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TDP-43 Pathology in the Setting of Intermediate and High Alzheimer's Disease Neuropathologic Changes: A Preliminary Evaluation Across Ethnoracial Groups

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Abstract

Background: Transactive Response DNA Binding Protein 43 kDa (TDP-43) pathology is frequently found in cases with Alzheimer's disease (AD). TDP-43 pathology is associated with hippocampal atrophy and greater AD severity denoted by cognition and clinical representation. Current TDP-43 pathology studies are predominantly based on non-Hispanic White cohorts.

Objective: We sought to evaluate the presence of TDP-43 pathology across ethnoracial groups utilizing the National Alzheimer's Coordinating Center; a database containing data from over 29 institutions across the United States. Cases (N=1135: Hispanic/Latino decedents =29, African

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report related to the current study.

Americans/Black American decedents=51, Asians/Asian American decedents =10, American Indian/Alaskan Native decedents =2, non-Hispanic White decedents =1043) with intermediate/high AD having data on TDP-43 pathology in the amygdala, hippocampus, entorhinal cortex, and neocortex were included.

Methods: TDP-43 pathology frequency in each neuroanatomic region among ethnoracial groups were compared using generalized linear mixed effects models with center as a random effect adjusting for age at death, education, and gender.

Results: Although groups were imbalanced, there was no significant difference across ethnoracial groups based on TDP-43 pathology (p=0.84). With respect to neuroanatomical regions evaluated, there were no significant differences across ethnoracial groups (p-values>0.06). There were also no significant differences for age at death and gender ratios across ethnoracial groups based on TDP-43 pathology. Although not statistically significant, TDP-43 pathology was present less often in Hispanic/Latino decedents (34%) when compared to non-Hispanic Whites decedents (46%).

Conclusion: While this is a preliminary evaluation, it highlights the need for diverse cohorts and on TDP-43 pathology research across ethnoracial groups. This is the first study to our knowledge having a focus on the neuroanatomical distribution of TDP-43 deposits in Hispanic/Latino decedents with AD.

Keywords

Alzheimer's Disease; Neuropathology; Cohort Studies; Brain; Minoritized Groups; Latino; Hispanic; Asian; African American

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia and is neuropathologically characterized by the deposition of senile plaques containing aggregates of amyloid-β (Aβ), and neurofibrillary tangles (NFT) containing aggregates of tau protein [1, 2]. While age is one of the primary determinants of developing AD, race and ethnicity are also key factors to consider due to the intertwined social and cultural inequities that may influence disease development and outcomes [3–8]. Previous studies have demonstrated differences in the underlying pathology of dementia based on ethnoracial status [9–11]. Various clinical based studies have shown African Americans/Black American and Hispanics/Latino individuals have the highest frequencies of AD type dementia, followed by non-Hispanic Whites, then by Asian/Asian American individuals [4, 7, 8, 11, 12]; yet the underlying neuropathology influencing these differences remains largely unknown due to insufficient autopsies studies on diverse cohorts [13].

In the brain, Transactive Response DNA Binding Protein (TDP-43), weighing 43 kilodaltons, is found to serve as a regulator for transcriptional events in neurons during the development of the central nervous system [13]. Due to its critical function in the brain's cellular processes, it is important to understand its potential role in neurodegenerative disease pathogenesis. TDP-43 pathology has been associated with numerous neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS),

frontotemporal lobar degeneration (FTLD-TDP), and hippocampal sclerosis (HS) [14–16]. TDP-43 pathology has also been found in 25–50% of all AD cases, primarily in limbic regions [17–20]. Various studies have identified TDP-43 immunoreactive inclusions as a potential mediator of AD pathogenesis, largely impacting people in advanced years (80+) [17, 19, 21]. Additionally, persons with TDP-43 pathology were noted to have greater hippocampal atrophy and more severe AD pathologies, illustrated by higher Braak neurofibrillary tangle (NFT) and Thal Amyloid Staging [17, 18, 22].

TDP-43 pathology in the context of AD is mainly found in limbic regions [20] and staging schemes of neuroanatomic progression have been proposed [20, 23, 24]. The amygdala is found to be the first region TDP-43 deposits are typically found and is therefore considered an early stage, whereas the neocortex is affected last and is reflective of a later disease stage [20, 22–24]. Additionally, studies evaluating the anatomical distribution of TDP-43 in the setting of AD have also found TDP-43 deposits to be most common in the amygdala, less common in the entorhinal cortex, and least common in the neocortex [25]. Individuals were also more likely to be pathologically diagnosed with AD when TDP-43 pathology was extended beyond the amygdala [22]. The generalizability of these anatomical staging schemes for cohorts other than non-Hispanic Whites has yet to be elucidated. In a study conducted by Nascimento *et al.,* 2016, researchers revealed the amygdala was the most frequently affected region in Asian participants from Brazil, followed by the neocortex, then the hippocampus [26]. Interestingly, in a study conducted by Nag *et al.,* 2020, including Black/African American decedents, a majority of TDP-43 inclusions were located in the amygdala, then the entorhinal cortex, followed by the hippocampus, and least in the mid frontal cortices [27]. The current study is a preliminary evaluation aimed to further understand whether there are differences in the neuroanatomical distribution of TDP-43 pathology in AD cases with respect to ethnoracial groups.

Minoritized/underrepresented populations, specifically Hispanic/Latino, Asian/Asian Americans, Black/African Americans, American Indian/Alaskan Native, and Native Hawaiian/Pacific Islander decedents, are projected to increase from representing 22% of the US population in 2014 to 45% in 2060 [8]. Due to an increasingly aging population, it is imperative to conduct research encompassing the diversity of the US, as there is heterogeneity in various risk factors related to social, economic, cultural, and behavioral characteristics related to AD [3–5, 28, 29]. To our knowledge, there are very few studies focused on neuroanatomical deposition of TDP-43 pathology in select minoritized/underrepresented groups; there has been some research including data on Black/African American and Brazilian Asian decedents [26, 27]. There are no published studies to our knowledge that have included TDP-43 neuroanatomical distribution within other groups, such as Hispanic/Latino decedents.

We investigated whether there are differences in overall distribution of TDP-43 pathology in AD cases of non-Hispanic White, Hispanics/Latino, Asians/Asian American, American Indian/Alaskan Native, and African American/Black American decedents and if there are differences in neuroanatomic distribution of TDP-43 deposition across ethnoracial groups in the following neuroanatomical regions: amygdala, hippocampus, entorhinal/inferior temporal cortex, and neocortex. This was done utilizing the National Alzheimer's

Coordinating Center's (NACC) Neuropathology (NP) Data Set and Uniform Data Set (UDS) [30–35]. In this study, the preliminary evaluation on the differences in TDP-43 pathology across select ethnoracial groups with AD highlights further work is needed with more diverse cohorts to understand the generalizability of works predominantly based on non-Hispanic White cohorts. Although there are relatively small numbers of individuals identifying in groups other than non-Hispanic Whites, this is the first study to our knowledge focused on evaluating TDP-43 pathology in the setting of AD across a broad group of minoritized/underrepresented groups. This study highlights the need for more diverse cohorts given the extreme imbalance in select groups.

MATERIALS AND METHODS

Participants

Data were obtained from the NACC database, which contains standardized neuropathological and clinical research evaluations from over 29 Alzheimer's Disease Research Centers (ADRCs) located across the US [30–35]. Collected race and ethnicity categories include White, Black or African American, Hispanic/Latino, American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, Asian, Other (write-in), and Unknown [31]. In this study, cases marked as Other in the race category and were also denoted as Hispanic/Latino were included in the sample. Cases marked as Unknown or Other and did not have any other denotation listed for another race category were excluded. The sample from NACC included UDS version 3.0 data from September 2005 to December 2021 data freeze and all cases had completed Neuropathology (NP) Data Form version 10 [31]. All research utilizing the NACC database was approved by the University of Washington Institutional Review Board. Written consent was retrieved from participants or their legal representative at all ADRCs associated with NACC prior to death and information was de-identified [31, 32].

Cohort Selection

Figure 1 provides an inclusion/exclusion flowchart for the study. Cases were included if they met the following criteria:

1. Were deceased and had a completed neuropathology data form (version 10) within NACC.
2. Did not have a neuropathologic diagnoses of Frontotemporal Lobar Degeneration with TDP-43 (FTLD-TDP), Amyotrophic Lateral Sclerosis with TDP-43 (ALS), and/or Chronic Traumatic Encephalopathy with TDP-43 (CTE) [36–38].
3. Had available data on the presence or absence of TDP-43 pathology in the amygdala, hippocampus, entorhinal cortex, inferior temporal cortex, and neocortex.
4. Had an Alzheimer's Disease Neuropathologic Change (ADNC) level of intermediate or high [39, 40].

Cases defined as having TDP-43 pathology (TDP-43 positive) had a score of 1 (denoting presence) in at least one of the following regions: amygdala, hippocampus, entorhinal/

inferior temporal cortex, and/or neocortex. Cases were considered not to have TDP-43 pathology (i.e. TDP-43 negative) if they had a score of 0 in all four regions mentioned above. Cases with missing or unknown data (which is scored by an 8 or 9 respectively) in any of the anatomical regions, with no TDP-43 pathology in non-missing regions, were excluded from evaluation since it could not be determined if TDP-43 pathology was present.

NACC Neuropathology Data

The NP Data Set is a post-mortem collection of autopsy and neuropathologic data from the standardized NP Data Form. In 2014, version 10 of the NP data-collection form was implemented to include updated hallmarks of neuropathological diagnoses of AD such as FTLD, cerebrovascular disease, HS, and TDP-43 [41].

Statistical Analysis

We utilized generalized mixed effects models with a logistic link to evaluate the association of presence/absence of TDP-43 pathology with ethnoracial status and other participant demographics, following an approach used in prior similar studies involving NACC data [42, 43]. Ethnoracial group, sex, age at death, and education were fixed effect variables and ADRC was a random effect. Demographics and presence of TDP-43 pathology were further compared across ethnoracial groups using mixed effects models (continuous variables) or generalized mixed effects models with a logistic link (categorical variables) using ADRC as a random effect and ethnoracial group as the only independent variable; gender was compared using standard logistic regression, because the data did not support inclusion of an ADRC random effect for this variable. All statistical analyses utilized SAS version 9.4 software (SAS Institute Inc.). Statistical significance was defined as $p < 0.001$).

RESULTS

Participant Demographics

After the inclusion and exclusion criteria were applied, the final cohort consisted of 1043 non-Hispanic Whites (92%), and 92 decedents from minoritized groups. This specific breakdown of this 8% minoritized representation included 10 Asian/Asian American decedents (0.9%), 51 African Americans/Black American decedents (4.5%), 29 Hispanic/Latino decedents (2.6%), and 2 American Indian/Alaskan Native decedents (0.2%) (Figure 2). It is important to note that while Native Hawaiian/Pacific Islander is an included variable for race within the NACC database, there were no cases of this group after the inclusion and exclusion criteria were applied.

Average age of death was 80.9±10.7 years. Of the 1135 total cases, females (n = 589) made up 52% of the analytic sample. Combining all anatomic areas, 519 cases (46%) had at least one anatomic area with TDP-43 pathology (Table 1). Congruent with previous studies, there was a significant difference with respect to age at death ($p < 0.001$) in the overall cohort and no significant differences by gender ($p=0.76$) or years of education ($p=0.72$) based on the presence/absence of TDP-43 pathology. More specifically, TDP-43 positive cases had a higher mean age at death (mean = 83.6, SD = 9.3) compared to cases without TDP-43 pathology(mean = 78.7, SD = 11.3). There was not an overall

significant difference in TDP-43 pathology by ethnoracial group (p=0.93). The overall p-value comparing the presence/absence of TDP-43 pathology for race and ethnicity having Non-Hispanic Whites as the reference was 0.93 and the respective odds ratio for Hispanic/Latino decedents was 0.64, African American/Black American decedents was 1.03, Asian/Asian American decedents 0.83, and American Indian/Alaskan Native decedents 0.94. There were no significant differences for age at death and gender ratios across ethnoracial groups (Table 2). Non-Hispanic White decedents had slightly more years of education compared to other ethnoracial groups, however this was not statistically significant (p = 0.10).

TDP-43 presence and absence across ethnoracial groups

A full breakdown of frequencies of cases with TDP-43 pathology by anatomical area as well as select demographic data are available in Supplementary Table 1. The frequency of TDP-43 pathology by ethnoracial groups were as follows: 53% of African Americans/Black American deceents had evidence of TDP-43 (n = 27), 34% of Hispanics (n = 10), and 46% of non-Hispanic Whites (n = 476) Figure 3). Asian/Asian American and American Indian/Alaskan Native decedents both had a 50% frequency of TDP-43 pathology; however, representation for these groups was low. There was no significant difference across ethnoracial groups in terms of overall TDP-43 pathology (p = 0.84).

TDP-43 neuroanatomical distribution across ethnoracial groups

The frequency of TDP-43 pathology in Non-Hispanic White decedents with AD was highest in the amygdala (38%), then hippocampus (36%), followed by entorhinal cortex (32%), and the least in neocortex (7%) (Figure 4). This trend was also observed in African Americans/Black American decedents with 48% in amygdala, 37% in hippocampus, 35% in entorhinal cortex, and 4% in neocortex. The frequency of TDP-43 pathology in Hispanics/Latino decedents with AD was highest in entorhinal cortex (31%), followed by hippocampus (19%), then amygdala (18%), and least in neocortex (14%). When comparing across ethnoracial groups, the amygdala was highest in non-Hispanic White decedents (38%), African American/Black American decedents (48%), Asian/Asian American decedents (50%), and American Indian/Alaskan Native decedents (50%), whereas in Hispanic/Latino decedents, the entorhinal cortex had the highest frequency of TDP-43 pathology (31%). The neocortex contained the lowest frequency of TDP-43 pathology in non-Hispanic White decedents (7%), Hispanic/Latino decedents (14%), and African American/Black American decedents (4%; p = 0.06). The frequency of TDP-43 pathology in the hippocampus was less in Hispanic/Latino decedents (19%) compared to non-Hispanic White decedents (36%), African Americans/Black American decedents (37%), and Asian/Asian American decedents (50%), although this was not statistically significant (p = 0.49).

DISCUSSION

This study is a preliminary evaluation of TDP-43 pathology in the setting of AD across multiple brain regions within Asians/Asian American, African Americans/Black American, Hispanics/Latino, and American Indian/Alaskan Native decedents using data from NACC. This is the first study to our knowledge focused on TDP-43 neuroanatomical deposition in multiple ethnoracial groups, especially examining TDP-43 pathology in AD in Hispanic/

Latino decedents. After querying PubMed.gov (September 28, 2022) using the terms TDP-43 and Hispanic or Latino, only two results were retrieved, but they did not focus on neuroanatomic distribution of TDP-43 pathology in AD [44, 45]. Congruent with previous studies, there was a significant difference between cases having TDP-43 pathology (TDP-43 positive) and those without (TDP-43 negative) with respect to age ($p < 0.001$) in the overall cohort [14, 17, 25], perhaps due, in part, to the predominantly make-up of Non-Hispanic White decedents in our analytic cohort. Additionally, there was no significant difference in age at death with respect to ethnoracial groups ($p = 0.25$), which is also in agreement with prior work [26].

While there were no significant differences between ethnoracial groups in our statistical models with respect to TDP-43 pathology or any neuroanatomic region evaluated, it is important to recognize this study is underpowered due to limited cohort sizes especially in select ethnoracial groups and more cases are required to draw more definite conclusions. However, future studies with sufficient numbers and adequate power may reveal differences in the anatomical distribution of TDP-43 pathology. Non-Hispanic White decedents followed similar trends in neuroanatomic distribution found in previous studies, with TDP-43 deposition highest in amygdala (38%), then hippocampus (36%), followed by entorhinal cortex (32%), and least in neocortex (7%) [25]. This trend was also observed in African Americans/Black American decedents from our NACC sample. This general trend is similar to what was found in Nag *et al.* 2020, in which African American/Black American decedents from a community-based cohort showed the amygdala had the highest frequency, then entorhinal cortex, followed by the hippocampus, and frontal cortices [27]; although the ranking was different in the current study, the difference in proportions for hippocampus and entorhinal cortex was only 4% (36 vs. 32%). With respect to Asians/Asian American decedents, TDP-43 deposition was 50% in the amygdala and hippocampus, and 30% in the entorhinal cortex and neocortex, although group numbers were very minimal. Other reports in larger cohorts such as Asian decedents in a Brazilian cohort, revealed TDP-43 deposition was highest in the amygdala, then entorhinal cortex, followed by hippocampus, then inferior/middle temporal gyrus [26]. Additionally, while the presence of TDP-43 pathology was not significantly different with respect to ethnoracial status in this study, it was found in Nascimento *et al.*, 2016, Asians were more likely to show TDP-43 proteinopathy than non-Hispanic White and Black/admixed decedents [26]. Moreover, given the low representation of this ethnoracial group more studies are needed that include Asian/Asian American decedents, which is an incredibly heterogeneous group in and of itself, to further identify the influence of TDP-43 pathology on AD in this population.

This is the first study to our knowledge that focused on the neuroanatomical distribution of TDP-43 deposits in Hispanic/Latino decedents with AD. It is interesting to note the relatively low percentage of TDP-43 pathology in Hispanic/Latino decedents compared to other ethnoracial groups (34%, 10/29; see Figure 3). Additional research with larger cohorts is needed to aid in understanding these trends. It is notable the amygdala contained the highest frequency of TDP-43 pathology across ethnoracial groups, except for the Hispanics/Latinos for which it was highest in the entorhinal cortex.

There are limitations and potential cautions to this study – while the NACC dataset is large, freely available and accessible for approved users, findings from this study may not be generalizable as ADRCs represent samples having varying enrollment and consenting protocols across centers[41], as well as different histological protocols (i.e. different TDP-43 antibodies and pre/post-processing procedures of samples); such distinctions may be exerting an effect on our results compared to others when investigating the TDP-43 profiles of minoritized/underrepresented groups. There is also the notion of the extreme imbalance in group numbers such as 10 Asian/Asian American and 2 American Indian/Alaskan Native decedents; this highlights the need for more diverse cohorts. Furthermore, in the current study the Limbic-predominant age-related TDP-43 (LATE) terminology is not utilized; this term has gained much traction since is proposal in 2019[24]. However, there are reservations regarding the use of the term encephalopathy as some argue it may presume causation of functional impairment implying a clinical entity[46]. Furthermore, within the current study we utilized data from NACC of which anatomic regions evaluated do not completely align with those proposed within the LATE realm. Another caution is the need for inter-rater reliability studies within the TDP-43 realm as has been done with other recently proposed criteria for other pathological entities such as the Rainwater Charitable Foundation criteria for progressive supranuclear palsy[47]. Another limitation is the categorization for race and ethnicity in the NACC database at the time of the data analyses were somewhat finite and based on historical categories that do not include details such as socioeconomic status, as well as other cultural aspects that may have an impact on disease development. Additionally, ADRCs have different recruitment processes and different exclusion criteria which may bias some centers for greater inclusivity of persons from certain backgrounds, and perhaps disproportionality restrict recruitment of minoritized/underrepresented groups [41]. It is essential to note the lack of minoritized participants in the NACC database and in research studies more generally may be multifactorial, resulting from limited access to healthcare, socioeconomic circumstance, cultural beliefs, language barriers, mistrust of the healthcare system, past abuses of minoritized groups for medical research, and/or discrimination in the process of receiving healthcare [10, 48–53]. Moreover, more work is needed exploring these social determinants of health as it pertains to the neuropathological profiles revealed in this study (for review see [54]).

Additional considerations concerning neuropathology data relate to the historical changes to NACC procedures and the inclusion of TDP-43 pathology denotation should be noted. Specifically, the NACC neuropathology form has had revisions since 2002 and here we utilized the 2014 revision, version 10 [41]. TDP-43 pathology data were only incorporated into the data forms starting in 2014, with the implementation of the version 10 NP form. For this reason, cases before 2014 may not have been assessed/collected for TDP-43, although there are works to retroactively input data, additional biases should be considered given select centers may have collected such data. Moreover, there is currently no consensus of immunohistochemical methods of staining to precisely assess TDP-43 pathology [22]. Of the 1135 cases within the NACC database fitting this study's inclusion/exclusion criteria: 8% were from minoritized groups which highlights the lack of research in these groups, especially from Asian/Asian American decedents (0.9%) and Native American decedents (0.2%). While cohort sizes were small, this serves as a preliminary evaluation to investigate

the relationship between TDP-43 deposition and AD in ethnoracial groups. Furthermore, due the impact of TDP-43 pathology in the context of AD and increasingly diverse, aging population, it is imperative future studies include minoritized/underrepresented groups to drive development of more inclusive therapeutics and grasp a deeper understanding of TDP-43 pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY

The data in this study were derived from the National Alzheimer's Coordinating Center database which is available at https://naccdata.org/.

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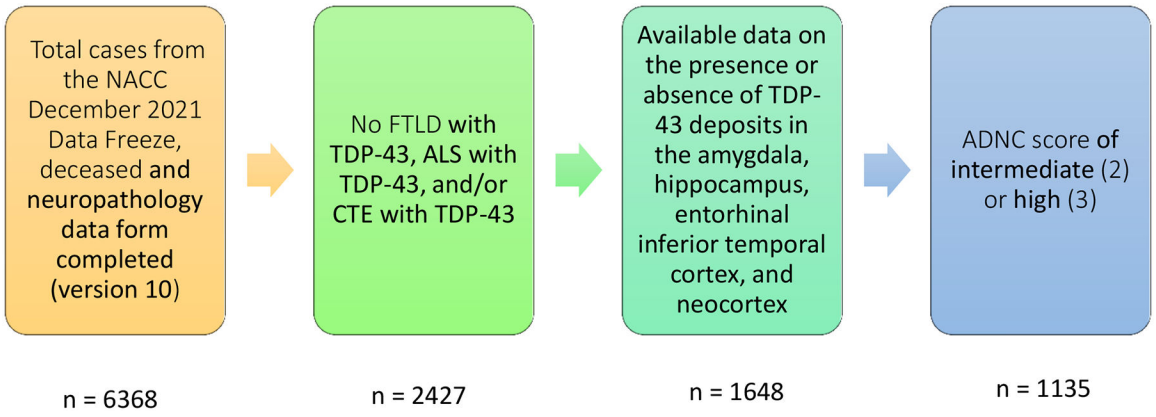

Figure 1.
Illustration of inclusion and exclusion criteria for cleaning data.

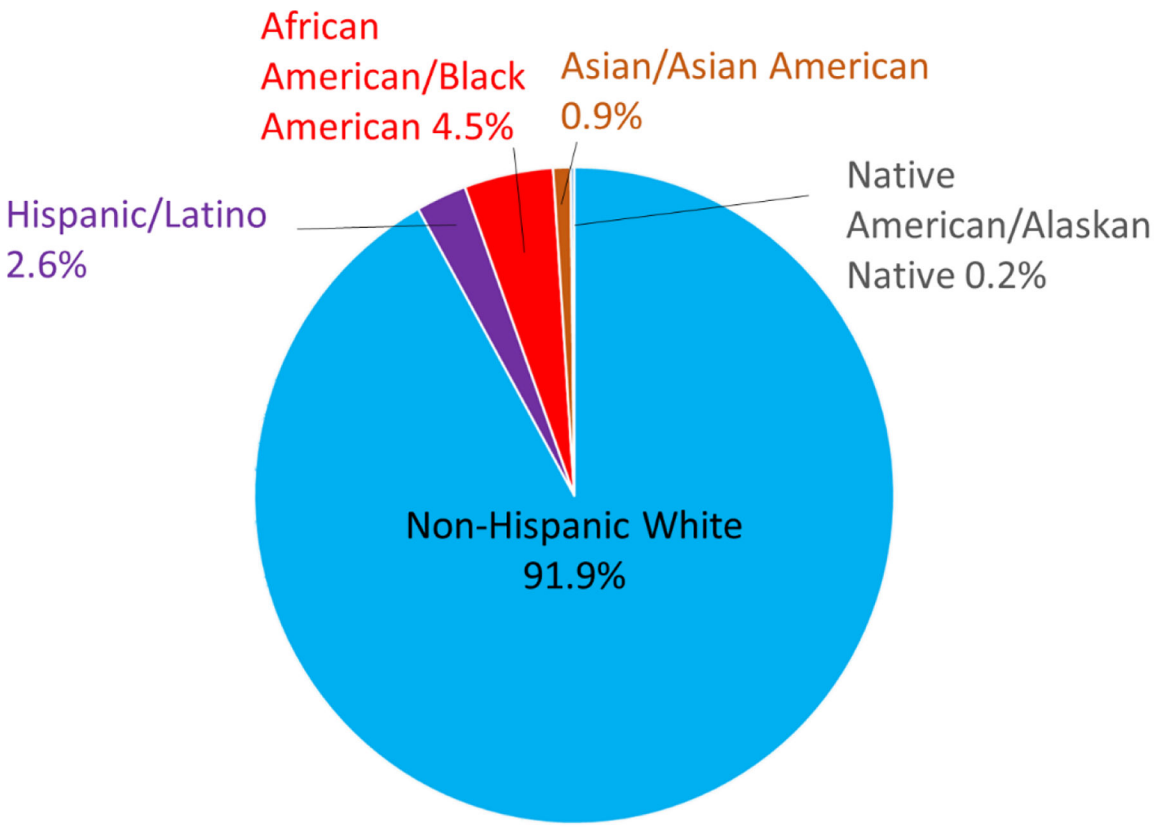

Figure 2.

Distribution of participants within the NACC UDS from the December 2021 data freeze after inclusion and exclusion criteria were applied (N=1135): 1043 non-Hispanic White (91.9%), 10 Asian/Asian American (0.9%), 51 African American/Black American (4.5%), 29 Hispanic/Latinos (2.6%), and 2 American Indian/Alaskan Native (0.2%).

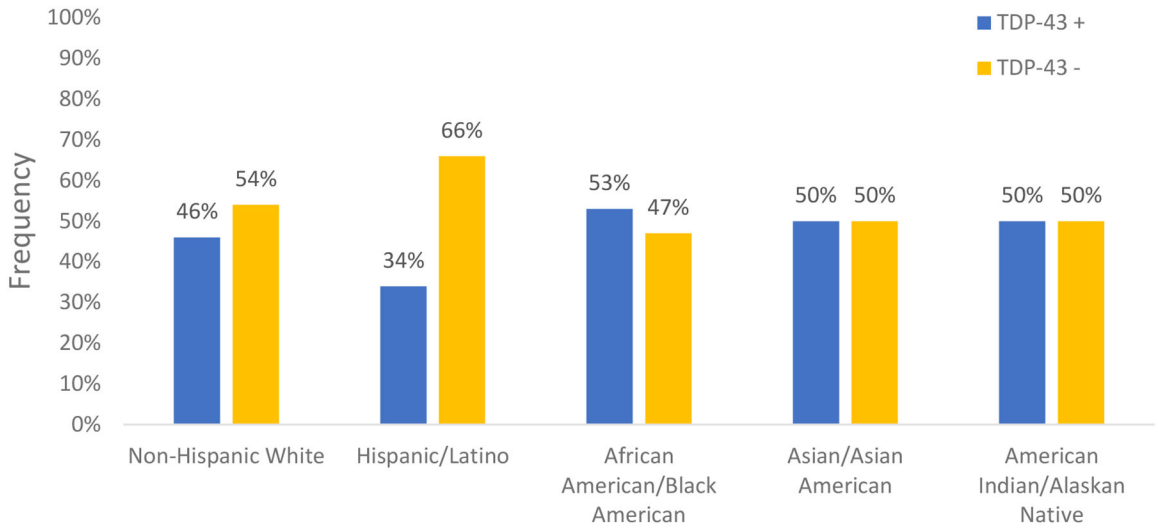

Figure 3.

TDP-43 pathology frequency across non-Hispanic Whites (n=1043), Hispanics/Latinos (n=29), African American/Black Americans (n=51), Asians/Asian Americans (n=10), and American Indians/Alaskan Natives (n=2).

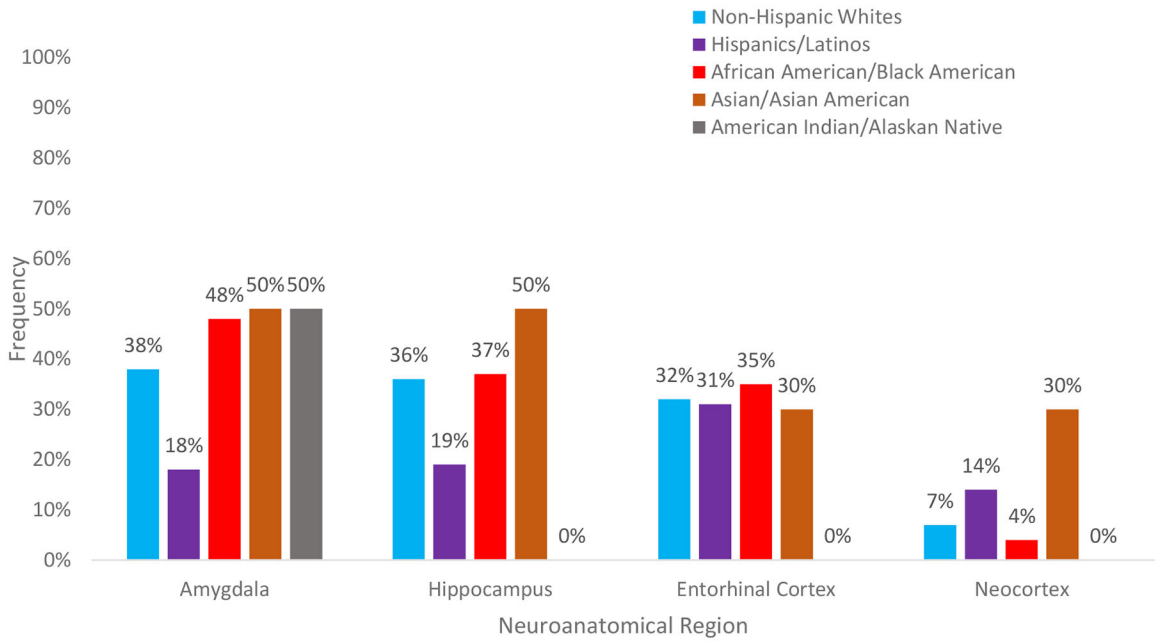

Figure 4.

Chart illustrating neuroanatomical distribution of TDP-43 positivity across ethnoracial groups: non-Hispanic Whites (n=1043), Hispanics/Latinos (n=29), African American/Black Americans (n=51), Asians/Asian Americans (n=10), and American Indians/Alaskan Natives (n=2). Full details of case numbers with respect to each anatomical region are in Supplementary Table 1.

Table 1.

Overall demographic characteristics including odds ratio and 95% confidence interval.

Characteristic	Total	TDP43(+)	TDP43(−)	Odds Ratio (95% CI)	P-value*
N	1135	542	636		
Age at death, mean (SD)	80.9 (10.7)	83.6 (9.3)	78.7 (11.3)	1.05 (1.03, 1.06)	<0.001
Education (years), mean(SD)	16.2 (7.9)	16.2 (7.8)	16.3 (8.0)	1.00 (0.99, 1.02)	0.72
Gender					0.76
Female, n (%)	606 (51.4%)	286 (52.8%)	320 (50.3%)	(ref)	
Male, n (%)	572 (48.6%)	256 (47.2%)	316 (49.7%)	0.96 (0.73, 1.26)	
Race/Ethnicity					0.93
Non-Hispanic White	1043	476 (45.6%)	567 (54.4%)	(ref)	
Hispanic/Latino	29	10 (34.5%)	19 (65.5%)	0.64 (0.24, 1.71)	
African American/Black American	51	27 (52.9%)	24 (47.1%)	1.03 (0.53, 1.99)	
Asian/Asian American	10	5 (50%)	5 (50%)	0.83 (0.22, 3.13)	
American Indians/Alaskan Native	2	1 (50%)	1 (50%)	0.94 (0.05,16.44)	

* p-value is from a generalized mixed effects logistic regression model with center as a random effect.

Table 2.

Demographic characteristics based on ethnoracial group.

	Non-Hispanic Whites	Hispanics/ Latinos	African Americans/Black Americans	Asians/Asian Americans	American Indians/Alaskan Natives	p-value*
N	1043	29	51	10	2	
M:F	509:534	15:14	16:35	4:6	2:0	0.19
Age at death (years)	80.8 ± 0.5	78.2 ± 15.2	83.2 ± 12.3	87.2 ± 6.3	84.0 ± 7.1	0.25
Education (years)	16.5 ± 8.2	13.1 ± 4.8	16.1 ± 12.5	14.5 ± 3.4	15.0 ± 4.2	0.10
TDP-43 (+)/(−)						0.84
TDP-43 Positive (+)	476 (45.6%)	10 (34.5%)	27 (52.9%)	5 (50.0%)	1 (50.0%)	
TDP-43 Negative (−)	567 (54.4%)	19 (65.5%)	24 (47.1%)	5 (50.0%)	1 (50.0%)	
APOE4						0.28
E4 (+)	539 (57.4%)	11 (50.0%)	31 (72.1%)	3 (37.5%)	0 (0%)	
E4 (−)	400 (42.6%)	11 (50.0%)	12 (27.9%)	5 (62.5%)	2 (100%)	

*p-value is from a mixed effects model (linear or logistic) with center as a random effect.