f). Scale bar in a = 1 mm for (a-c), scale bar in d = 100  $\mu$ m, and scale bar in e = 5 mm for (e, f). CA1-4 denote the hippocampal subfields; DG, dentate gyrus.



**Fig. 3.** The NFTs of PART resemble those of AD by immunohistochemistry, biochemistry, and ultrastructure. (a, b) NFTs in PART reveal immunoreactivity with both 3R and 4R anti-tau monoclonal antisera (RD3 and RD4 respectively). Scale bar = 200  $\mu$ m for a, b. (c) Immunoblot using polyclonal antisera targeting total tau (tau C) shows a banding pattern similar to that in AD (from ref [122] with permission). (d) The tau fibrils (paired helical filaments) in PART show similar ultrastructural features and periodicity as in AD. Scale bar = 100 nm.

**Table 1**  
**Clinical features of primary age-related tauopathy (PART)<sup>†</sup>**

	Amyloid plaque density	Braak Stage				
		0	I	II	III	IV
<i>Number of subjects</i>						
PART, definite	None	11	22	25	15	15
PART, possible	Low	4	16	27	16	31
-	Mod	2	11	15	32	50
-	High	3	7	10	39	83
<i>Age at death (average)</i>						
PART, definite	None	81.3	82.4	88.5	<b>88.4*</b>	<b>92.0<sup>*,**</sup></b>
PART, possible	Low	88.4	80.4	84.7	<b>89.7*</b>	<b>87.6*</b>
-	Mod	89.0	80.2	87.4*	84.9	86.5
-	High	77.0	84.9	86.7	85.3	84.6
<i>Final MMSE scores</i>						
PART, definite	None	28.0	28.4	26.5	<b>25.1<sup>****</sup></b>	<b>24.3<sup>****</sup></b>
PART, possible	Low	28.5	25.8	24.4	24.6	<b>21.9*</b>
-	Mod	26.5	26.8	27.3	<b>23.2*</b>	<b>19.8*</b>
-	High	<b>25.5*</b>	24.5	<b>27.9*</b>	<b>21.2*</b>	<b>18.8<sup>*,**</sup></b>
<i>APOE ε4 positive</i>						
PART, definite	None	9.1	13.6	0.0	20.0	13.3
PART, possible	Low	25.0	12.5	14.8	37.5	<b>35.5*</b>
-	Mod	0.0	36.4	13.3	<b>34.4*</b>	<b>50.0*</b>
-	High	<b>66.7*</b>	28.6	<b>50.0*</b>	<b>33.3*</b>	<b>56.6<sup>*,**</sup></b>

<sup>†</sup> Patients from the National Alzheimer's Disease Coordinating Center (NACC) Neuropathology Database who died after 2005, with Mini-Mental State Examination (MMSE) during life, but no evidence of severe AD, frontotemporal lobar degeneration, triplet repeat disorder, amyotrophic lateral sclerosis, or other known neurological syndrome at autopsy. A total of 434 individuals met inclusion criteria. Statistical comparisons versus Braak NFT stage 0 cases. Age and MMSE were assessed with one-way ANOVA. *APOE* was assessed with Fisher's Exact test.

\*  $p < 0.05$  as individual test

\*\*  $p < 0.05$  after Bonferroni-Holm correction for multiple comparisons

Combining Braak III/IV comparing to Braak 0 leads to  $p = 0.003$  (Student's t-test)

\*\*\*

**Table 2**  
**Primary age-related tauopathy (PART): working classification**

*1. Requires:*

NFT present with Braak stage IV (usually III or lower)

*2. Then subclassify as follows:*

Category	Thal A $\beta$ Phase <sup>a</sup>	Other disease associated with NFT <sup>b</sup>
Definite	0	Absent
Possible	1-2	Absent

*Examples:*

“Primary age-related tauopathy (PART), Definite, Braak stage II”

“Primary age-related tauopathy (PART), Possible, Braak stage III, Thal A $\beta$  phase 2”

*3. Ancillary studies (not required):*

- Immunohistochemistry: 3R and 4R tau-positive
- Electron microscopy: paired helical filaments present
- Genetics: absence of pathogenic FTLT-tau mutation

<sup>a</sup>See [116, 135]. Laboratories using the CERAD neuritic plaque density score [96, 97] may classify subjects with neuritic plaque frequency of “None” as “Definite” and “Sparse” as “Possible.”

<sup>b</sup>For example, progressive supranuclear palsy, corticobasal degeneration, Pick's disease, frontotemporal lobar degeneration with *MAPT* mutation, and chronic traumatic encephalopathy.