Conclusions

Although this report has the limitation of all retrospective analyses: the lack of randomization, we found a positive effect of donepezil on lifetime expectancy after onset of AD. This may be due to a decreased mortality rate caused by reduction of concomitant diseases such as pneumonia. The similar life expectancies in patients taking donepezil at home and those not taking donepezil in a nursing home indicated a positive health economic effect of the drug.

Competing interests

We declare that we have no financial competing interests or non-financial competing interests.

Authors' contributions

KM: data analysis and writing an article. MK: data analysis. KA, MM: data collection. HI, SY: physicians in charge and data collection. All authors read and approved the final manuscript.

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CONSENSUS PAPER

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

John F. Crary · John Q. Trojanowski · Julie A. Schneider · Jose F. Abisambra · Erin L. Abner · Irina Alafuzoff · Steven E. Arnold · Johannes Attems · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Marla Gearing · Lea T. Grinberg · Patrick R. Hof · Bradley T. Hyman · Kurt Jellinger · Gregory A. Jicha · Gabor G. Kovacs · David S. Knopman · Julia Kofler · Walter A. Kukull · Ian R. Mackenzie · Eliezer Masliah · Ann McKee · Thomas J. Montine · Melissa E. Murray · Janna H. Neltner · Ismael Santa-Maria · William W. Seeley · Alberto Serrano-Pozo · Michael L. Shelanski · Thor Stein · Masaki Takao · Dietmar R. Thal · Jonathan B. Toledo · Juan C. Troncoso · Jean Paul Vonsattel · Charles L. White 3rd · Thomas Wisniewski · Randall L. Woltjer · Masahito Yamada · Peter T. Nelson

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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 (NFTs) that are indistinguishable from those of Alzheimer's disease (AD), in the absence of amyloid (Aβ) plaques. For these "NFT+/Aβ−" brains, for which formal criteria for AD neuropathologic changes are not met, the NFTs 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 amnestic 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 Aβ 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.

J. F. Crary (✉) · I. Santa-Maria · M. L. Shelanski · J. P. Vonsattel
Department of Pathology and 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
e-mail: john.crary@mountsinai.org

J. Q. Trojanowski · J. B. Toledo
Department of Pathology, Division of Neuropathology, University of Pennsylvania, Philadelphia, PA 19104, USA

J. A. Schneider
Departments of Pathology (Neuropathology) and Neurological Sciences, Rush University Medical Center, Chicago, IL 60612, USA

J. F. Abisambra
Department of Physiology and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA

E. L. Abner
Department of Public Health and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA

I. Alafuzoff
Department of Immunology, Genetics and Pathology, Uppsala University, SE-751 85 Uppsala, Sweden

S. E. Arnold
Departments of Psychiatry and Neurology, University of Pennsylvania, Philadelphia, PA 19104, USA

J. Attems
Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne NE45PL, UK

T. G. Beach
Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, AZ 85351, USA

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Introduction

We propose a new term, "primary age-related tauopathy" (PART), to describe a pathologic continuum ranging from focally distributed neurofibrillary tangles (NFTs) 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, because the term "dementia", as in "tangle-only dementia", implies a multidomain 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 Aβ 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]. NFTs 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)

E. H. Bigio
Department of Pathology (Neuropathology), Northwestern Cognitive Neurology and Alzheimer Disease Center, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA

N. J. Cairns
Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO 63110, USA

D. W. Dickson · M. E. Murray
Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA

M. Gearing
Department of Pathology and Laboratory Medicine (Neuropathology), Emory University School of Medicine, Atlanta, GA 30322, USA

L. T. Grinberg
Departments of Neurology and Pathology, UC, San Francisco, CA 94110, USA

L. T. Grinberg
Department of Pathology, University of Sao Paulo, Sao Paulo, Brazil

P. R. Hof
Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

B. T. Hyman
Department of Neurology, Harvard Medical School and Massachusetts General Hospital, Charlestown, MA 02129, USA

K. Jellinger
Institute of Clinical Neurobiology, 1070 Vienna, Austria

G. A. Jicha
Department of Neurology and the Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA

G. G. Kovacs
Institute of Neurology, Medical University Vienna, 1090 Vienna, Austria

D. S. Knopman
Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA

J. Kofler
Department of Pathology (Neuropathology), University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA

W. A. Kukull
Department of Epidemiology, University of Washington, Seattle, WA 98104, USA

I. R. Mackenzie
Department of Pathology, University of British Columbia, 855 West 12th Avenue, Vancouver, BC V5Z 1M9, Canada

lacking Aβ 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 clinicopathologic correlations challenging in this population [76, 80, 108, 109, 117, 125], and the entire clinicopathologic 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.) displays 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

E. Masliah
Departments of Neurosciences and Pathology, University of California, San Diego, La Jolla, CA 92093, USA

A. McKee
Department of Pathology (Neuropathology), Boston University, Boston, MA 02118, USA

T. J. Montine
Department of Pathology, University of Washington, Seattle, WA 98104, USA

J. H. Neltner
Department of Pathology, University of Kentucky, Lexington, KY 40536, USA

W. W. Seeley
Departments of Neurology and Pathology, University of California, San Francisco, CA 94143, USA

A. Serrano-Pozo
Department of Neurology, University of Iowa Hospitals and Clinics, Iowa city, IA 52242, USA

T. Stein
Department of Pathology (Neuropathology), VA Medical Center and Boston University School of Medicine, Boston, MA 02118, USA

M. Takao
Department of Neuropathology, Tokyo Metropolitan Geriatric Hospital, Tokyo 173-0015, Japan

D. R. Thal
Laboratory of Neuropathology, University of Ulm, 89081 Ulm, Germany

J. C. Troncoso
Department of Pathology and Laboratory Medicine, Institute on Aging, Center for Neurodegenerative Disease Research, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA

C. L. White 3rd
Department of Pathology (Neuropathology), University of Texas Southwestern Medical School, Dallas, TX 75390, USA

T. Wisniewski
Departments of Neurology, Pathology and Psychiatry, New York University School of Medicine, New York, NY 10016, USA

R. L. Woltjer
Department of Pathology L113, Oregon Health Sciences University, Portland, OR 97239, USA

M. Yamada
Departments of Neurology & Neurobiology of Aging, Kanazawa University Graduate School of Medical Sciences, Kanazawa 920-8640, Japan

P. T. Nelson (✉)
Department of Pathology (Neuropathology) and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA
e-mail: pnels2@email.uky.edu

Table 1 Clinical features of primary age-related tauopathy (PART)

	Amyloid plaque density	Braak stage				
		0	I	II	III	IV
Number of subjects						
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
Age at death (average)						
PART, definite	None	81.3	82.4	88.5	88.4*	92.0*,**
PART, possible	Low	88.4	80.4	84.7	89.7*	87.6*
–	Mod	89.0	80.2	87.4*	84.9	86.5
–	High	77.0	84.9	86.7	85.3	84.6
Final MMSE scores						
PART, definite	None	28.0	28.4	26.5	25.1***	24.3***
PART, possible	Low	28.5	25.8	24.4	24.6	21.9*
–	Mod	26.5	26.8	27.3	23.2*	19.8*
–	High	25.5*	24.5	27.9*	21.2*	18.8*,**
APOE ε4 positive (%)						
PART, definite	None	9.1	13.6	0.0	20.0	13.3
PART, possible	Low	25.0	12.5	14.8	37.5	35.5*
–	Mod	0.0	36.4	13.3	34.4*	50.0*
–	High	66.7*	28.6	50.0*	33.3*	56.6*,**

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)

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 Aβ-type amyloidosis is common. Reported biomarkers include CSF Aβ(1–42) or positron emission tomography (PET) imaging for Aβ 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 Aβ-type amyloidosis [75, 87]. In persons with amnestic 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 Aβ- or tau-related pathogenic mechanisms. PART and AD may well respond differently to those therapeutic interventions [23], which underscore 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 NFTs 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 NFTs 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. NFTs 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 NFTs 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 transsynaptically [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 NFTs in PART, as in AD, contains accumulation of both 3-repeat (3R) and 4-repeat (4R) tau isoforms (Fig. 3a–c) [70, 79, 122, 130]. In AD NFTs, electron microscopy has revealed predominantly paired helical filaments (PHFs), 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: the NFT is one of the two defining pathological hallmarks of AD, the other is the Aβ plaque. However, AD-type NFTs are almost ubiquitously observed in older persons' brains, even in the absence of Aβ plaques

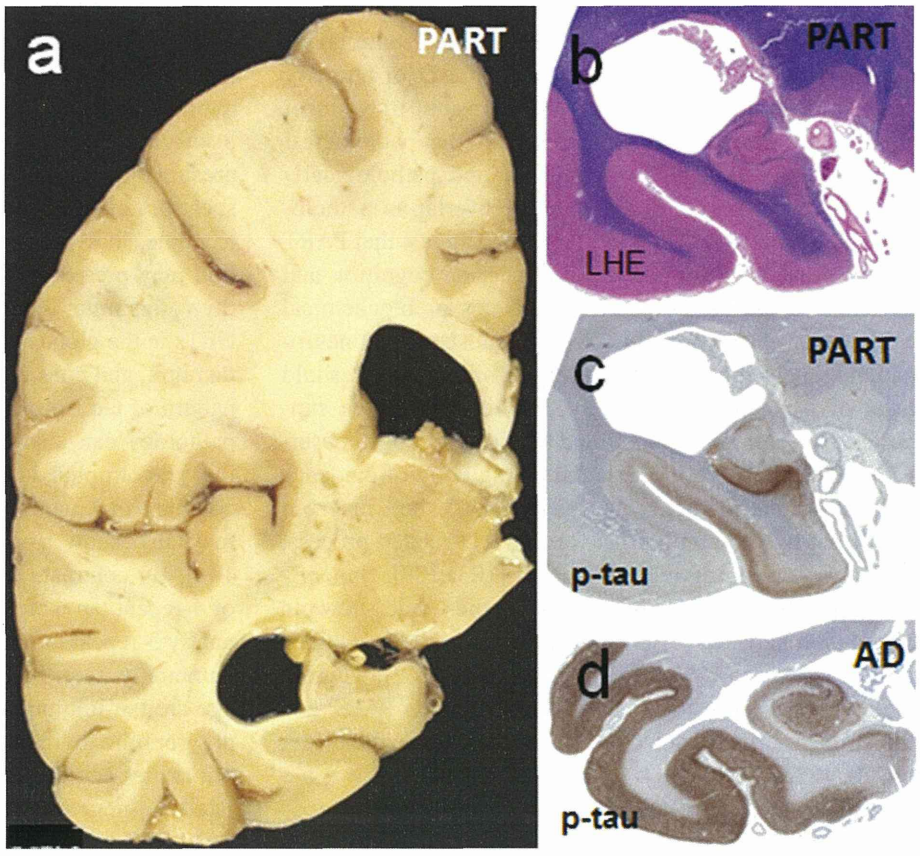

Fig. 1 Primary age-related tauopathy (PART): gross pathology and low-power photomicrographs. **a** A formalin-fixed left hemisphere from a 103-year-old woman reveals enlargement of the inferior horn of lateral ventricle and severe medial temporal atrophy. Only mild neocortical atrophy is present. **b** 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

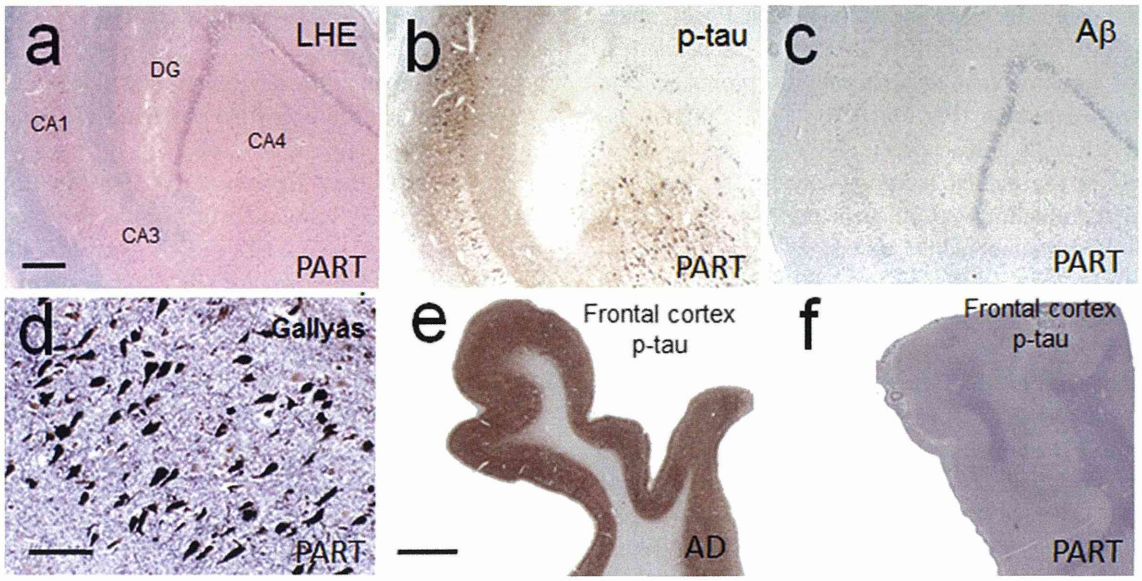

Fig. 2 Primary age-related tauopathy (PART): histopathology. The neuropathology corresponds to Braak stages I–IV, with involvement of the hippocampal formation (**a**–**c** are nearly serial sections from the hippocampus of the same patient) as shown with Luxol fast *blue*-counterstained hematoxylin–eosin (LHE) (**a**), and p-tau (AT8) immunohistochemistry (**b**). However, unlike cases with AD, Aβ 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 μm, and *scale bar* in **e** 5 mm for (**e**, **f**). *CA1-4* denote the hippocampal subfields, *DG* dentate gyrus

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, NFTs in the brainstem of younger adults show features in common with the pathological processes of AD [31]. Yet clinically and pathologically salient features may differ despite the overlap in pathologies. In comparison to AD, current data suggest that PART typically has a far more limited impact on cognition and develops in persons without Aβ plaques or biochemical evidence of elevated Aβ [122]. A diagnosis of AD neuropathologic changes requires at least a minimum threshold level of Aβ 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 NFTs 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* ε4 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 germline *MAPT* R406W mutation may present as a temporal lobe predominant tauopathy with similar features to TPSD [63], but the presence of NFTs in the globus pallidus, subthalamic nucleus, substantia nigra, and pons in such cases is 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 α-synuclein and TDP-43 pathology [50, 140]. By contrast, PSP and CBD display a predominance of 4-repeat tau isoforms, and Pick disease shows 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, and 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 Aβ deposition below which a diagnosis of definite PART is appropriate, and the relative importance of diffuse amyloid and neuritic plaques, require further study. In addition, 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 NFTs, 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-Aβ tauopathy with features that overlap pathologically with PART [95], and in the future markers may be developed to better discriminate between disorders in which NFTs 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.

Neuropathologic criteria

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, Aβ 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,

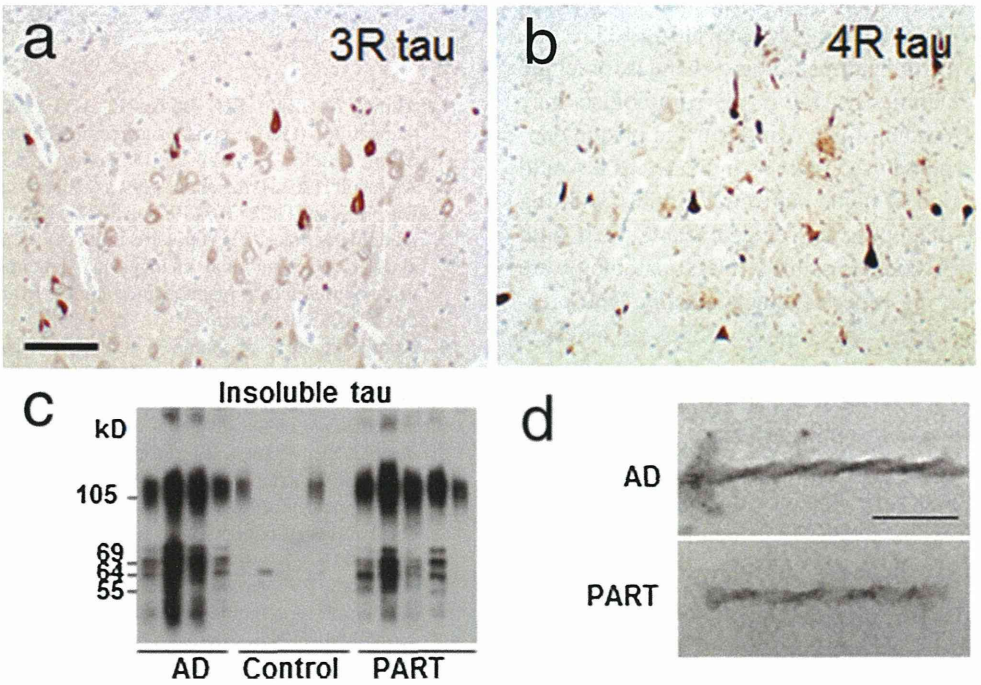

Fig. 3 The NFTs of PART resemble those of AD by immunohistochemistry, biochemistry, and ultrastructure. **a**, **b** NFTs in PART reveal immunoreactivity with both 3R and 4R anti-tau monoclonal antisera (RD3 and RD4, respectively). *Scale bar* 200 μm for **a**, **b**. **c** Immunoblot using polyclonal 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 2 Primary age-related tauopathy (PART): working classification

1. Requires		
NFTs present with Braak stage ≤IV (usually III or lower)		
2. Then subclassify as follows		
Category	Thal Aβ Phase[a]	Other disease associated with NFT[b]
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 Aβ phase 2		
3. Ancillary studies (not required)		
Immunohistochemistry: 3R and 4R tau-positive		
Electron microscopy: paired helical filaments present		
Genetics: absence of pathogenic FTLD-tau mutation		

[a] 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"

[b] For example, "progressive supranuclear palsy", "corticobasal degeneration", "Pick's disease", "frontotemporal lobar degeneration with *MAPT* mutation", and "chronic traumatic encephalopathy"

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 Aβ 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 is 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 Aβ plaques is unusual and in these cases the possibility of a FTLD-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.

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Short Communication

Lack of Genetic Association Between *TREM2* and Late-Onset Alzheimer's Disease in a Japanese Population

Akinori Miyashita[a,*], Yanan Wen[a], Nobutaka Kitamura[b], Etsuro Matsubara[c,1], Takeshi Kawarabayashi[c], Mikio Shoji[c], Naoki Tomita[d], Katsutoshi Furukawa[d], Hiroyuki Arai[d], Takashi Asada[e], Yasuo Harigaya[f], Masaki Ikeda[g], Masakuni Amari[g], Haruo Hanyu[h], Susumu Higuchi[i], Masatoyo Nishizawa[j], Masaichi Suga[k], Yasuhiro Kawase[l], Hiroyasu Akatsu[m,2], Masaki Imagawa[n], Tsuyoshi Hamaguchi[o], Masahito Yamada[o], Takashi Morihara[p], Masatoshi Takeda[p], Takeo Takao[q], Kenji Nakata[r], Ken Sasaki[r], Ken Watanabe[s], Kenji Nakashima[t], Katsuya Urakami[u], Terumi Ooya[v], Mitsuo Takahashi[w], Takefumi Yuzuriha[x], Kayoko Serikawa[y], Seishi Yoshimoto[y], Ryuji Nakagawa[y], Yuko Saito[z], Hiroyuki Hatsuta[aa], Shigeo Murayama[aa], Akiyoshi Kakita[bb], Hitoshi Takahashi[bb], Haruyasu Yamaguchi[cc], Kohei Akazawa[b], Ichiro Kanazawa[dd], Yasuo Ihara[ee], Takeshi Ikeuchi[a] and Ryozo Kuwano[a,*]

[a]*Department of Molecular Genetics, Brain Research Institute, Niigata University, Niigata, Japan*
[b]*Department of Medical Informatics, Niigata University, Niigata, Japan*
[c]*Department of Neurology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan*
[d]*Department of Geriatric and Complementary Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan*
[e]*Department of Psychiatry, University of Tsukuba, Tsukuba, Japan*
[f]*Department of Neurology, Maebashi Red Cross Hospital, Maebashi, Japan*
[g]*Department of Neurology, Gunma University Graduate School of Medicine, Maebashi, Japan*
[h]*Department of Geriatric Medicine, Tokyo Medical University, Tokyo, Japan*

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[1]Present address: Department of Neurology, Oita University Faculty of Medicine, Yufu, Japan.

[2]Present address: Department of Medicine for Aging Place Community Health Care/Community-Based Medical Education, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

*Correspondence to: Ryozo Kuwano, 1-757 Asahimachi, Chuo-ku, Niigata, Niigata 951-8585, Japan. Tel.: +81 25 227 2274; Fax: +81 25 227 0793; E-mail: ryosun@bri.niigata-u.ac.jp (R. Kuwano); and Akinori Miyashita, 1-757 Asahimachi, Chuo-ku, Niigata 951-8585, Japan. Tel.: +81 25 227 2344; Fax: +81 25 227 0793; E-mail: miyashi@bri.niigata-u.ac.jp.

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[i]*Division of Clinical Research, Kurihama Alcoholism Center, Yokosuka, Japan*
[j]*Department of Neurology, Brain Research Institute, Niigata University, Niigata, Japan*
[k]*Higashi Niigata Hospital, Niigata, Japan*
[l]*Kawase Neurology Clinic, Sanjo, Japan*
[m]*Choju Medical Institute, Fukushimura Hospital, Toyohashi, Japan*
[n]*Imagawa Clinic, Osaka, Japan*
[o]*Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan*
[p]*Department of Psychiatry, Osaka University Graduate School of Medicine, Suita, Japan*
[q]*Kurashiki Heisei Hospital, Kurashiki, Japan*
[r]*Kinoko Espoir Hospital, Kasaoka, Japan*
[s]*Watanabe Hospital, Tottori, Japan*
[t]*Department of Neurology, Tottori University, Yonago, Japan*
[u]*Department of Biological Regulation, Section of Environment and Health Science, Tottori University, Yonago, Japan*
[v]*Town Office, Onan, Japan*
[w]*Department of Clinical Pharmacology, Fukuoka University, Fukuoka, Japan*
[x]*Department of Psychiatry, National Hospital Organization, Hizen Psychiatric Center, Saga, Japan*
[y]*Ureshino-Onsen Hospital, Saga, Japan*
[z]*Department of Pathology, National Center Hospital of Neurology and Psychiatry, Tokyo, Japan*
[aa]*Department of Neuropathology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan*
[bb]*Department of Pathology, Brain Research Institute, Niigata University, Niigata, Japan*
[cc]*Graduate School of Health Sciences, Gunma University, Maebashi, Japan*
[dd]*National Center Hospital of Neurology and Psychiatry, Tokyo, Japan*
[ee]*Department of Neuropathology, Doshisha University, Kizugawa, Japan*

Abstract. Rare non-synonymous variants of *TREM2* have recently been shown to be associated with Alzheimer's disease (AD) in Caucasians. We here conducted a replication study using a well-characterized Japanese sample set, comprising 2,190 late-onset AD (LOAD) cases and 2,498 controls. We genotyped 10 non-synonymous variants (Q33X, Y38C, R47H, T66M, N68K, D87N, T96K, R98W, H157Y, and L211P) of *TREM2* reported by Guerreiro *et al.* (2013) by means of the TaqMan and dideoxy sequencing methods. Only three variants, R47H, H157Y, and L211P, were polymorphic (range of minor allele frequency [MAF], 0.0002–0.0059); however, no significant association with LOAD was observed in these variants. Considering low MAF of variants examined and our study sample size, further genetic analysis with a larger sample set is needed to firmly evaluate whether or not *TREM2* is associated with LOAD in Japanese.

Keywords: Alzheimer's disease, Japanese, rare variants, SNP, *TREM2*

INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia in the elderly. AD is thought to be caused by complex interactions between genetic and environmental factors. A twin study demonstrated that the heritability of late-onset AD (LOAD) is approximately 60~80% [1]. It is also assumed that multiple genes/loci contribute to LOAD development [2]. Rare non-synonymous mutations of *APP*, *PSEN1*, and *PSEN2* are well known to cause familial cases of early-onset AD (EOAD) [3], which accounts for several percent of AD. Concerning LOAD, genome-wide association studies with large numbers of subjects have been conducted, based on the common diseases-common variants hypothesis. As a result, over a dozen genes other than *APOE* have been to be associated with the susceptibility to LOAD [4–10].

TREM2 was recently identified as a novel susceptibility gene for LOAD in Caucasians by two independent study groups [11, 12], both studies being performed on the basis of the common diseases-rare variants hypothesis. A noteworthy fact is that the most significant non-synonymous variant, R47H

(rs75932628: CGC⟶CAC; and minor allele frequency [MAF] < about 1%), located within exon 2 of *TREM2*, shows an odds ratio (OR) range of 2.0–5.0 [11, 12], which is almost equal to the risk magnitude for the *APOE*-ε4 allele [13, 14]. The association of this variant with LOAD [15–19] as well as EOAD [20] has been reproducibly confirmed in multiple Caucasian populations. As to Asians, at present there has only been one genetic association study on *TREM2* variants and LOAD, a northern Han Chinese population being involved [21]. In that study, it was demonstrated that no *TREM2* variants, including R47H, examined show significant association with LOAD [21]. It is assumed that *TREM2* may be a Caucasian-specific susceptibility gene for AD. Therefore, in this study we attempted to replicate the association of *TREM2* with LOAD utilizing a Japanese sample set, comprising 4,688 subjects in total.

SUBJECTS AND METHODS

Subjects

This study was approved by the Institutional Review Board of Niigata University and by all participating institutes. All subjects were Japanese and anonymously genotyped.

We prepared a Japanese sample set, comprising 2,190 LOAD cases (clinically-verified, $n = 1{,}977$; and neuropathologically-characterized, $n = 213$) and 2,498 controls (clinically-verified, $n = 2{,}128$; and neuropathologically-characterized, $n = 370$) (Table 1). From power analysis on the basis of Guerreiro et al.'s study with Caucasians [11], this sample set was estimated to be large enough to detect risk alleles with an OR of 1.1–2.5 (range of risk allele frequency = 0.01–0.99, $\alpha = 0.05$, power = 80%) [29]. A large proportion of the clinically-verified subjects were the same (74.8%) as those in the overall sample set used in our previous genetic study on *GAB2* [22]. The LOAD patients met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association for a diagnosis of probable AD [23]. Non-dementia controls were recruited from among elderly people living in an unassisted manner in the local community. Mini-Mental State Examination [24], Clinical Dementia Rating [25], and/or Function Assessment Staging [26] were applied to assess the severity of the cognitive impairment. All neuropathologically-characterized subjects were utilized in our recent genetic study on *SORL1* [27].

Extraction and quantification of genomic DNA, and *APOE* genotyping are described elsewhere [27, 28]. The *APOE* alleles exhibited strong association with LOAD, as expected: $p_{\text{allele}} = 6.71\text{E-}171$ with χ^2 test (χ^2 value = 783.7, degree of freedom = 2), and $\text{OR}_{\varepsilon 4/\varepsilon 3}$ (95% confidence interval [CI]) = 4.81 (4.26–5.42) and $\text{OR}_{\varepsilon 2/\varepsilon 3}$ (95% CI) = 0.59 (0.46–0.76).

TREM2 variants and genotyping

To determine whether or not *TREM2* is associated with LOAD in Japanese, we focused on 12 non-synonymous variants of this gene, which were examined in Guerreiro *et al.*'s study with Caucasians [11]: Q33X (rs104894002), Y38C (rs ID, not available), R47H (rs75932628), R62H (rs143332484), T66M (rs201258663), N68K (rs ID, not available), D87N (rs142232675), T96K (rs2234253), R98W (rs147564421), R136Q (rs149622783), H157Y (rs2234255), and L211P (rs2234256). However, two variants, R62H and R136Q, were excluded since one (R62H) did not satisfy the design criteria for the TaqMan® genotyping assay and the other (R136Q) did not work well on TaqMan® genotyping. Consequently, we determined the genotypes of the remaining ten *TREM2* variants using the TaqMan® method (Table 2, Supplementary Table 1). Heterozygotes were further evaluated by means of dideoxy DNA sequencing. Information on sequencing primers is available on request.

Statistical analysis

To detect genotyping errors, a Hardy-Weinberg equilibrium (HWE) test based on Fisher's exact test was conducted. From a 2 × 2 contingency table (case-control status and genotype [MM and Mm]), we computed genotypic p (p_{genotype}) based on Fisher's exact test and OR with 95% CI as the relative risk of disease for each polymorphic variant. We further performed multiple variant analysis as one of gene-based case-control association studies: distribution of minor-allele carriers (Mm) and non-carriers (MM) as to three polymorphic variants, R47H, H157Y and L211P, was compared between cases and controls on the basis of χ^2 test from a 2 × 2 contingency table. Subjects with undetermined genotype data in these variants were omitted for this analysis, with 4,582 subjects remaining. We used SNPAlyze software (DYNACOM, Japan; http://www.dynacom.co.jp/) for these statistical analyses, as described in detail elsewhere [35].

The statistical significance was set at $p < 0.05$.

Table 1
Demographics of the study sample set

	No. of subjects	Age		*APOE* allele frequency		
	(Female %)	Mean (SD)	Range	ε2	ε3	ε4
Cases	2,190 (70.1)	75.2 (6.2)	57–102	0.02	0.67	0.31
Controls	2,498 (54.9)	76.3 (6.6)	65–105	0.05	0.87	0.08

SD, standard deviation.

RESULTS AND DISCUSSION

We attempted to replicate the association of *TREM2* with LOAD in a Japanese sample set, comprising 4,688 subjects in total: cases, $n = 2,190$; and controls, $n = 2,498$ (Table 1). Three variants, R47H, H157Y, and L211P, were found to be polymorphic; however, the remaining seven, Q33X, Y38C, T66M, N68K, D87N, T96K, and R98W, did not show polymorphisms (Table 2, Supplementary Table 1). The MAF of the variants, R47H, H157Y, and L211P, were less than 0.01 (Supplementary Table 1). Concerning variant R47H [11, 12], three heterozygous subjects were observed: one clinically-verified case (female, age at onset of 76 years old, and *APOE*-ε3*3) and two neuropathologically-characterized controls (one female, age at death of 99 years old, and *APOE*-ε3*3; and one male, age at death of 79 years old, and *APOE*-ε3*3). Variant L211P exhibited the highest MAF among them: 0.0041 in cases and 0.0059 in controls (Supplementary Table 1). Variants R47H, H157Y, and L211P were all in HWE (Supplementary Table 1). In both single and multiple variant analyses, we observed no significant association of *TREM2* with LOAD (Table 2).

TREM2 is mainly expressed in microglia in the brain [30]. This protein directly interacts with a type I transmembrane adapter protein, DAP12 [30]. Recent whole transcriptome analysis of microglia, purified from mouse brains by means of flow cytometry, revealed that *TREM2* belongs to a DAP12-centered protein network, in which multiple microglial marker proteins such as Cd68 are included [31]. A *TREM2*-DAP12 signaling pathway is involved in innate immune responses as well as the differentiation of myeloid progenitor cells into mature microglia [30, 32]. Microglia play an important role in the clearance of amyloid-β protein in the brain [33]. Thus, it is likely that genomic variants of not only *TREM2* but also other genes involved in the *TREM2*-DAP12 signaling pathway may accelerate amyloid plaque deposition through microglial dysfunction [34]. Although none of the rare non-synonymous *TREM2* variants investigated here exhibited association with LOAD in our sample sets (Table 2), we could not rule out the possibility that *TREM2* is one of the crucial proteins for AD from the point of view of biological functions of this protein.

In conclusion, we were not able to detect the significant association of *TREM2* variants examined with LOAD in Japanese, which is consistent with a recent study involving Chinese [21]. On the other hand, *TREM2* has been reproducibly shown to be strongly associated with both LOAD [15–19] and EOAD [20] in multiple Caucasian sample sets. Given these data, *TREM2* may contribute to the susceptibility of LOAD only in Caucasians, i.e., not or only weakly in Asians. However, considering the very low MAF of variants investigated (Table 2, Supplementary Table 1) and our study sample size (Table 1), a large-scale meta-analysis is further needed to comprehensively evaluate whether or not *TREM2* is associated with LOAD in Asians.

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Table 2
Genotypic distribution of three polymorphic variants, R47H, H157Y, and L211P, on *TREM2* in Japanese

Single variant analysis		Allele		Cases (frequency)			Controls (frequency)			$P_{genotype}$ [a]	OR_{Mm} (95% CI)[b]
Variant	dbSNP	M	m	MM	Mm	mm	MM	Mm	mm		
R47H	rs75932628	G	a	2,171 (0.9995)	1 (0.0005)	0 (0.0)	2,477 (0.9992)	2 (0.0008)	0 (0.0)	1.00E+00	0.57 (0.05–6.30)
H157Y	rs2234255	C	t	2,147 (0.9972)	6 (0.0028)	0 (0.0)	2,474 (0.9984)	4 (0.0016)	0 (0.0)	5.29E-01	1.73 (0.49–6.13)
L211P	rs2234256	T	c	2,161 (0.9917)	18 (0.0083)	0 (0.0)	2,461 (0.9884)	29 (0.0116)	0 (0.0)	3.04E-01	0.71 (0.39–1.28)
Multiple variant analysis		Combind genotype		Cases (frequency)			Controls (frequency)			$P_{genotype}$ [c]	OR_{CG-2} (95% CI)[d]
Combind variant	Combind dbSNP	CG-1	CG-2	CG-1	CG-2	others	CG-1	CG-2	others		
R47H-H157Y-L211P	rs75932628-rs2234255-rs2234256	GG-CC-TT	Ga-CC-TT, GG-Ct-TT, GG-CC-Tc	2,104 (0.9883)	25 (0.0117)	0 (0.0)	2,419 (0.9861)	34 (0.0139)	0 (0.0)	5.26E-01	0.85 (0.50–1.42)

In single variant analysis, only three variants, L211P, H157Y, and R47H, are shown here since heterozygotes (Mm) were observed. M, major allele; m, minor allele; MM, major genotype; Mm, heterozygous genotype; mm, minor genotype; CG, combined genotype. [a]Fisher's exact test; [b]OR_{Mm} (95% CI) for the heterozygote (Mm); [c]chi-squared test (degree of freedom = 1); [d]OR_{CG-2} (95% CI) for CG-2 (Ga-CC-TT, GG-Ct-TT, and GG-CC-Tc).

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SUPPLEMENTARY MATERIAL

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