“New Old Pathologies”: AD, PART, and Cerebral Age-Related TDP-43 With Sclerosis (CARTS)

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Abstract

The pathology-based classification of Alzheimer’s disease (AD) and other neurodegenerative diseases is a work in progress that is important for both clinicians and basic scientists. Analyses of large autopsy series, biomarker studies, and genomics analyses have provided important insights about AD and shed light on previously unrecognized conditions, enabling a deeper understanding of neurodegenerative diseases in general. After demonstrating the importance of correct disease classification for AD and primary age-related tauopathy, we emphasize the public health impact of unrecognized conditions, enabling a deeper understanding of neurodegenerative diseases. For most neurodegenerative diseases, neuropathologic observations constitute the “gold standard” used in diagnosis and nosology. Yet the pathology-based classifications of neurodegenerative diseases are also dynamic and have evolved recently to capture an increased proportion of the changes in the aged brain that are associated with cognitive impairment. These advances have come about with the help of larger and more diverse autopsy cohorts, increasingly robust and quantitative pathological parameters, and greater collaboration among neuropathologists, clinician-scientists, and basic researchers. Here we discuss both recent advances and some areas that merit revision in the study of dementia-related neurodegenerative diseases.

INTRODUCTION

Prospects for diagnosing and treating neurodegenerative diseases are enhanced when disease classifications reflect the underlying biologic complexity of these conditions. For most neurodegenerative diseases, neuropathologic observations constitute the “gold standard” used in diagnosis and nosology. Yet the pathology-based classifications of neurodegenerative diseases are also dynamic and have evolved recently to capture an increased proportion of the changes in the aged brain that are associated with cognitive impairment. These advances have come about with the help of larger and more diverse autopsy cohorts, increasingly robust and quantitative pathological parameters, and greater collaboration among neuropathologists, clinician-scientists, and basic researchers. Here we discuss both recent advances and some areas that merit revision in the study of dementia-related neurodegenerative diseases (Table 1). These studies are directly relevant to the most well-known dementia-inducing disorder, Alzheimer disease (AD).

Focusing on AD

AD has an enormous impact on public health and recent studies have substantially revised the classic literature on AD clinico-pathologic correlations. For example, we have learned that much of the morbidity attributed to AD as recently as 20 years ago is more accurately associated with non-AD diseases. A basic assumption is that AD is defined by 2 pathologic hallmarks: Aβ amyloid plaques and tau neurofibrillary tangles (NFTs) (2). The complex but coherent association between AD pathologies and cognitive status was previously addressed for this disease is required. We recommend “cerebral age-related TDP-43 and sclerosis” (CARTS). A detailed case report is presented, which includes neuroimaging and longitudinal neurocognitive data. Finally, we suggest a neuropathology-based diagnostic rubric for CARTS.

Key Words: Arteriosclerosis, Cerebrovascular disease, Frontotemporal lobar degeneration, Genome-wide association study, Neurofibrillary tangles, Plaques, VCID.
(3, 4). Here, we focus on 3 basic factors that must be taken into account in disease classifications: autopsy data, non-AD pathologies, and chronological age.

Autopsy-based neuropathological diagnoses are central to AD research. The salience of neuropathological data and, by extension, pathology-based classification schemes, is illustrated by many prior studies that arrived at correct conclusions only when using the pathological criteria for AD diagnosis rather than using purely clinical criteria for AD diagnosis. One example selected from among many is in testing the association between AD and type 2 diabetes mellitus (T2D), the latter of which affects over a quarter of individuals 65 years of age (5). Studies analyzing clinical data have reported that T2D is a risk factor for AD (6–8). By contrast, studies that incorporated autopsy results have consistently arrived at the opposite conclusion, i.e. that T2D is not a risk factor for AD pathology. Instead, T2D appears to exert its impact through a different disorder, that is cerebrovascular disease (9–14). The inclusion of the single study design element of autopsy data is critical to guide all other related work.

The reason for the discrepancy between clinical and pathology-based AD diagnoses relates to the prevalence of non-AD brain diseases, including α-synucleinopathies, non-AD tauopathies, hippocampal sclerosis (HS-Aging) as discussed below, and many subtypes of cerebrovascular disease, all of which can mimic AD clinically (4, 15–17). In Table 2 we provide data from the University of Kentucky autopsy series (18, 19) listing the frequency of non-AD pathologies by Braak NFT stage (20). Note that >95% of brains in this cohort have at least 1 brain pathology and most participants had more than 1 pathologic diagnosis. These results are consistent with prior autopsy series (4, 19, 21–35).

Biomarker studies confirm the prevalence of in vivo “suspected non-Alzheimer pathology” (SNAP) (36, 37), which refers to neurodegeneration without Aβ amyloidosis according to biomarkers. Approximately 25% of “mild cognitive impairment” (MCI) cases show the SNAP biomarker signature (36). This does not indicate that only approximately 25% of MCI subjects show substantial non-AD pathology, but instead, approximately 25% of MCI subjects show impairment that is almost exclusively related to non-AD pathology.

The clinical and biomarker data on patients with cognitive impairments must be guided by pathologic classification to appreciate the heterogeneous diseases underlying these impairments. A first-line biomarker used for diagnosing the cause of cognitive impairment in the elderly is brain MRI (38). Although MRI-detected hippocampal shrinkage is a relatively strong predictor of subsequent cognitive deterioration (39–41), this finding has low specificity because multiple separate brain pathologies are associated with hippocampal atrophy. For example, HS of aging (HS-Aging) is a common condition that causes even more severe hippocampal atrophy than AD (42–44). Distinguishing between causes of hippocampal atrophy is critical because therapies that might impact one condition (eg AD) may not have any effect in another disease (eg HS-Aging). Thus, optimal AD biomarkers would indicate the severity of AD neuropathology rather than cognitive impairment per se, which is not specific to AD (27, 29, 45).

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**TABLE 2.** Even in an Autopsy Cohort That Includes Many Subjects Free of Dementia, Most Individuals Manifest More Than 1 Subtype of Brain Pathology

| Braak NFT Stages | 0 | I | II | III | IV | V | VI |
|------------------|---|---|----|-----|----|---|----|
| Cases (n)        | 20 | 57 | 97 | 58  | 57 | 101| 188|
| Cases with B-ASC: moderate or severe | 0% | 12.3% | 21.6% | 12.1% | 21.1% | 19.8% | 14.4% |
| Cases with CAA: moderate or severe | 20.0% | 10.5% | 20.6% | 19.0% | 24.6% | 37.6% | 50.5% |
| Cases with Lacunar and/or microinfarcts | 35.0% | 36.8% | 43.3% | 37.9% | 49.1% | 46.5% | 38.3% |
| Cases with Neocortical Lewy bodies | 5.0% | 14.0% | 9.3% | 10.3% | 7.0% | 10.9% | 19.7% |
| Cases with HS-Aging | 15.0% | 10.5% | 6.2% | 17.2% | 8.8% | 18.8% | 15.4% |
| Cases with >1 non-AD pathology* | 20.0% | 21.1% | 27.0% | 24.1% | 33.3% | 43.6% | 40.1% |
| Cases with PART | n/a | 71.9% | 56.7% | 37.9% | 17.5% | n/a | n/a |

Shown are pathologies among subjects at the University of Kentucky Alzheimer’s Disease Center autopsy cohort who died after age 75 years (total n = 578, of whom 161 subjects had final MMSE score of 28/30 or better) without frontotemporal dementia, stratified by Braak NFT stages. Data are presented as percentages.

B-ASC: brain arteriolosclerosis; CAA: cerebral amyloid angiopathy; HS-Aging: hippocampal sclerosis of aging; PART: primary age-related tauopathy.

*For this purpose, PART is not considered “non-AD” pathology.
Recent autopsy studies have also shed new light on the interaction between aging and brain disease. The classic AD clinical-pathologic correlation studies of Tomlinson and colleagues were performed on cohorts with average age of death in their early 70s (46–49). However, the fastest growing population group is persons older than 85 years of age (10). It is increasingly clear that this “oldest-old” population is affected by conditions that differ from younger cohorts (10, 50–52). “Pure” AD cases tend to be younger and to have particular gene variants (10, 29, 31, 53–55), whereas the prevalence of AD pathology levels off or decreases in advanced old age whereas other pathologies (HS-Aging, cerebrovascular diseases) increase in that group. Panel (B) shows the same conditions ranked according to the morbidity (neurologic impact and rate of disease progression). Prevalence, morbidity, and age range vary significantly. For example, FTLD is a rare but devastating illness whereas PART is relatively common but lower morbidity, and each mostly afflicts people at separate parts of the human aging spectrum.

Although new insights into AD-related brain pathologies have been achieved, many more questions remain. These questions illustrate that there are controversies about disease classifications: What, other than APOE ε4, leads to the development of plaques and tangles? Do some cognitively intact individuals tolerate a high burden of plaques and tangles for long periods? Are there environmental and genetic influences that confer protection against the disease? And why do many individuals in advanced old age lack amyloid plaques but still develop hippocampal NFTs?
A Common Pathology With a New Classification: Primary Age-Related Tauopathy (PART)

We consider PART to represent a distinct non-AD pathology (59, 88), as indicated in the most recent consensus-based guidelines for the neuropathologic assessment of AD (2) (Fig. 3). However, since tau, α-synuclein, Aβ, and TDP-43 are all pathologically aggregated in multiple diseases (1, 4, 92–98), there are debates about the pathology-based criteria applied to define each disease, including PART (99, 100). What is agreed upon is that NFTs are virtually always seen with advanced age, whereas Aβ amyloid plaques are absent in a substantial proportion of elderly brains (24, 59, 87—91, 101–103). The NFT+/Aβ-pathologic combination (PART) is common, occurring in approximately 20% of all individuals (Table 2).

The update of pathology classification to include PART (59) provides a universal terminology with both theoretical and clinical implications. To summarize multiple prior studies, human autopsy data indicate the existence of at least 2 common but distinct biologic processes producing NFTs in the hippocampus of elderly persons (23, 60, 104–106). One process (AD) includes Aβ plaques as well as tau NFTs and tends to evolve into dementia. The other (PART) lacks the Aβ plaques and is associated with lesser degree of cognitive impairment and/or other morbidities. Notably, APOE e4 genotype does not appear to be a risk factor for PART, whereas the MAPT “H1” haplotype confers an increased risk for PART (59, 105, 107) and for less common non-AD tauopathies (108, 109).

PART differs from AD in terms of overall morbidity and the age range of maximum vulnerability (59) (Fig. 2). The higher stage PART cases (Braak NFT stages III/IV) tend to show evidence of cognitive impairment (59). Prior biomarker studies identified neurodegeneration biomarkers in the absence of brain or cerebrospinal fluid Aβ amyloidosis (37, 110–112). We also found evidence that PART is a pathologic substrate for individuals who die with subjective memory complaints (113), which is a very common clinical phenomenon among elderly individuals (114, 115).

Whether PART pathology inevitably progresses to AD is controversial (99, 107). Approximately 20% of individuals have PART pathology by their ninth decade (87). The overall proportion of AD and PART cases seems to be stable in centenarians, supporting the hypothesis that PART pathology is not necessarily destined to progress to AD (24, 87). A separate issue that remains to be addressed relates to the presence of PART in individuals who satisfy criteria for AD (i.e. moderate or frequent neuritic plaques). Using current diagnostic classification (Fig. 3), those cases are not classifiable as PART. However, with the identification of PART, clinicians, pathologists, and basic scientists worldwide can better discriminate amongst various tauopathic diseases, aiding both clinical and basic research. Such studies will set the stage for future preventive or therapeutic strategies.

At the Frontier of Disease Classification: HS-Aging

Despite the recent progress in the field, there are still common and high-morbidity age-related brain diseases that lack a consensus-based classification. Here, we focus on a specific brain disease, with clinical manifestations that overlap with AD, and which has been classified using the term “HS” based on pathologic observations (116–126). HS in aged individuals is diagnosed at autopsy (according to consensus-based guidelines) when neuron loss and astrocytosis are observed in the hippocampal formation, “out of proportion to AD neuropathologic change in the same structures” (2).

Unfortunately, the current terminology is suboptimal. There is no formal operationalization of what “out of proportion” exactly means. Moreover, the word “sclerosis” (Gr., sklerōsis, “hardness”) lacks a specific connotation in terms of molecular pathogenesis. Pathologists observe what they describe as HS in widely differing conditions including epilepsy, hypoxia and hypoglycemia, frontotemporal lobar degeneration (FTLD), chronic traumatic encephalopathy, and some tauopathies (125, 127–133). Recently, a group of experts discussed HS pathologic classification terminology (134); however, the research subjects in that study were relatively young (most <80 years at death) in comparison to many HS-Aging cases (53, 116, 135, 136).

The term “HS-Aging” was previously applied to separate this disease from other conditions referred to as HS (15, 56, 116, 137–139). HS-Aging is distinguished by the advanced age of the affected individuals, by the usual lack of either seizure disorder or frontotemporal dementia symptoms clinically, and by the presence of hippocampal TDP-43 pathology (116, 117, 140–143). Other terms that have been applied include “HpSel” (124, 125, 144) and “HS dementia” (125, 145, 146), with “combined” and “pure” subtypes recognized according to the presence or absence of comorbid pathologies (128). We note that fewer than 2% of citations returned after a current PubMed search using the words...
“hippocampal sclerosis” are related to HS-Aging, HpScl, or HS dementia. Thus, whatever final terminology is adopted, it should not be simply “HS” because this is clearly not a disease-defining pathologic endpoint. Here, we describe what is known about this disease including data germane to a useful new terminology.

**HS-Aging Is a Common High-Morbidity Disease of Advanced Old Age**

The disease referred to as “HS-Aging” affects up to 25% of individuals beyond 85 years of age (53, 56, 116, 117, 135, 136, 147). The reported prevalence varies across cohorts, perhaps because the “sclerosis” is diagnosed subjectively. Further, 40%–50% of the HS-Aging cases have unilateral HS pathology on hematoxylin and eosin (H&E) stain (116, 147). Because this unilateral pathology is associated with cognitive impairment (34), there would be a large number of false-negatives reported if only one side of the brain were evaluated. Another very important variable is study design. Among research cohorts that are linked to dementia clinics, the samples have tended to be enriched with “pure” AD and FTLD cases, whereas in community-based cohorts, FTLD is quite rare and there are greater numbers of cognitively intact subjects as well as those with dementia due to cerebrovascular disease and HS-Aging (22, 25, 33, 61, 62, 116, 117, 148–153).

Research from many centers has found that HS-Aging-type pathology is associated with impaired cognition (15, 34, 42, 44, 53, 56, 119, 122–124, 136, 147, 154–162). Lacking more specific biomarkers, some studies have demonstrated associations between HS-Aging pathology and particular cognitive domains (116, 119, 135, 136). A cognitive profile in patients with autopsy-confirmed HS-Aging was described with relatively impaired Logical Memory Delayed Recall, yet with preserved verbal fluency (116). These findings were validated in a separate sample to differentiate cognitive impairment with HS-Aging pathology, versus AD or FTLD pathologies, at the group level (15).

HS-Aging is generally misdiagnosed in living individuals as AD because of the presence of a memory impairment and cognitive deterioration (15, 124). Put another way, a relatively large proportion (>10%, increased in advanced age) of “clinical AD” is actually HS-Aging. This may improve as some individuals with SNAP (36), based on clinical biomarkers, are removed from clinical AD cohorts. However, identification of HS-Aging cases will remain challenging in the large group of individuals with comorbid AD and HS-Aging pathologies because they are not SNAP (15, 53, 116, 163). Indeed, HS-Aging was found in 2 (9%) of the first 22 subjects followed to autopsy among intensely longitudinally studied subjects with clinical AD in the AD Neuroimaging Initiative (ADNI) cohort (164), whereas only 4 (18%) of these cases had pure AD pathology (165).

**HS-Aging: Clues About Pathogenesis and the Preclinical State**

Although the pathogenesis of HS-Aging is incompletely understood, some prior findings suggest that ischemia or other vascular dysfunction may contribute to the disease phenotype. As stated by Zarow et al (117), “HS has long been hypothesized to result from ischemic–hypoxic insult to the brain”. The CA1 sector is fed by small end-arterioles from the anterior choroidal and posterior cerebral arteries and is known to be susceptible to hypoxic injury (166). In a study of 13 aged individuals with HS, Dickson et al reported severe “arteriosclerosis” in 12 of the 13 cases (121), and others have also published data compatible with a link between HS-Aging and cerebrovascular disease (117, 123, 157, 167, 168). Subsequent studies have provided a more specific focus. We found that among vascular neuropathologies, only arteriosclerosis is associated with HS-Aging pathology (169). The association between HS-Aging and arteriosclerosis pathology throughout the brain was confirmed in a subsequent study (24) and is discussed further below.

In apparent contradiction to the hypothesis that HS-Aging is purely associated with cerebrovascular disease, HS-Aging brains also demonstrate characteristics that are indicative of a neurodegenerative condition. The clinical course of HS-Aging tends to follow the trajectory of a neurodegenerative disease (53, 116). A key pathologic biomarker for HS-Aging is aberrant hippocampal TDP-43 pathology that often resembles the pathologic pattern observed in FTLD-TDP (140, 141, 146, 170–172). In both HS-Aging and FTLD-TDP, slender TDP-43-immunoreactive neurites are observed in hippocampus, subiculum, and amygdala (termed “Type A” TDP-43 pathology) (86, 140, 170). Some gene variants that are associated with increased risk for HS-Aging (53, 124, 144, 173, 174) were previously associated with increased risk for FTLD (175, 176).

Thus, HS-Aging has been suggested to reflect both cerebrovascular dysfunction and abnormal proteostasis leading to protein misfolding, a mechanistic leitmotif of neurodegenerative processes (177, 178). Although these dual vascular and proteostasis mechanisms may seem contradictory, there is increasing evidence of synergistic “mixed” mechanisms that could lead to neurodegeneration (179–181). Analyzing this requires insights into TDP-43 pathology, which is the most specific marker for HS-Aging (116, 117, 140).

TDP-43 pathology was discovered in the context of brains along the clinical/genetic/pathologic spectrum that includes both amyotrophic lateral sclerosis (ALS) and FTLD (141); however, TDP-43 pathology is not specific for ALS/FTLD spectrum disorders. TDP-43 pathology has been reported in Alexander disease, Cockayne syndrome, Down syndrome, Guam ALS-parkinsonism-dementia, a subset of Lewy body disorders, low-grade glial neoplasms, inclusion body myositis, and chronic traumatic encephalopathy (97, 120, 142, 182–187). As such, TDP-43 pathology in some cases must represent a secondary (“downstream”) manifestation of diverse neurodegenerative, developmental, and “reactive” influences. Moreover, monogenic, early onset familial AD is frequently comorbid with hippocampal TDP-43 pathology (120, 188), which indicates molecular synergy for specific misfolded proteins, likely due to abnormal proteostasis. These observations argue strongly that conditions outside the ALS/FTLD spectrum may include TDP-43 pathology. A staging schema has been proposed to describe how TDP-43 pathology...

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is distributed in brains with comorbid AD pathology, many of which also had HS-Aging (189, 190). Notably, in multiple cohorts of aged persons, TDP-43 pathology is far more strongly linked to HS-Aging than early AD pathology (15, 53, 116, 136, 191). However, within the amygdala of subjects with advanced AD, protein misfolding of tau, Aβ, α-synuclein, and TDP-43 pathologies tends to occur (61, 192, 193). Accounting for the existing uncertainties, the above findings collectively indicate that multiple mechanisms can result in hippocampal TDP-43 pathology. The challenge is to define a unique condition with both TDP-43 (TDP[+]) and HS (HS[+]) pathologies.

For determining “boundary zones” that are meaningful for pathology-based classification, a key goal is to understand the disease in its preclinical stage(s). Current knowledge derives predominantly from cross-sectional data, and here we are referring mostly to autopsy series that include subjects over 85 years of age. The term “pre-HpScI” was used to describe hippocampal pathology characterized by none to minimal neuronal loss yet with abundant TDP-43 pathology (170). This partially overlaps with “segmental” HS-Aging, where only select portions of the TDP[+] hippocampal formation showed evidence of neuronal loss on H&E despite extensive additional sampling (194). Notably, in cases with unilateral HS according to H&E evaluation, the contralateral side is almost always positive for TDP-43 pathology (116).

Prior autopsy studies that reported a relatively high proportion of cases with HS[−]TDP[+] pathology (136, 61, 195), in contrast to studies with a higher proportion of HS[+]TDP[+] cases (116, 147), reflect the lack of universally applied diagnostic criteria for aging-related TDP-43 or HS-Aging pathologies. Thus, what one group may call HS[+]TDP[+], another would categorize as HS[−]TDP[+]. Yet taken together, the published studies are compatible with a progressive disease with limbic TDP-43 pathology in the early stages and HS in later stages.

Do TDP[+] cases in advanced age represent a subtype of FTLD-TDP? This is debatable, but there are reasons to consider TDP[+] in older subjects to be separate from FTLD-TDP. TDP-43 pathology seen in HS-Aging cases does not appear to progress to full-blown frontotemporal dementia (clinically) or FTLD-TDP (pathologically) when evaluated in community-based cohorts (25, 26, 135, 151, 61). TDP-43 pathology is rare before 65 years but allocortical TDP-43 pathology (i.e. within amygdala, hippocampus, entorhinal cortex) is common in octogenarians and nonagenarians (136, 196, 197). In a high-quality community-based cohort (n = 544, average age of death 89.0 years), 52% had limbic TDP-43 pathology but none had FTLD-TDP (198). Likewise, in the largest neuropathologic study to date of centenarians, there was not a single example of FTLD-TDP (24). The enormous difference in prevalence (Fig. 2) is a key point: FTLD-TDP affects approximately 20 000 individuals in United States (62), whereas HS-Aging afflicts well over 10 times as many if we extrapolate from large autopsy series (15, 56, 116, 117, 120, 135, 157, 199). In Figure 4, we provide cognitive, neuroimaging, and neuropathologic data on a patient with clinical “probable AD” yet whose autopsy showed HS[+]TDP[+] pathology by our criteria, and with very minimal Aβ deposition. To make progress in studying this common disease phenotype, it is critical to generate consensus about the disease-defining criteria. These efforts will be aided by clinical studies because there currently is no validated animal model.

In a recent neuroimaging study, Kotrotsou et al found that in elderly individuals dying with eventual autopsy-proven HS-Aging, premortem MRI studies showed extensive brain atrophy outside of the hippocampal formation, particularly in the frontal lobes (200). Furthermore, in the AD Neuroimaging Initiative (ADNI) data set (164), the HS-Aging risk alleles (described below) were associated with widespread MRI-detected brain atrophy outside of the hippocampus (201). Previous pathologic observations are compatible with the hypothesis that HS-Aging is actually a generalized disease that is often comorbid with pan-cerebral arteriolar sclerosis pathology, rather than one localized to medial temporal lobe structures (15, 56, 136, 158, 169, 194).

We interpret these prior findings to indicate that there is a common cerebral disease, affecting persons in advanced age, characterized by a spectrum of pathologies:

- preclinical disease → TDP – 43 pathology
- TDP – 43 pathology with HS and cerebral atrophy

In other words, the signal feature of the disease is TDP-43 pathology, rather than HS. Yet, there are more complexities. Perhaps analogous to the many non-AD diseases that are associated with hippocampal NFTs (202–204), some rare diseases, fundamentally different from HS-Aging, also show the HS[+]TDP[+] pattern (127, 132, 205, 206). To understand what makes HS-Aging unique, further knowledge is required about its specific pathogenesis.

**Genetics of HS-Aging**

Genetic risk factors can provide insights into disease-specific mechanisms. For example, APOE gene variants are not associated with altered risk for either TDP[+] or HS[+] neuropathology (15, 116, 124, 135, 207). This supports the hypothesis that HS-Aging is a separate disease entity from AD.

Genotypes linked to HS-Aging pathology have now been identified (Table 3). Potential risk alleles were first analyzed in 2 specific genes (GRN and TMEM106B), in line with the hypothesis that HS-Aging is related pathogenetically to FTLD-TDP. The first gene variant linked to HS-Aging pathology was rs5848, a single nucleotide polymorphism (SNP) located in the 3’UTR of GRN (173). This SNP is also associated with altered expression of GRN (144, 211). Whereas many different GRN mutations cause FTLD-TDP (212–216), the HS-Aging SNP (rs5848) is apparently a disease-modifying allele that impacts the manifestation of multiple different diseases rather than specifically of HS-Aging. For example, rs5848 has been linked to AD, Parkinson disease, C9ORF72 neurodegeneration, and bipolar disorder (173, 217–221), whereas several groups have reported that rs5848 is not linked to FTLD (208, 222).

The TMEM106B SNP rs1990622 is a risk allele for FTLD-TDP, as determined using a genome-wide association study (GWAS) (223), and the same SNP is linked to a coding variant and altered protein expression (224). TMEM106B...
Case Report: Patient followed longitudinally (>20yrs) with neurocognitive testing, brain MRI, and autopsy

FIGURE 4. Case study illustrates clinical and neuropathologic features of common comorbid diseases. The female subject was followed from 77 years until death at age 102 years. Detailed neurocognitive tests were performed until age 98 years; MCI was diagnosed clinically at age 93, “Probable Alzheimer Disease” at age 95. APOE genotype was ε3/ε3. (A) Panel shows results of MMSE (global cognition) and animal naming (verbal fluency) results; note that the verbal fluency was relatively stable even after global cognitive status was impaired. A brain MRI (horizontal plane) 10 years before death (B) showed hippocampal atrophy (arrows). Immunohistochemistry demonstrated extremely sparse Aβ amyloid pathology in temporal neocortex (C) and no neuritic plaques. Aβ amyloid in AD brain (D) is shown for comparison. In the hippocampal formation there was Braak NFT stage II tauopathy (E) and PART and HS-Aging were both diagnosed. Note that the hippocampal sclerosis is diagnosed according to consensus-based criteria (2): “cell loss and gliosis out of proportion to plaques and tangles,” rather than complete destruction of the structure. TDP-43 pathology was present in the hippocampus; (F) shows dentate gyrus with inclusions (arrows) and (G) shows subiculum with neuronal inclusion (arrow) and slender nontapering TDP-43 neurites (arrowheads). Widespread brain arteriolosclerosis pathology was also observed (Fig. 5). Panel (H) is a low-power photomicrograph showing the hippocampal formation including CA1, dentate granule (dg), and subiculum (Sub) regions. Adjacent sections were stained for phospho-Tau (P-Tau) and P-TDP-43 and the pathology was depicted schematically (inset I) using an Aperio ScanScope as described previously (56): red dots for NFTs, green dots for P-TDP-43 inclusions, and cyan region shows area with P-TDP-43 neurites. As noted previously (56), the tauopathic distribution in TDP[+]HS[+] cases is slightly different from “classic” early Braak NFT stages. Scale bars: C, 100 μm; D, 80 μm; E, 40 μm; F, 30 μm; G, 70 μm; H, 2 mm.
polypeptide is a lysosomal protein that apparently affects \textit{GRN} expression (225–227). The risk allele is associated with increased vulnerability to ALS and for neurodegeneration linked to \textit{C9orf72} repeat expansions (209,228). Further, in SNP-focused studies, rs1990622 status was found to be associated with HS pathology (53, 151, 229), altered AD phenotype (210, 229, 230), and cognition independent of AD or HS pathologies (196).

The studies on specific \textit{GRN} and \textit{TMEM106B} gene variants due to their link with other diseases left unaddressed the possibility of genotypes associated specifically with HS-Aging. A complementary experimental approach is GWAS, which is unbiased by prior mechanistic hypotheses. GWASs have now identified 2 putative HS-Aging risk genes, both of which encode potassium channel regulators: \textit{ABCC9} and \textit{TMEM106B} (151, 231).

The association between \textit{ABCC9} SNP rs704180 and HS-Aging pathology attained genome-wide significance in the GWAS paper (151), and has since been replicated (174), although not as extensively as \textit{GRN} and \textit{TMEM106B}. This intronic SNP is associated with altered \textit{ABCC9} mRNA expression (232), and nearby \textit{ABCC9} gene variants are also linked to other neurologic diseases such as sleep disorder and depression (233–235). The \textit{ABCC9} gene encodes proteins that regulate potassium channels (233, 234), serving as a metabolic “sensor” relevant to vascular responses to hypoxia, ischemia, and inflammation (236). There are published studies that support direct connections between \textit{ABCC9} and neurodegenerative disease mechanisms (237–244).

A second gene linked through GWAS to HS-Aging pathology is \textit{TMEM106B} (231). Intriguingly, Zarei et al found that the \textit{TMEM106B} gene product could be relevant to hippocampal physiology (245). As yet, the finding of association between the \textit{TMEM106B} SNP rs9637454 and HS-Aging remains to be replicated.

In summary, genomic studies provided meaningful indications about what may cause or protect against HS-Aging. The associations for both \textit{GRN} and \textit{TMEM106B} SNPs with HS-Aging risk have now been replicated, providing strong support for a mechanism relevant to both HS-Aging and FTLD-TDP. However, these HS-Aging risk SNPs are risk-modifying alleles in multiple diseases, thereby begging the question about the disease-specific “upstream” factors. The impact of these particular gene variants may be analogous to the \textit{MAPT} H1 haplotype that confers increased risk for PART, progressive supranuclear palsy, and other “sporadic” tauopathies (57, 105, 108, 246, 247), as opposed to \textit{MAPT} mutations that directly cause familial FTLD-MAPT (248–250). As with PART in comparison to FTLD-MAPT, the ultimate manifestations of HS-Aging and FTLD-TDP are also profoundly different from each other in terms of clinical (i.e. course and age range) and pathological features (15, 56). Although it is an important insight that particular \textit{GRN} and \textit{TMEM106B} SNPs can increase risk for TDP-43 pathology in multiple diseases, the experiments that discovered these phenomena were blind to the disease-specific “upstream” mechanisms involved in a disease that is far more common than FTLD-TDP. Published genome-wide analyses have implicated \textit{ABCC9} gene variants specific to HS-Aging. Because genomics information provides insights into pathogenesis, this may help in the delineation of the disease phenotype, shifting the focus to another brain pathology, namely aging-related brain arteriolosclerosis (B-ASC).

\textbf{Previously Unsuspected Pathologic Synergies: B-ASC and HS-Aging}

B-ASC describes pathologic thickening of the walls of brain arterioles not due to brain amyloid (58, 63, 169, 251–255). This subtype of small vessel pathology is very common in the brains of older individuals and is associated with impaired cognitive status, independent of other pathologies (255). In prior studies by us and others, it was implied that B-ASC represents a well-defined and classifiable subtype of vascular pathology in the CNS.

However, we have much to learn about brain arterioles in healthy and disease states. A recent review made trenchant points: “The term arteriolosclerosis actually does not define a lesion at all. It is a generic term meaning ‘hardening of small arteries’. In fact, the term encompasses 2 distinct lesions: (1) a fibromuscular proliferation of the intima, the ‘hyperplastic type’ and (2) a deposition of amorphous material in the arteriolar wall, the ‘hyaline type’” (256). Moreover, the current classification of arteriolosclerosis is not based on a consensus document by a major cerebrovascular, cardiovascular, or pathology organization (256). Despite progress in the field, relatively little is known about the neuropathology of elements that comprise brain arterioles, a complicated arrangement of endothelial cells, pericytes, smooth muscle cells, basement membrane, astrocyte end-feet, and extracellular matrix (64, 255, 257–261). Small blood vessels participate in energy exchange, removal of waste, blood pressure regulation, neuralgial activity, and neuroimmune functions and it seems clear that we still have much to learn.

\textit{TABLE 3.} Genes and Single Nucleotide Polymorphisms Associated With Risk for Hippocampal Sclerosis of Aging

| Gene     | SNP     | Experiment that Linked the Gene to HS-Aging: SNP-Focused or GWAS | Replicated? | References                  |
|----------|---------|------------------------------------------------------------------|------------|-----------------------------|
| GRN      | rs5848  | SNP-focused                                                      | Yes        | (124, 144, 173, 174)       |
| TMEM106B | rs1990622| SNP-focused                                                      | Yes        | (170, 174, 194, 196, 208, 209) |
| ABCC9    | rs704180| GWAS                                                             | Yes        | (24, 151, 174, 58) a       |
| KCNMB2   | rs9637454| GWAS                                                             | No         | (210)                       |

aReference (58) refers only to \textit{ABCC9} association with brain arteriolosclerosis.
Photomicrographs to convey some of the heterogeneity of vascular changes that may be diagnosed as B-ASC at autopsy are shown in Figure 5. In aged brains, arteriolar morphologies include pathologic variants other than "hyperplastic-" and "hyaline"-type changes. For example, some arterioles show degenerative changes in smooth muscle cells, whereas other arteriolar structures comprise multiple lumens (262, 263). Future work may better capture the heterogeneity of arteriolar disease phenotypes and provide the basis for robust clinical-pathologic correlations.

Although many unknowns remain in the study of B-ASC, insights have been gained. Studies of organs outside the brain indicate that arteriolosclerosis is associated with metabolic or cardiovascular disorders such as diabetes and hypertension (57, 256, 264–267). Ighodaro et al recently tested risk factors of B-ASC among 2390 persons who had come to autopsy with known B-ASC status using the National Alzheimer’s Coordinating Center data set (255, 268). These analyses indicated that advanced age at death was associated with B-ASC severity. Self-reported hypertension was only associated with B-ASC in the <80 years age at death group.

Interestingly, in the ≥80 years age at death group, the ABCC9 gene variant rs704180, previously associated with HS-Aging, was also associated with B-ASC (255). By contrast, neither GRN nor TMEM106B SNPs were associated with B-ASC (255). The hypothesis that ABCC9 is associated with arteriolosclerosis pathology throughout many different brain regions was supported in analyses of centenarians’ brains (24). Intriguingly, Lim et al recently reported that B-ASC is associated with “sleep fragmentation,” (269) and ABCC9 gene variants have been linked to sleep problems (235, 270, 271).

The observation that the same ABCC9 gene variant is associated with risk for both B-ASC and HS-Aging pathologies in old age provides the basis for a novel hypothesis combining cerebrovascular and neurodegenerative paradigms (255). One exciting aspect of implicating ABCC9 in disease pathogenesis is that ABCC9 gene product-modifying drugs (both agonists and antagonists) are widely used in the human pharmacopeia (272–275). We emphasize that the findings of ABCC9 require further validation; this is still a new hypothesis that requires more study.

**FIGURE 5.** Brain arteriolosclerosis (B-ASC) pathology is a complex phenotype. These panels show B-ASC vascular profiles in brains from different aged individuals to provide a small sampling of the heterogeneity of B-ASC. (A–C) Panels show hematoxylin and eosin staining. Panel (A) is a low-power photomicrograph depicting a vessel in the amygdala of a person with advanced AD and cerebrovascular disease. Note the large expanse of hyalinized material (*) that extends from the vessel wall, along with a patch of lymphocytic inflammation (arrow). By contrast, in the hippocampus of the case study (Fig. 4) there is a smaller blood vessel (boxed in B, magnified in C) that shows a vascular profile with apparent fibrinoid necrosis and/or microcalcifications in the paucicellular vessel wall. Another pattern we have seen in many cases is multiple vascular profiles in the same vessel bed, as shown in panel (D) (arterioles are here visualized using α-SMA immunohistochemistry). Collagen can be visualized using a trichrome stain (panels E, F are separate HS-Aging cases); a B-ASC profile is shown in E with the collagen labeled green. Cases with hippocampal TDP-43 in our experience often show neocortical B-ASC as visualized by the green-staining arterioles (arrows) in this low-power photomicrograph near the pia (*) of frontal neocortex, Brodmann Area 9. Scale bars: A, 200 μm; B, 90 μm; C, 10 μm; D, 25 μm; E, 70 μm; F, 100 μm.
Any hypothesis to conceptualize the aging-related disease that was previously labeled HS-Aging or HS dementia must include TDP-43 pathology. In each of the many conditions associated with TDP-43 pathology there is a chronic genetic and/or environmental insult to the brain. It is possible that a subtype of chronic vascular insult(s) could induce TDP-43 phosphorylation and misfolding. Numerous studies indicate that TDP-43 pathology does not appear to arise following...
acute hypoxic/ischemic neuronal injury (116, 117, 140, 142). This would be directly analogous to brain trauma, where a single traumatic event is not associated with TDP-43 pathology (276), yet approximately 80% of brains with chronic traumatic encephalopathy are positive for TDP-43 pathology (127). If chronic vascular dysfunction can lead to TDP$^-^+$ disease phenotype, then that disease may constitute a novel targetable cause of dementia. An intriguing possibility is that epidemiologic phenomena previously attributed to AD (65, 66) are related instead to this common, high-morbidity, but hitherto largely ignored disease.

Revised Terminology: A Recommendation

Whatever the pathogenetic mechanisms are, new terminology is required. Neither “HS-Aging,” nor any other extant term, is truly applicable. A terminology that focuses on FTLD, TDP-43, or HS in isolation would not be accurate based on the experimental data. Because the disease preferentially affects the “oldest-old,” often includes TDP-43 pathology and arteriolosclerosis well beyond the hippocampus, and may evolve to HS, we recommend the term “cerebral age-related TDP-43 and sclerosis” (CARTS). Features seen in CARTS are illustrated in Figure 6.

A diagnosis of CARTS indicates robust TDP-43 pathology in the hippocampus of persons aged >85 years at death and would otherwise incorporate the current TDP$^[+\text{]}$ cases termed HS-Aging, HpScl, and HS dementia. As stated above, it is relevant that both HS and arteriolosclerosis are often parts of the phenotype. We recommend that HS is not necessary for the diagnosis of CARTS because HS is ill-defined, nonspecific, and often segmental and, therefore, sampling bias would be considerable. Although B-ASC may well play a role in pathogenesis, the current diagnosis of B-ASC is too inconsistent to be practical as part of the diagnostic rubric at this time. The TDP-43 pathology frequently extends outside the hippocampus, but CARTS should not have the extremely dense subcortical TDP-43 pathology that occurs in FTLD-TDP. A hypothetical staging schema is presented in Table 4. Some older FTLD-TDP cases may be challenging to discriminate from CARTS in the absence of other biomarkers, but CARTS affects a virtually nonoverlapping age group in comparison with FTLD-TDP. AD and CARTS pathologies are both common pathologies and thus are expected to be comorbid frequently, although distinct ‘boundary zones’ will require further research.

CONCLUSION

High-quality, large autopsy cohorts and collaborative efforts among neuropathologists have enabled recent advances in the field of disease classification relevant to dementia. There are diagnostic “border zones” that need to be clarified and a better understanding of the “mixed” pathologies that are typical in advanced old age is needed. As these challenges are
addressed, the diagnoses increasingly reflect the biologic complexity and should help in efforts to identify appropriate patient groups for clinical trials. Particular diagnostic categories are in different stages of scientific “maturity,” with some having been studied in thousands of published papers, whereas others will require substantial additional work to achieve an accurate nosology. TDP-43 pathologies appear to be analogous to tau tangles, “upstream” factors and comorbid pathologies can disturb protein homeostasis, especially with the added influence of gene variants that increase risk across different diseases (Fig. 7). Categorizing the “downstream” pathology is complex because of the overlapping pathologic phenotypes. This is particularly true for CARTS because TDP-43, HS, and B-ASC pathologies all occur in multiple conditions. The recently revised pathologic concepts are not all truly novel. On the contrary, investigators had previously reported many of the manifestations of the brain diseases but lacked adequate contextual data. It is safe to assert that for all prior advances, current data are imperfect and skepticism should be sustained in considering the current diagnostic terms and criteria. Categorization of brain diseases of aging is still a work in progress.

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REFERENCES

1. Kovacs GG. Molecular pathological classification of neurodegenerative diseases: Turning towards precision medicine. Int J Mol Sci 2016;17
2. 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
3. Nelson PT, Braak H, Markesbery WR. Neuropathology and cognitive impairment in Alzheimer disease: A complex but coherent relationship. J Neuropath Exp Neurol 2009;68:1–14
4. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: A review of the literature (Review). J Neuropathol Exp Neurol 2012;71:362–81
5. Caspersen CJ, Thomas GD, Boeseman LA, et al. Aging, diabetes, and the public health system in the United States. Am J Public Health 2012; 102:1482–97
6. Chatterjee S, Peters SA, Woodward M, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: A pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diab Care 2016;39:300–7
7. Profenno LA, Porsteinsson AP, Faroane SV. Meta-analysis of Alzheimer’s disease risk with obesity, diabetes, and related disorders. Biol Psychiatry 2010;67:505–12
8. Lu FP, Lin KP, Kuo HK. Diabetes and the risk of multi-system aging phenotypes: A systematic review and meta-analysis. PLoS One 2009;4: e4144
9. Abner EL, Nelson PT, Kryscio RJ, et al. Diabetes is associated with cerebrovascular but not Alzheimer neuropathology. Alzheimer’s Dement 2016
10. Nelson PT, Head E, Schmitt FA, et al. Alzheimer’s disease is not “brain aging”: Neuropathological, genetic, and epidemiological human studies. Acta Neuropathol 2011;121:571–87
11. Nelson PT, Smith CD, Abner EA, et al. Human cerebral neuropathology of Type 2 diabetes mellitus. Biochim Biophys Acta 2009;1792: 454–69
12. Dugger BN, Malek-Ahmadi M, Monsell SE, et al. A cross-sectional analysis of late-life cardiovascular factors and their relation to clinically defined neurodegenerative diseases. Alzheimer Dis Assoc Disord 2016 [Epub ahead of print]
13. Beeri MS, Silverman JM, Davis KL, et al. Type 2 diabetes is negatively associated with Alzheimer’s disease neuropathology. J Gerontol A Biol Sci Med Sci 2005;60:471–5
14. Ahituv S, Polvikoski T, Petlonen M, et al. Diabetes, Alzheimer disease, and vascular dementia: A population-based neuropathologic study. Neurology 2010;75:1195–202
15. Brenowitz WD, Monsell SE, Schmitt FA, et al. Hippocampal sclerosis of aging is a key Alzheimer’s disease mimic: Clinical-pathologic correlations and comparisons with both Alzheimer’s disease and non-ataxic frontotemporal lobar degeneration. J Alzheimers Dis 2014; 39:691–702
16. Kovacs GG, Ferrer I, Grinberg LT, et al. Aging-related tau astrogliopathy (ARTAG): Harmonized evaluation strategy. Acta Neuropathol 2016;131:87–102
17. Dickson DW. Neuropathology of non-Alzheimer degenerative disorders. Int J Clin Exp Pathol 2009;3:1–23
18. Schmitt FA, Nelson PT, Abner E, et al. University of Kentucky Sanders-Brown Healthy Brain Aging Volunteers: Donor characteristics, procedures, and neuropathology. Curr Alzheimer Res 2012;9:724–33
19. 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;66:1136–46
20. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 1991;82:239–59
21. Jicha GA, Abner EL, Schmitt FA, et al. Preclinical AD workgroup staging: Pathologic correlates and potential challenges. Neurobiol Aging 2012;33:622 e1–e16
22. Jicha GA, Parisi JE, Dickson DW, et al. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. Arch Neurol 2006;63:674–81
23. 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;68:774–84
24. Neltner JH, Abner EL, Jicha GA, et al. Brain pathologies in extreme old age. Neurobiol Aging 2016;37:1–11
25. Rahimi J, Kovacs GG. Prevalence of mixed pathologies in the aging brain. Alzheimers Res Ther 2014;6:82
26. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 2006;66:1837–44
27. Schneider JA, Arvanitakis Z, Wang W, et al. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197–204
28. Robinson JL, Molina-Porcel L, Corrada MM, et al. Perforant path synaptic loss correlates with cognitive impairment and Alzheimer’s disease in the oldest-old. Brain 2014;137:2578–87
29. Barker WW, Luis CA, Kashuba A, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the state of Florida. Brain 2014;137:2578–87
30. Sanders-Brown Healthy Brain Aging Volunteers: Donor characteristics, procedures, and neuropathology. Curr Alzheimer Res 2012;9:724–33
31. Jellinger KA. Clinicopathological analysis of dementia disorders in the elderly—An update. J Alzheimers Dis 2006;9:61–70
32. Brenowitz WD, Nelson PT, Besser LM, et al. Cerebral amyloid angiopathy and its co-occurrence with Alzheimer’s disease and other cerebrovascular neuropathologic changes. Neurobiol Aging 2015;36: 2702–8
33. Jellinger KA. Clinicopathological analysis of dementia disorders in the elderly—An update. J Alzheimers Dis 2006;9:61–70
34. Schneider JA, Aggarwal NT, Barnes L, et al. Cerebral amyloid angiopathy and its co-occurrence with Alzheimer’s disease and other cerebrovascular neuropathologic changes. Neurobiol Aging 2015;36: 2702–8
35. Yarchosn M, Xie SX, Kling MA, et al. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. Brain 2012;135:3749–56
36. Schneider JA, Aggarwal NT, Barnes L, et al. Cerebral amyloid angiopathy and its co-occurrence with Alzheimer’s disease and other cerebrovascular neuropathologic changes. Neurobiol Aging 2015;36: 2702–8
37. Yarchosn M, Xie SX, Kling MA, et al. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. Brain 2012;135:3749–56
38. Schneider JA, Aggarwal NT, Barnes L, et al. The neuropathology of older persons with and without dementia from community versus clinic cohorts. J Alzheimers Dis 2009;18:691–701
39. Nelson PT, Abner EL, Schmitt FA, et al. Modeling the association between 43 different clinical and pathological variables and the severity of cognitive impairment in a large autopsy cohort of elderly persons. Brain Pathol 2010;20:56–79
135. Leverenz JB, Agustín CM, Tsuang D, et al. Clinical and neuropathological characteristics of hippocampal sclerosis: A community-based study. Arch Neurol 2002;59:1099–106

136. Nag S, Yu L, Capuano AW, et al. Hippocampal sclerosis and TDP-43 pathology in aging and Alzheimer disease. Ann Neurol 2015;77:942–52

137. Bachstetter AD, Van Eldijk LJ, Schmitt FA, et al. Disease-related microglia heterogeneity in the hippocampus of Alzheimer’s disease, dementia with Lewy bodies, and hippocampal sclerosis of aging. Acta Neuropathol Commun 2015;3:32

138. Hebert SS, Wang WX, Zhu Q, et al. A study of small RNAs from cerebral neocortex of pathology-verified Alzheimer’s disease, dementia with Lewy bodies, hippocampal sclerosis, frontotemporal lobar dementia, and non-demented human controls. J Alzheimers Dis 2013;35:335–48

139. Scheff SW, Neltner JH, Nelson PT. Is synaptic loss a unique hallmark of Alzheimer’s disease? Biochem Pharmacol 2014;88:517–28

140. Amador-Ortiz C, Lin WL, Ahmed Z, et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer’s disease. Ann Neurol 2007;61:435–45

141. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 2006;314:130–3

142. Lee EB, Lee VM, Trojanowski JQ, et al. TDP-43 immunoreactivity in axo-, ischemic and neoplastic lesions of the central nervous system. Acta Neuropathol 2008;115:305–11

143. Wilson RS, Yu L, Trojanowski JQ, et al. TDP-43 pathology, cognitive decline, and dementia in old age. JAMA Neurology 2013;70:1418–24

144. Dickson DW, Baker M, Radenkamas R. Common variant in GRN is a genetic risk factor for hippocampal sclerosis in the elderly. Neurodegener Dis 2010;7:170–4

145. Blass DM, Hatanpaa KJ, Brandt J, et al. Dementia in hippocampal sclerosis resembles frontotemporal dementia more than Alzheimer disease. Neurology 2004;63:492–7

146. Amador-Ortiz C, Ahmed Z, Zehr C, et al. Hippocampal sclerosis dementia differs from hippocampal sclerosis in frontal lobe degeneration. Acta Neuropathol 2007;113:245–52

147. Zarow C, Weiner MW, Ellis WG, et al. Prevalence, laterality, and comorbidity of hippocampal sclerosis in an autopsy sample. Brain Behav 2012;2:435–42

148. Mortimer JA. The Nun Study: Risk factors for pathology and clinical-pathologic correlations.Curr Alzheimer Res 2012;9:621–7

149. Bennett DA, Schneider JA, Aggarwal NT, et al. Decision rules guiding the clinical diagnosis of Alzheimer’s disease in two community-based cohort studies compared to standard practice in a clinic-based cohort study. Neuroepidemiology 2006;27:109–76

150. Jicha GA, Abner E, Schmitt FA, et al. Clinical features of mild cognitive impairment differ in the research and tertiary clinic settings. Dement Geriatr Cogn Disord 2008;26:187–92

151. Nelson PT, Estus S, Abner EL, et al. ABCCC9 gene polymorphism is associated with hippocampal sclerosis of aging pathology. Acta Neuropathol 2014;127:825–43

152. Whitwell JL, Wiste HJ, Weigand SD, et al. Comparison of imaging biomarkers in the Alzheimer Disease Neuroimaging Initiative and the Mayo Clinic Study of Aging. Arch Neurol 2012;69:614–22

153. Jack CR Jr, Thernau TM, Wiste HJ, et al. Transition rates between amyloid and neurogeneration biomarker states and to dementia: a population-based, longitudinal cohort study. Lancet Neurol 2016;15:56–64

154. Kawas CH, Kim RC, Sonnen JA, et al. Multiple pathologies are common and related to dementia in the oldest-old: The 90+ study. Neurology 2015;85:535–42

155. Zabar Y, Carson KA, Troncoso JC, et al. Dementia due to hippocampal sclerosis: Clinical features and comparison to Alzheimer’s disease. Neurology 1998;50:559–60

156. Crystal HA, Dickson DW, Slivinski MJ, et al. Pathological markers associated with normal aging and dementia in the elderly. Ann Neurol 1993;33:566–73

157. White L. Brain lesions at autopsy in older Japanese-American men as related to cognitive impairment and dementia in the final years of life: A summary report from the Honolulu-Asia aging study. J Alzheimers Dis 2009;18:713–25

158. Keage HA, Hunter S, Matthews FE, et al. TDP-43 pathology in the population: Prevalence and associations with dementia and age. J Alzheimers Dis 2014;42:641–50

159. Crystal HA, Dickson D, Davies P, et al. The relative frequency of “dementia of unknown etiology” increases with age and is nearly 50% in nonagenarians. Arch Neurol 2000;57:713–9

160. Clark AW, White CL III, et al. Primary degenerative dementia without Alzheimer pathology. Can J Neurol Sci 1986;13:462–70

161. Corrada MM, Berlau DJ, Kawas CH. A population-based clinicopathological study in the oldest-old: The 90+ study. Curr Alzheimer Res 2012;9:709–17

162. 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;134:3708–15

163. Mok W, Chow TW, Zheng L, et al. Clinicopathological concordance of dementia diagnoses by community versus tertiary care clinicians. Am J Alzheimers Dis Other Demen 2004;19:161–5

164. Weiner MW, Aisen PS, Jack CR Jr, et al. The Alzheimer’s disease neuroimaging initiative: Progress report and future plans. Alzheimers Dement 2010;6:202–11 e7

165. Toledo JB, Cairns NJ, Da X, et al. Clinical and multimodal biomarker correlates of ADNI neuropathological findings. Acta Neuropathologica Commun 2013;1:65

166. Duvernoy HM. The Human Hippocampus: Functional Anatomy, Vasculization and Serial Sections With MRI. New York: Springer-Verlag 2005

167. White L, Petrovitch H, Hardman J, et al. Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. Ann N Y Acad Sci 2002;977:9–23

168. Reed BR, Mungas DM, Kramer JH, et al. Profiles of neuropsychological impairment in autopsy-defined Alzheimer’s disease and cerebrovascular disease. Brain 2007;130:731–9

169. Neltner JH, Abner EL, Baker S, et al. Arteriosclerosis that affects multiple brain regions is linked to hippocampal sclerosis of ageing. Brain 2014;137:255–67

170. Aoki N, Murray ME, Ogaki K, et al. Hippocampal sclerosis in Lewy body disease is a TDP-43 proteinopathy similar to FTLD-TDP Type A. Acta Neuropathol 2015;129:53–64

171. Arai T, Hasegawa M, Akiyama H, et al. TDP-43 is a component of Lewy body disease. Cell Death Differ 1998;5:832–7

172. Davidson Y, Kelley T, Mackenzie IR, et al. Ubiquitinated pathological granulin mutations. Arch Neurol 2007;64:1148–53

173. Nelson PT, Wang WX, Partch AB, et al. Reassessment of risk genotypes in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochem Biophys Res Commun 2006;351:602–11

174. Trojanowski JQ, Lee VM. “Fatal attractions” of proteins. A comprehensive review. J Clin Invest 2000;105:1651–3

175. Trojanowski JQ, Lee VM. “Fatal attractions” of proteins. A comprehensive review. J Clin Invest 2000;105:1651–3

176. Deming Y, Cruchaga C. TMEM106B: A strong FTLD disease modifier. Acta Neuropathol 2014;127:825–43

177. Aoki N, Murray ME, Ogaki K, et al. Hippocampal sclerosis in Lewy body disease is a TDP-43 proteinopathy similar to FTLD-TDP Type A. Acta Neuropathol 2015;129:53–64

178. Arai T, Hasegawa M, Akiyama H, et al. TDP-43 is a component of endosomal Lewy body disease is a TDP-43 proteinopathy similar to FTLD-TDP Type A. Acta Neuropathol 2014;127:825–43

179. Deming Y, Cruchaga C. TMEM106B: A strong FTLD disease modifier. Acta Neuropathol 2014;127:825–43

180. Van Deursen VM, Wood EM, Moore P, et al. Clinical, genetic, and pathologic characteristics of patients with frontotemporal dementia and progranulin mutations. Arch Neurol 2007;64:1148–53

181. Trojanowski JQ, Lee VM. “Fatal attractions” of proteins. A comprehensive review. J Clin Invest 2000;105:1651–3

182. Trojanowski JQ, Goedert M, Ivatsubo T, et al. Fatal attractions: Abnormal protein aggregation and neuron death in Parkinson’s disease and Lewy body dementia. Cell Death Differ 1998;5:832–7

183. Snyder HM, Corriveau RA, Craft S, et al. Vascular contributions to cognitive impairment and dementia including Alzheimer’s disease. Alzheimers Dement 2015;11(6):710–7

184. 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;134:3708–15

185. Wellner RO, Hawkes CA, Carare RO, et al. Does the difference between PART and Alzheimer’s disease lie in the age-related changes in cerebral...
arteries that trigger the accumulation of Abeta and propagation of tau? Acta Neuropathol 2015;129:763–6
182. Walker AK, Daniels CM, Goldman JE, et al. Astrocytic TDP-43 pathology in Amyotrophic Lateral Sclerosis. J Neurol Sci 2014;34:648–58
183. Ling H, Holton JL, Lees AJ, et al. TDP-43 pathology is present in most post-encephalitic parkinsonism brains. Neuropathol Appl Neurobiol 2014;40:654–7
184. McKee AC, Gavett BE, Stern RA, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. J Neuropathol Exp Neurol 2010;69:918–29
185. Sakurai A, Makioka K, Fukuda T, et al. Accumulation of phosphorylated TDP-43 in the CNS of a patient with Cockayne syndrome. Neurobiology 2013;33:673–7
186. Geser F, Winton MJ, Kwong LK, et al. Pathological TDP-43 in Alzheimer’s disease brains. Acta Neuropathol Commun 2015;3:35
187. Walker AK, Daniels CM, Goldman JE, et al. Astrocytic TDP-43 pathol-
188. Uchikado H, Lin WL, DeLucia MW, et al. Alzheimer disease with parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam. Acta Neuropathol 2008;115:133–45
189. Nakashima-Yasuda H, Uryu K, Robinson J, et al. Co-morbidity of TDP-43 proteinopathy in lewy body related diseases. Acta Neuropathol 2007;114:212–9
190. Lippa CF, Rosso AL, Stutzbach LD, et al. Transactive response DNA-binding protein 43 burden in familial Alzheimer disease and Down syndrome. Arch Neurol 2009;66:1483–8
191. Josephs KA, Murray ME, Whitwell JL, et al. Staging TDP-43 pathology in Alzheimer’s disease. Acta Neuropathol 2014;127:441–50
192. Josephs KA, Murray ME, Whitwell JL, et al. Updated TDP-43 in Alzheimer’s disease staging scheme. Acta Neuropathol 2016 Apr;131(4):571–85
193. Cykowsky MD, Takei H, Van Eldik LJ, et al. Hippocampal sclerosis but not normal aging or Alzheimer’s disease is associated with TDP-43 pathology in aged persons’ basal forebrain. J Neuropathol Exp Neurol 2016;75:397–407
194. Uchikado H, Lin WL, DeLucia MW, et al. Alzheimer disease with amygdala lewy bodies: A distinct form of alpha-synucleinopathy. J Neuropathol Exp Neurol 2006;65:685–97
195. Chiche A, Takao M, Hatsuta H, et al. Incidence and extent of TDP-43 accumulation in aging human brain. Acta Neuropathol Commun 2015;3:35
196. Ighodaro ET, Jicha GA, Schmitt FA, et al. Hippocampal sclerosis of aging can be segmental: Two cases and review of the literature. J Neuropathol Exp Neurol 2015;74:62–52
197. Nascimento C, Suemoto CK, Rodriguez RD, et al. Higher Prevalence of TDP-43 proteinopathy in cognitively normal Asians: A clinicopathological study on a multiethnic sample. Brain Pathol 2016;26:177–85
198. Yu L, De Jager PL, Yang J, et al. The TMEM106B locus and TDP-43 pathology in older persons without FTLD. Neurology 2015;85:1354–5
199. Fenoglio C, Galimberti D, Cortini F, et al. R5848 variant influences GRN mRNA levels in brain and peripheral mononuclear cells in patients with Alzheimer’s disease. J Alzheimers Dis 2009;18:603–12
200. Baker M, McMackin RJ, Pickering-Brown SM, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006;442:916–17
201. Boeve BF, Baker M, Dickson DW, et al. Frontotemporal dementia and parkinsonism associated with the IVS1 +1G→A mutation in progranulin. Clinincopathologic study. Brain 2006;129:3103–14
202. Cruts M, Gijselink I, van der Zee J, et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 2006;442:920–4
203. Cruts M, Kumar-Singh S, Van Broeckhoven C. Progranulin mutations in ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Curr Alzheimer Res 2006;3:485–91
204. Snowden JS, Pickering-Brown SM, McMackin RJ, et al. Progranulin gene mutations associated with frontotemporal dementia and progressive non-fluent aphasia. Brain 2006;129:3091–102
205. van Blitterswijk M, Mullien B, Wojtas A, et al. Genetic modifiers in carriers of repeat expansions in the C9ORF72 gene. Mol Neurodegener 2014;9:38
206. Kamalainen A, Viswanathan A, Natunen T, et al. GRN variant rs5848 reduces plasma and brain levels of granulin in Alzheimer’s disease patients. J Alzheimers Dis 2013;33:23–7
207. Chang KH, Chen CM, Chen YC, et al. Association between GRN rs5848 polymorphism and Parkinson’s disease in Taiwanese population. PLoS One 2013;8:e54448
208. Galimberti D, Dell’Osso B, Fenoglio C, et al. Progranulin gene variability and plasma levels in bipolar disorder and schizophrenia. PloS One 2012;7:e32164
209. Pickering-Brown SM, Rollinson S, Du Plessis D, et al. Frequency and clinical characteristics of progranulin mutation carriers in the Manchester frontotemporal lobar degeneration cohort: Comparison with patients with MAPT and no known mutations. Brain 2008;131:721–31
210. Rollinson S, Rohrer JD, van der Zee J, et al. No association of PGRN 3’UTR rs5848 in frontotemporal lobar degeneration. Neurobiol Aging 2011;32:754–5
211. Van Deurinck VM, Sleiman PM, Martinez-Lage M, et al. Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions. Nat Genet 2010;42:234–9
212. Nicholson AM, Finch NA, Wojtas A, et al. TMEM106B p.T1855 regulates TMEM106B protein levels: implications for frontotemporal dementia. J Neurochem 2013;126:781–91
213. Brady OA, Zheng Y, Murphy K, et al. The frontotemporal lobar degeneration risk factor, TMEM106B, regulates lysosomal morphology and function. Hum Mol Genet 2013;22:685–95
214. Lang CM, Fellerer K, Schwenk BM, et al. Membrane orientation and subcellular localization of transmembrane protein 106B (TMEM106B), a major risk factor for frontotemporal lobar degeneration. J Biol Chem 2012;287:19355–65
215. Finch N, Carrasquillo MM, Baker M, et al. TMEM106B regulates progranulin and the penetrance of FTLD in GRN mutation carriers. Neurology 2011;76:467–74
216. Wood HB. TMEM106B is a susceptibility locus for FTD. Nat Rev Neurol 2010;6:184
217. Rutherford NJ, Carrasquillo MM, Li M, et al. TMEM106B risk variant is implicated in the pathologic presentation of Alzheimer disease. Neurology 2012;79:717–8
218. Lu RC, Wang H, Tan MS, et al. TMEM106B and APOE polymorphisms interact to confer risk for late-onset Alzheimer’s disease in Han Chinese. J Neurol Transm 2014;121:283–7
