Published in final edited form as:
Alzheimer Dis Assoc Disord. 2011 ; 25(2): 159–163. doi:10.1097/WAD.0b013e318201f249.

APOE E4 is a susceptibility factor in amnestic but not aphasic dementias

Emily Rogalski, PhD[1], **Alfred Rademaker, PhD**[2], **Theresa M Harrison, BS**[1], **Irene Helenowski, MS**[2], **Nancy Johnson, PhD**[1,3], **Eileen H. Bigio, MD**[1,4], **Manjari Mishra, PhD**[1], **Sandra Weintraub, PhD**[1,3], and **M.-Marsel Mesulam, MD**[1,5]

[1] Cognitive Neurology and Alzheimer's Disease Center, Northwestern University Feinberg School of Medicine, Chicago, IL

[2] Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

[3] Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL

[4] Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL

[5] Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

Abstract

The goal of this study was to determine if the apolipoprotein ε (ApoE) gene, which is a well-established susceptibility factor for Alzheimer's disease (AD) pathology in typical amnestic dementias, may also represent a risk factor in the language-based dementia, primary progressive aphasia (PPA). Apolipoprotein E genotyping was obtained from 149 patients with a clinical diagnosis of PPA, 330 cognitively healthy individuals (NC) and 179 patients with a clinical diagnosis of probable Alzheimer's disease (PrAD). Allele frequencies were compared among the groups. Analyses were also completed by gender and in two subsets of PPA patients, one where patients were classified by subtype (logopenic, agrammatic and semantic) and another where pathologic data were available. The allele frequencies for the PPA group (ε2:5%, ε3:79.5%, and ε4:15.4%) showed a distribution similar to the NC group but significantly different from the PrAD group. The presence of an ε4 allele did not influence the age of symptom onset or aid in the prediction of AD pathology in PPA. These data show that the ε4 polymorphism, which is a well-known risk factor for AD pathology in typical amnestic dementias, has no similar relationship to the clinical syndrome of PPA or its association with AD pathology.

INTRODUCTION

Primary progressive aphasia is a clinical neurodegenerative dementia syndrome characterized by a gradual dissolution of language but relative sparing of other cognitive domains (e.g. memory, reasoning) during the initial stages of the disease. The diagnostic criteria (Table 1) have been adopted by the Alzheimer's Disease Centers of the National Institute on Aging and implemented in the Uniform Data Set [1]. These criteria allow for the language-based dementia of PPA to be distinguished from the memory-based dementia of probable Alzheimer's disease (PrAD a.k.a. Dementia of the Alzheimer Type, DAT) and the behavioral-based frontotemporal dementia (bvFTD) syndrome. Despite substantial progress

Corresponding Author: Emily J Rogalski, PhD, Assistant Research Professor, Northwestern University, Cognitive Neurology and Alzheimer's Disease Center (CNADC), 320 E Superior Street, Searle Building 11th Floor, Chicago, IL 60611, 312-503-1155 phone, 312-908-8789 fax, erogalski@gmail.com.

in our understanding of PPA little is known about the epidemiology and risk factors associated with this relatively rare dementia syndrome.

The apolipoprotein ε (ApoE) gene is localized on chromosome 19 and has three common alleles (ε2, ε3, and ε4) that determine six genotypes in the general population. It is thought to play a fundamental role in cell maintenance and repair through its function in lipid transport and cellular metabolism [2]. The ε4 allele of this gene is a well-established susceptibility factor in AD and may influence the rate of progression in other neurological disorders [3–8]. However, the role of the ε4 allele as a risk factor in the clinical syndrome of PPA is less clear. In 1997 Mesulam and colleagues found no association between the presence of the of an ε4 allele in a group of 12 patients with a clinical diagnosis of PPA [9]. This finding was supported in a report by Masullo who examined patients with focal cortical atrophy, including individuals with a clinical diagnosis of PPA [10]. In contrast, however, other reports suggest that the ε4 allele may represent a risk factor in PPA [11–13]. Specifically, Acciarri found an increased incidence of the ε2/ε4 genotype in 15 patients with PPA [12] and Daniele extended this finding by suggesting the ε2/ε4 genotype may represent a significant risk factor for women [14]. Common challenges, which restrict the interpretation of these reports, are the relatively low number of patients (n< 40) and the mixture of clinical phenotypes (e.g. PPA, bvFTD and focal cortical atrophy patients).

The present study contributes additional information on ApoE allele and genotype distributions in a significantly larger sample of 149 patients with the clinical syndrome of PPA. These distributions were compared with those in a group of cognitively healthy controls and a group of individuals with a clinical amnestic dementia diagnosis. Analyses were also completed by gender and in two subsets of PPA patients, one where patients were classified by subtype (logopenic, agrammatic and semantic) and another where pathologic data were available. Prior studies have reported that up to 30% of patients with clinical PPA are found to have AD pathology at post mortem brain autopsy. Therefore, a subsequent analysis also was undertaken to determine if the presence of at least one ε4 allele predicted AD pathology in the PPA group.

METHODS

Participants in the Clinical Core of the Northwestern Alzheimer's Disease Center registry (NADC), Chicago, IL, gave written informed consent and provided a blood sample, from which DNA was extracted for genotyping. ApoE genotyping was completed at Northwestern University following the method described by Hixson and colleagues [15]. Briefly, this method includes the amplification of DNA by PCR in a Thermal Cycler. After PCR amplification, the resulting products were cut with a restriction enzyme and incubated overnight in a 37° C oven. Following incubation, the samples were run on a vertical electrophoresis device for several hours over polyacrylamide gels stained with ethidium bromide to highlight the bands of the DNA. A CCD camera system was used to visualize the banding patterns. The banding patterns were then compared to the known ApoE control patterns that were run with each batch of samples to determine the genotype of each DNA product.

Inclusion criteria for this study required 1) ApoE genotype testing and 2) a clinical diagnosis of PrAD by established research diagnostic criteria [16], PPA by published criteria [17, 18] or cognitively healthy normal control (NC) based on neuropsychological test scores and informant report. All participants in the NADC registry who met these criteria were included. Participants' genotypes were not known prior to inclusion to avoid selection bias. The PrAD group was included because the clinical dementia profile differs from PPA and there is a well-known ε4-risk profile. Using both a healthy and an at-risk population as

comparison groups provides greater context for understanding the allele and genotype frequencies of the PPA group.

Information was available for 658 individuals. Of these, 330 were classified as NC, 179 PrAD, and 149 PPA. Clinical diagnoses were made by the consensus of a neurologist (including M.M.) and a neuropsychologist (including N.J. and S.W.) at the Northwestern Alzheimer's Disease Center. All PPA patients in this sample shared the common feature of a salient aphasia with relative preservation of other cognitive domains. The demographic characteristics for the each of the groups (NC, PPA and PrAD) are provided in Table 2.

PPA has been divided into agrammatic (PPA-G), semantic (PPA-S), logopenic (PPA-L) and mixed (PPA-M) variants [19, 20]. Using the descriptive criteria provided by Mesulam and colleagues [19], two cohorts of PPA patients were subtyped in this study: 1) A prospective cohort (n=31) of patients enrolled in a longitudinal project; and 2) A retrospective chart review of patients that had come to autopsy (n=31).

Statistical Analysis

The main analyses consist of the comparison of genotype or allele frequencies among diagnostic groups and between gender groups. For the comparison of genotypes, the person is the unit of analysis and these analyses were done using a chi-square test for a 2 × 2 table, yielding p-values, odds ratios, and confidence intervals. For the comparison of allele frequencies, the allele is the unit of analysis and these comparisons were done using a generalized linear model taking into account the repeated measures due to alleles within person. Comparisons were completed for single genotypes or allele types between groups. For the comparisons with the control group, the control group is the reference category. For the comparison of PrAD with PPA, the PPA group is the reference category. Odds ratios are defined as the odds of the genotype (or allele) in the group of interest versus the odds in the reference group. Since the gender distributions differed between the PPA group and the comparison groups all comparisons were adjusted for age and gender.

The association between number of ApoE alleles and age of onset was assessed using the Kruskal-Wallis test. A Fisher's exact test was used to examine the relationship between the presence of an ε4 allele and its association with AD neuropathology.

The chi-square goodness of fit test was used to compare observed genotype frequencies with hardy-Weinberg expected frequencies.

RESULTS

Allele Frequency

The allele distributions for each group are reported in Table 3. Results revealed no significant differences in allele frequency between PPA patients and controls ($p \geq 0.66$ for each comparison). The amnestic dementia group had significantly more ε4 alleles than the PPA group ($p < 0.0001$; odds ratio (OR) = 0.27, 95% confidence interval (CI) = 0.18 to 0.41), while the PPA patients had more ε3 alleles than the amnestic dementia group ($p < 0.0001$; OR = 2.89, CI = 1.96, 4.24). The ε2 frequency did not differ between the PPA and PrAD groups ($p = 0.15$), though allele sample was small in this comparison. As expected, individuals with a clinical diagnosis of PrAD also showed significant difference in allele counts from NC for each of the alleles (ε2 $p = 0.02$; OR = 0.46, CI = 0.24, 0.91; ε3 $p < 0.0001$; OR = 0.35, CI = 0.26, 0.46; *ε4* $p < 0.0001$; OR = 3.99, CI = 2.96, 5.39). Taken together the results suggest that the PPA and NC have similar allele distributions while the amnestic dementia group has a unique allele profile.

Previous reports suggest that the ε*4* allele frequencies may differ between PPA variants[20]. Subtyping information was available for a subset of 62 PPA patients from our cohort and their allele frequencies are reported in Table 4. The allele frequencies for each PPA subtype were compared to the allele frequencies of the NC group. Results from these analyses revealed no significant differences in allele frequency between each PPA subtype and the NC frequencies ($p \geq 0.05$, for each comparison).

Genotype Frequency

The genotype distributions for each group are reported in Table 3. Similar to the allele frequency results, there were no the differences in the frequencies of the 6 genotype comparisons between PPA patients and NC ($p \geq 0.41$ for all 6 genotype comparisons). As expected, the amnestic dementia patients showed a distinct genotype frequency profile from both PPA and NC (Table 3). The ε2/ε3 and ε3/ε3 genotype frequencies were significantly lower in the PrAD group compared to the NC group (ε2/ε3: $p = 0.02$; OR = 0.38, CI = 0.16, 0.87; ε3/ε3: $p < 0.0001$; OR = 0.27, CI = 0.18, 0.40). The ε3/ε4 and ε4/ε4 genotype frequencies were significantly higher in the PrAD group compared to the NC group (ε3/ε4: $p < 0.0001$; OR =3.14, CI = 2.12, 4.65; ε4/ε4: $p < 0.0001$; OR = 9.25 CI = 3.7, 23.15). The ε3/ε3 genotype frequencies were significantly lower in the PrAD group compared to the PPA group (ε3/ε3: $p < 0.0001$; OR = 3.85, CI = 2.36, 6.26). The ε3/ε4 and ε4/ε4 genotype frequencies were significantly higher in the PrAD group compared to the PPA group (ε3/ε4: $p < 0.0001$; OR = 0.35, CI = 0.21, 0.59; ε4/ε4: $p = 0.0003$; OR = 0.13 CI = 0.04, 0.39).

Allele and Genotype Distribution by Gender

Recent reports suggest that susceptibility factors may differ by gender in PPA [14]. The allele frequency analysis by gender and diagnosis (PPA and NC) did not show differences in allele frequency by gender in the PPA and control groups ($p \geq 0.46$ for each comparison). The genotype frequency analysis by gender also failed to show significant differences ($p \geq 0.15$ for each comparison).

Dose of ε4 and its relationship to age of onset

Data from a previous study examining a group of "frontal lobe dementia" patients indicated an inverse relationship with age of onset and the number of ε4 alleles, such that, the age of onset decreased as the number of ε4 alleles increased [21]. We completed a similar analysis to determine if this relationship was evident in our cohort of patients with PPA. The results failed to show a relationship between age of onset and the number of ε4 alleles ($p = 0.43$; median age of onset for zero ε4 alleles = 62.0, n = 107; 1 ε4 allele = 64.0, n = 38; 2 ε4 alleles = 64.5, n = 4).

Neuropathology and ε4

Neuropathology in post mortem brains of individuals with PPA is mixed, with nearly 30% of PPA patients showing plaques and tangles sufficient for the pathological diagnosis of AD. One hypothesis is that PPA patients with ε4 are more likely to have AD pathology. To investigate this hypothesis, we analyzed a subset of 31 patients who had come to autopsy with a clinical diagnosis of PPA and also had ApoE genotyping information available (see Table 5 in the supplementary material for information on the subset of PPA patients used in this analysis). Results from the Fisher's exact test revealed no significant association between the presence of an ε4 allele and the presence of AD pathology ($p = 0.71$). Eleven patients had at least one ε4 allele and 20 patients did not have an ε4 allele. Sixty-four percent of the patients with at least one ε4 allele had AD pathology, while 50% of the cases with no ε4 alleles had AD pathology.

Hardy-Weinberg Equilibrium

For each diagnostic group, the allele frequencies were used to calculate expected Hardy-Weinberg genotype equilibrium probabilities. Goodness of fit tests indicated that the observed genotype frequencies fit the expected frequencies ($p > 0.99$ for NC, PPA and PrAD). For the autopsy cohort, using an average allele frequency across all groups, the 35% occurrence of any e4 genotype fit Hardy-Weinberg expected values (p=0.64).

DISCUSSION

This study examined the frequency of the ε4 allele and its combinatorial genotypes in patients with the clinical syndrome of primary progressive aphasia and compared them with frequencies in patients with the memory-based dementia of the Alzheimer type and in cognitively healthy controls. Findings showed that the ApoE allele distribution in PPA is significantly different from the group with a clinical diagnosis of PrAD and similar to that of the cognitively healthy control group. These data suggest that the ε4 polymorphism, a well-known risk factor for the memory-based dementia, Alzheimer's disease, has no similar relationship to the clinical syndrome of PPA. Furthermore, in the PPA group the ε4 dose was not related to gender or age of symptom onset. In fact, the median age of onset was highest in individuals with the twoε4 alleles, in contrast to the tendency for *earlier* onset disease in patients with Alzheimer's dementia and an ε4 allele. However, only four patients had two ε4 alleles making this finding difficult to interpret. It will be interesting to see if this relationship remains true in a larger sample. Finally, there was no relationship between the presence of an ε4 allele and the post mortem neuropathology for those in whom those data were available. Taken together, the results of this study suggest that the clinical syndrome of PPA and/or its pathologic etiology have no association relative to the ApoE genotype or allele distribution.

The conclusion that the ε4 allele is not a risk factor in PPA is at odds with some reports [11, 12, 14, 21] but in line with others, including one from this laboratory with a smaller number of subjects [9, 10]. The differences between our findings and others may be attributable to the relatively small sample sizes in previous studies. The current study, while still limited in size in comparison to population based studies, has at least three times more patients than the previously published reports on this topic.

The presence of an ε4 allele did not increase the accuracy in predicting AD pathology in the sample of 31 PPA patients with pathological diagnoses. Sixty-four percent of the patients with at least one ε4 allele had AD pathology, while 50% of the cases with no ε4 alleles had AD pathology. These observations highlight the differences in disease risk factors for the clinical aphasic versus amnestic dementia even at the pathologic level.

The ability to reliably predict the pathologic etiology of PPA continues to be a primary need, since accurate pathologic forecasting is critical for the development and, eventually, the delivery of treatment. Currently, there are no definitive *in vivo* biomarkers for the underlying pathologies, though postmortem series and *in vivo* amyloid imaging suggest that individual clinical variants of PPA have distinctive probabilities of being caused by AD pathology versus one of the several forms of frontotemporal lobar degeneration (FTLD) [22–24]. The are three readily recognized clinical variants of PPA, namely, PPA-G, PPA-S and PPA-L, which can be distinguished by their clinical and anatomical features [19] (Table 1). Previous reports suggest that the PPA-L variant may be more likely to have AD pathology [22–24]. We addressed this issue using two cohorts of PPA patients: 1) A cohort (n=62) of patients who had been classified by subtype; and 2) A subset patients who had also come to autopsy (n=31). The first analysis compared allele frequencies of the NC group to each of the PPA subtypes and results demonstrated allele frequencies for each subtype were not significantly

different from the from the control cohort. Though not significant, the ε4 allele was present more frequently in the PPA-L (20%) and PPA-S (21.4%) groups compared to the PPA-G (6.8%) group (Table 4). Nonetheless, the frequencies for each subtype were still lower than that of the PrAD (39.4%) group. The ε4 allele frequency in our PPA-L group was also lower than that reported by Gorno-Tempini and colleagues, namely, 67% [20] and Migliaccio and colleagues (55%) [25]. However, these observations were made in small sample sizes (n< 13 for each study) making a clear interpretation difficult. It will be important for future studies to be based on large sample sizes.

In our cohort with autopsy information, the likelihood of pathologic changes consistent with AD was more frequent in the PPA-L group 57% (8/14 patients) than the PPA-G group 20% (2/10 patients), which is consistent with the previous literature. However, the ε4 allele frequency was not elevated in the PPA-L group, suggesting that the presence of an ε4 allele does not offer additional predictive value.

In summary, the results show that the ApoE allele and genotype distribution in PPA is significantly different from the one observed in PrAD and comparable to that of a nondemented older control population. Though this is the largest report of ApoE distribution in PPA, it is still a relatively small group and larger prospective studies incorporating subtype classification and pathologic characterization are needed.

In addition to their practical implications for predicting the nature of the underlying pathology, these results also have implications for understanding the molecular basis of selective vulnerability patterns. One possible interpretation is that the ε4 allele may be a risk factor specifically for the type of amyloid and tangle pathology that selectively targets the hippocampo-entorhinal complex and that leads to the typical amnestic phenotype. Another more speculative interpretation suggests that AD pathology in PPA may not reflect the causative mechanism for the aphasic phenotype and that we may need to look further for alternative neuropathologic processes that may have triggered the initial aphasic phenotype but that may have been obscured, 10–15 years after onset, by the secondary or age-related emergence of plaques and tangles. It is also possible that the role of ApoE may uniquely affect the morphologic expression in different neurodegenerative diseases. This theory was proposed by Agosta and colleagues who demonstrated that the presence of an ε4 allele influences both disease risk and brain atrophy in AD but only brain atrophy in bvFTD[13]. At the epidemiological level, the results from this study show that the clinical diagnosis of aphasic versus amnestic dementia reflect two different genetic pools with respect to disease risk factors.

Acknowledgments

This project was supported by DC008552 from the National Institute on Deafness and Communication Disorders; AG13854 (Alzheimer Disease Center) from the National Institute on Aging; and 5KL2RR025740 from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

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Table 1
Diagnostic features for primary progressive aphasia and its variants

(adapted from Mesulam and Weintraub 2008; Mesulam 2009):

Descriptive clinical profile: An aphasic dementia where the language impairment (aphasia) emerges in relative isolation and is the major determinant in the limitation of daily living activities. Perception, memory, personality are relatively preserved initially (usually 2 years or more).

Core diagnostic features: These features are integral to the clinical syndrome. Both must be present for making the diagnosis.

- Insidious onset and gradual progression
- Early onset of aphasic disturbance (including any combination of the following): Word-finding pauses, word comprehension deficits, naming impairments, circumlocutions speech lacking specific nouns and verbs, speech and/or writing that has impaired grammar and syntax, syntactic comprehension deficits, dysgraphia

Exclusionary features:

- Abrupt onset
- Brain imaging showing lesions other than focal atrophy that can account for the aphasia

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PPA Variants

Agrammatic (PPA-G): The central feature is an abnormality in syntax (word order) or some other aspect of grammar in spoken or written language in the presence of relatively preserved single-word comprehension. Fluency is usually impaired, and speech is usually effortful and hesitant.

Semantic (PPA-S): The central feature is an abnormality in single-word comprehension in the presence of relatively preserved grammar and fluency. Output is circumlocutory, occasionally uninformative, and frequently paraphasic. Naming is severely impaired.

Logopenic (PPA-L): The central features are intermittent word-finding hesitations and phonemic paraphasias. Naming is impaired but not as severely as in PPA-S and improves on phonemic cueing. Repetition may be impaired. Fluent output in casual conversation can alternate with dysfluent speech, which emerges when the patient needs to convey precise information and cannot use circumlocution. Spelling can be impaired.

Mixed (PPA-M): Combination of agrammatism with comprehension deficit, usually accompanied by poor fluency and frequent paraphasias or whose language output was too limited for specific characterization.

Table 2

Demographic characteristics

	NC (n=330)	PPA (n=149)	PrAD (n=179)
Median Age*	70	62	72
Age Range*	50–91	42–81	40–89
Women: Men	249:81	77:72	120:59
Education (years)	15.7	15.3	14.1

* Represents age at ApoE testing for the NC group and age at onset for the PPA and PrAD patient groups.

Table 3

ApoE allele and genotype frequencies in PPA, PRAD and NC

	APOE genotype						Allele frequency		
	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4	ε2	ε3	ε4
PPA									
All n=149	1 (0.7)	11 (7.4)	2 (1.3)	95 (63.8)	36 (24.2)	4 (2.7)	15 (5.0)	237 (79.5)	46 (15.4)
Male n=72	0 (0)	7 (9.7)	0 (0)	43 (44.3)	20 (27.8)	2 (2.6)	7 (4.9)	113 (78.5)	24 (16.7)
Female n=77	1 (1.3)	4 (5.2)	2 (2.6)	52 (67.5)	16 (20.8)	2 (2.8)	8 (5.2)	124 (80.5)	22 (14.3)
PRAD									
All n=179	0 (0)	7 (3.9)	4 (2.2)	56 (31.3)	87 (48.6)	25 (14.0)	11 (3.1)	206 (57.5)	141 (39.5)
Male n=59	0 (0)	1 (1.7)	1 (1.7)	21 (35.6)	29 (49.2)	7 (11.9)	2 (1.7)	72 (61.0)	44 (37.3)
Female n=120	0 (0)	6 (5.0)	3 (2.5)	35 (29.2)	58 (48.3)	18 (15.0)	9 (3.7)	134 (55.8)	97 (40.4)
NC									
All n=330	1 (0.3)	33 (10.0)	8 (2.4)	207 (62.7)	75 (22.7)	6 (1.8)	43 (6.5)	522 (79.1)	95 (14.4)
Male n=81	0 (0)	6 (7.4)	2 (2.5)	54 (66.7)	17 (21.0)	2 (2.5)	8 (4.9)	131 (80.9)	23 (14.2)
Female n=249	1 (0.4)	27 (10.8)	6 (2.4)	153 (61.5)	58 (23.3)	4 (1.6)	35 (7.0)	391 (78.5)	72 (14.5)

The numbers in ( ) represent the % of each allele or genotype.

Alzheimer Dis Assoc Disord. Author manuscript; available in PMC 2012 April 1.

Table 4
ApoE allele frequencies by PPA subtype

	Allele frequency		
	ε2	**ε3**	**ε4**
PPA-G			
n=22	4 (9.1)	37 (84.1)	3 (6.8)
PPA-L			
n=25	1 (2.0)	39 (78.0)	10 (20.0)
PPA-S			
n=7	0 (0)	11 (78.6)	3 (21.4)
PPA-M			
n=8	0 (0)	12 (75.0)	4 (25.0)

NA: The numbers in () represent the % of each allele. PPA-G =agrammatic variant PPA-L = logopenic variant, PPA-S semantic variant, PPA-M = mixed variant (see Table 1 for subtype descriptions)

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Table 5

Clinical and pathological characteristics of 31 PPA patients with pathological diagnoses

Subtype	Ed	Age at Onset	Age at Death	Sex	ApoE	Neuropath	Asymmetry	ATAC	TDP43	Braak Stage	Imaging
PPA-G	**16**	**72**	**77**	**M**	**2,3**	**FTLD-Tau (CBD)**	No	*	**ND**	**0**	MRI= unremarkable; EEG= L frontotemporal slowing
PPA-G	**16**	**46**	**60**	**F**	**2,3**	**FTLD-Tau (Pick)**	a, nlg (F, T, P) L>R	*	**No**	**0**	MRI= atrophy L frontotemporal
PPA-G	**12**	**59**	**67**	**F**	**2,4**	FTLD-Tau (CBD)	?**	*	**ND**	**0**	MRI= L temporal atrophy; SPECT= L hypometabolism
PPA-L	**14**	**68**	**73**	**M**	**3,3**	AD	a (T) L>R	**No**	**No**	**6**	MRI= nonspecific subcortical changes; SPECT= normal
PPA-M	**16**	**52**	**72**	**M**	**3,3**	AD	a (T) L>R	**No**	**No**	**6**	CT= L perisylvian atrophy
PPA-G	**12**	**57**	**62**	**F**	**3,3**	FTLD-TDP	a (F, T, P) L>R	**0**	**Yes**	**2**	SPECT= L frontotemporal hypoperfusion
PPA-M	**14**	**68**	**78**	**M**	**3,3**	FTLD-Tau (CBD)	sm, nlg (F)	*	**No**	**0**	MRI= L perisylvian and temporal/parietal atrophy
PPA-L	**16**	**72**	**78**	**F**	**3,3**	AD	sm (F, T, P) L>R	**Single cluster**	**No**	**6**	MRI= L perisylvian atrophy
PPA-L	**20**	**59**	**65**	**M**	**3,3**	FTLD-TDP + ALS	a, nlg (T) L>R	**0**	**Yes**	**2**	MRI= L perisylvian and inferotemporal atrophy; SPECT= patchy hypoperfusion mostly L
PPA-M	**14**	**61**	**78**	**F**	**3,3**	DLBD/AD	F, T, P, O, L>R	**0**	**Aymgdala & dentate gyrus**	**6**	MRI = L severe perisylvian atrophy
PPA-G	**20**	**65**	**72**	**M**	**3,3**	AD	**0**	**0**	**No**	**6**	MRI= unremarkable
PPA-L	**12**	**49**	**70**	**M**	**3,3**	AD	a, nlg (T) L>R	**Single cluster**	**0**	**5**	PET= L perisylvian and parietofrontal hypometabolism
PPA-G	**14**	**60**	**65**	**F**	**3,3**	FTLD-Tau (CBD)	**No**	*	**No**	**1**	MRI= unremarkable; PET= mild hypometabolism L parietal
PPA-L	**16**	**49**	**59**	**F**	**3,3**	AD	sm (F, T, P) L>R	**Multiple clusters**	**No**	**6**	SPECT= decreased perfusion R hemisphere
PPA-L	**24**	**54**	**62**	**M**	**3,3**	FTLD-TDP	?**	**0**	**Yes**	**0**	MRI= L perisylvian atrophy: PET= L temp hypoperfusion
PPA-L	**16**	**59**	**68**	**F**	**3,3**	AD	a, sm (F, T, P) L>R	**Single cluster**	**No**	**6**	PET= L temporoparietal hypometabolism
PPA-G	**14**	**57**	**66**	**M**	**3,3**	FTLD-Tau (CBD)	?**	*	**No**	**0**	MRI= L perisylvian atrophy

Subtype	Ed	Age at Onset	Age at Death	Sex	ApoE	Neuropath	Asymmetry	ATAC	TDP43	Braak Stage	Imaging
PPA-L	**12**	**68**	**77**	**M**	**3,3**	FTLD-Tau (CBD)	**0**	*	**ND**	**1**	MRI= unremarkable
PPA-G	**18**	**73**	**78**	**F**	**3,3**	FTLD-Tau (CBD)	F, T, P L>R	*	**ND**	**1**	MRI: bilateral perisylvian atrophy L>R
PPA-L	**16**	**64**	**72**	**M**	**3,3**	FTLD-Tau (Pick)	Inf F (Broca's) & T L>R	*	**No**	**2**	MRI = L anterior temp and L frontal atrophy
PPA-G	**20**	**69**	**81**	**M**	**3,3**	AD	**0**	**0**	**No**	**5**	MRI = nonspecific signal abnormalities in the white matter; EEG = L slight slowing
PPA-G	**12**	**69**	**80**	**M**	**3,3**	FTLD-Tau (PSP)	**0**	*	**No**	**2**	MRI = posterior parietal atrophy L>R; CT = unremarkable
PPA-L	**8**	**57**	**70**	**M**	**3,4**	FTLD-Tau (Pick)	No	*	**ND**	**0**	EEG= left slowing; SPECT= L frontotemporal hypoperfusion
PPA-L	**12**	**64**	**69**	**F**	**3,4**	FTLD-TDP	No	**0**	**Yes**	**2**	MRI= unremarkable
PPA-M	**14**	**66**	**69**	**F**	**3,4**	FTLD-TDP + ALS	No	**0**	**Yes**	**2**	MRI= symmetric; SPECT= L temporal hypoperfusion
PPA-L	**16**	**72**	**78**	**M**	**3,4**	AD	sm (F) L>R	**No**	**No**	**6**	SPECT= L temporoparietal hypoperfusion
PPA-M	**15**	**60**	**71**	**M**	**3,4**	AD	a (H, T, P) L>R	**Multiple clusters**	**No**	**6**	MRI= unremarkable
PPA-L	**16**	**81**	**87**	**M**	**3,4**	AD	?**	**0**	**0**	**6**	MRI= atrophy L temporal pole and bilateral frontal
PPA-L	**19**	**64**	**75**	**M**	**3,4**	AD	F, T, P L>R	**Multiple clusters**	**No**	**6**	SPECT= L temp hypoperfusion
PPA-M	**16**	**59**	**73**	**M**	**3,4**	AD	No	**No**	**No**	**6**	MRI= atrophy, most prominent L temporal lobe
PPA-S	**16**	**71**	**76**	**F**	**4,4**	AD	No	**No**	**No**	**6**	MRI= small cerebellar infarct, otherwise unremarkable

All brains were evaluated grossly for atrophy, and microscopically with hematoxylin and eosin, thioflavin-S, and the Gallyas stain. Additional procedures included thioflavine-S histofluorescence, Gallyas stain for argyrophilia, and immunohistochemistry for tau (AT8; Pierce-Endogen, Rockford, IL), β amyloid (4G8; Signet, Dedham, MA), α-synuclein (LB509; Zymed-Invitrogen, Carlsbad, CA), ubiquitin (polyclonal; DAKO, Carpinteria, CA), and TDP-43 (polyclonal; ProteinTech, Chicago, IL).

*cannot identify ATAC in tauopathies.

**Asymmetry cannot be determined because only one hemisphere was available. a = atrophy determined by gross examination of brain surface; AD = Alzheimer's disease; ATAC = argyrophilic thorny astrocyte clusters; CBD = corticobasal degeneration-type tauopathy; CT = computed tomography; EEG = electroencephalogram; F = inferior frontal gyrus; FTLD-T = frontotemporal lobar degeneration with tau-positive inclusions; FTLDU = frontotemporal lobar degeneration with ubiquinated inclusions; H = hippocampus; MND = motor neuron disease type; MRI = magnetic resonance imaging; ND = not done; nlg = neuronal loss and gliosis; no = none found; P = inferior parietal lobule; PET = positron emission tomography; sm = superficial cortical layer microvacuolation; SPECT = single-photon emission computed tomography; T = superior temporal gyrus.