Title

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ABSTRACT

Limbic-predominant age-related TDP-43 encephalopathy (LATE) affects approximately one-third of older individuals and is associated with cognitive impairment. However, there is a highly incomplete understanding of the genetic determinants of LATE neuropathologic changes (LATE-NC) in diverse populations. The defining neuropathologic feature of LATE-NC is TDP-43 proteinopathy, often with comorbid hippocampal sclerosis (HS). In terms of genetic risk factors, LATE-NC and/or HS are associated with single nucleotide variants (SNVs) in 3 genes—*TMEM106B* (*rs1990622*), *GRN* (*rs5848*), and *ABCC9* (*rs1914361* and *rs701478*). We evaluated these 3 genes in convenience samples of individuals of African ancestry. The allele frequencies of the LATE-associated alleles were significantly different between persons of primarily African (versus European) ancestry: In persons of African ancestry, the risk-associated alleles for *TMEM106B* and *ABCC9* were less frequent, whereas the risk allele in *GRN* was more frequent. We performed an exploratory analysis of data from African-American subjects processed by the Alzheimer's Disease Genomics Consortium, with a subset of African-American participants (n = 166) having corroborating neuropathologic data through the National Alzheimer's Coordinating Center (NACC). In this limited-size sample, the *ABCC9*/rs1914361 SNV was associated with HS pathology. More work is required concerning the genetic factors influencing non-Alzheimer disease pathology such as LATE-NC in diverse cohorts.

KEYWORDS: Dementia, Diversity, Epidemiology, Genome-Wide Association Studies (GWAS), *KCNMB2*, FTLD, KATP

INTRODUCTION

Aging-related dementia is highly heritable, yet a large proportion of this genetic risk remains unexplained (1–3), particularly in populations of non-European ancestry. Further, the pathogenesis of amnestic dementia is quite complex: Pathologies other than Alzheimer disease (AD)-type Aβ plaques and tau tangles often contribute to the dementia phenotype in aging (4–6). For example, in approximately 30% of aged individuals with clinical dementia, autopsy reveals TDP-43 pathology (7, 8). A term for the prevalent non-Alzheimer amnestic dementia associated with TDP-43 pathology was recently proposed: limbic predominant age-related TDP-43 encephalopathy (LATE) (9). The presence of LATE neuropathologic change (LATE-NC) often co-occurs with hippocampal sclerosis (HS) (10), which indicates cell loss and gliosis in the hippocampal formation.

While most prior studies on LATE-NC and HS have been in European ancestry-predominant cohorts, there have also been prior studies of LATE-NC phenotypes in non-European populations (11–15). However, pending the availability of more data, it is currently challenging to draw inferences based on these studies about commonalities and differences between ethnoracial populations that are attributable to genetic and/or environmental factors.

Prior published data indicated that there are specific alleles conferring risk for LATE-NC and/or HS in aging. Single nucleotide variants (SNVs) that were associated with risk for LATE-NC and/or HS, and in which the primary observations were replicated, are granulin (*GRN*), transmembrane protein 106B (*TMEM106B*), and ATP-binding cassette, subfamily C, member 9 (*ABCC9*) (16–21). It also has been shown that the *APOE* allele linked to risk for AD risk is also associated with LATE-NC (18, 22), but this phenomenon is not a focus of the current study.

To date, the genetic architecture of LATE-NC and associated pathologies is poorly characterized in diverse populations. Here we evaluated the risk alleles in *TMEM106B*, *GRN*, and *ABCC9*, which have previously been associated with LATE-NC pathological phenotypes, among convenience samples of persons of African ancestry.

MATERIALS AND METHODS
SNVs from LDLink online database

The characterization of LATE-NC and/or HS-associated gene variants by geographical-related ancestry was accomplished through the public access database, NIH-sponsored LDLink (https://ldlink.nih.gov) (23), and more specifically the LDpop Tool, which is described on the website (https://ldlink.nih.gov/?tab=ldpop) as a resource to "Investigate allele frequencies and linkage disequilibrium (LD) patterns across 1000G populations" (24). All of the accessioned populations in the LDLink database of African and European ancestry were included in the current study.

Participants for genotype/phenotype association testing

The National Alzheimer's Coordinating Center (NACC) phenotype data were derived from 37 different US Alzheimer's Disease Research Centers (ADRCs) with autopsies measured via the NACC neuropathology v10-11 forms through the September 2022 data freeze (https://www.alz.washington.edu/). Autopsies were performed within each of the contributory ADRCs. We excluded participants diagnosed with at least 1 of 19 rare brain diseases at autopsy (e.g. prion disorders, multiple sclerosis, corticobasal degeneration, triplet repeat diseases) as described previously (25). For example, FTLD-TDP, ALS, and most other non-LATE-NC conditions with TDP-43 pathology were excluded.

Neuropathology data

TDP-43/LATE-NC neuropathological data were operationalized as follows: TDP-43 pathology with $0 =$ none and $1 =$ present in any brain regions including amygdala, hippocampus, entorhinal/inferior temporal cortex, and neocortex (binary LATE-NC); TDP-43 pathology with $0 =$ none and $1 =$ present in hippocampus and/or entorhinal/inferior temporal cortex (these indicate LATE-NC Stage >1) (26); and

HS with $0 =$ none and $1 =$ present either unilaterally or bilaterally. Alzheimer disease neuropathologic change (ADNC) was operationalized using semiquantitative metrics as described previously (27–30).

Genetic data for genotype-pathology correlations

We obtained ADRC genotype data from the Alzheimer's Disease Genomics Consortium (ADGC; n = 23 131). The genotype data were imputed using the TOPMed Imputation Server (https://imputation.biodatacatalyst.nhlbi.nih.gov/) based on the Genome Reference Consortium Human Build 38 (GRCh38) (31). To identify predominant genetic ancestry for each participant, we calculated principal components (PCs) using a LD pruned subset of genomewide SNVs (pairwise r^2 < 0.2) and ran Uniform Manifold Approximation and Projection (UMAP) based on the first 20 PCs (32).

Statistical analysis

For each of the neuropathology outcomes, we performed association tests under an additive mode of inheritance using logistic regression and adjusted for age at death, sex, and the top 3 PCs computed in PLINK v1.90a (33, 34).

RESULTS
SNV frequencies in African and European ancestry samples

The allele frequencies of the LATE-NC associated alleles were quite different between persons of African (versus European) ancestry: In persons of African ancestry, the LATE-NC-associated risk alleles for *TMEM106B* and HS risk alleles in *ABCC9* were relatively less frequent, whereas the *GRN* risk allele was more frequent in persons of African ancestry. Primary data are shown in Table 1. In contrast to the large difference between European and African ancestry groups, the variability within groups (standard deviation, as denoted by

Table 1. Frequencies of selected single nucleotide variants that have been linked to altered risk for LATE-NC pathological phenotype(s) in cohorts of African or European ancestry*

Ancestry group*		Sample size, n	TMEM106B rs1990622, A = risk	GRN rs5848, T = risk	ABCC9 rs1914361, G = risk	ABCC9 rs704178, G = risk
YRI	Yoruba in Ibadan, Nigeria	108	A: 23.6%, G: 76.4%	C: 21.8%, T: 78.2%	A: 97.7%, G: 2.3%	G: 22.7%, C: 77.3%
LWK	Luhya in Webuye, Kenya	99	A: 32.3%, G: 67.7%	C: 38.4%, T: 61.2%	A: 92.4%, G: 7.6%	G: 41.9%, C: 58.1%
GWD	Gambian in Western Gambia	113	A: 31.0%, G: 69.0%	C: 23.9%, T: 76.11%	A: 91.6%, G: 8.41%	G: 31.9%, C: 68.1%
MSL	Mende in Sierra Leone	85	A: 24.1%, G: 75.9%	C: 14.1%, T: 85.9%	A: 88.8%, G: 11.2%	G: 35.9%, C: 64.1%
ESN	Esan in Nigeria	99	A: 15.1%, G: 84.9%	C: 24.9%, T: 75.3%	A: 96.0%, G: 4.0%	G: 23.7%, C: 76.3%
ASW	Americans of African Ancestry in SW USA	61	A: 33.6%, G: 66.4%	C: 42.6%, T: 57.4%	A: 83.6%, G: 16.4%	G: 38.5%, C: 61.5%
ACB	African Caribbeans in Barbados	96	A: 25.0%, G: 75.0%	C: 25.5%, T: 74.5%	A: 94.3%, G: 5.7%	G: 29.2%, C: 70.8%
African ancestry, total		**661**	**A: 26.1%, G: 73.9%**	**C: 26.6%, T: 73.45%**	**A: 92.7%, G: 7.3%**	**G: 31.4%, C: 68.6%**
CEU	Utah residents from N&W Europe	99	A: 54.0%, G: 45.96%	C: 75.3%, T: 24.8%	A: 46.5%, G: 53.5%	G: 57.1%, C: 42.9%
TSI	Toscani in Italia	107	A: 61.2%, G: 38.8%	C: 70.6%, T: 29.4%	A: 51.9%, G: 48.1%	G: 45.8%, C: 54.2%
FIN	Finnish in Finland	99	A: 61.6%, G: 38.4%	C: 66.7%, T: 33.3%	A: 50.0%, G: 50.0%	G: 53.0%, C: 47.0%
GBR	British in England and Scotland	91	A: 54.4%, G: 45.6%	C: 70.9%, T: 29.1%	A: 55.5%, G: 44.5%	G: 46.2%, C: 53.9%
IBS	Iberian population in Spain	107	A: 64.0%, G: 36.0%	C: 66.4%, T: 33.6%	A: 61.7%, G: 38.3%	G: 44.4%, C: 55.6%
European ancestry, total		**503**	**A: 59.2%, G: 40.8%**	**C: 69.9%, T: 30.1%**	**A: 53.2%, G: 46.8%**	**G: 49.2%, C: 50.8%**

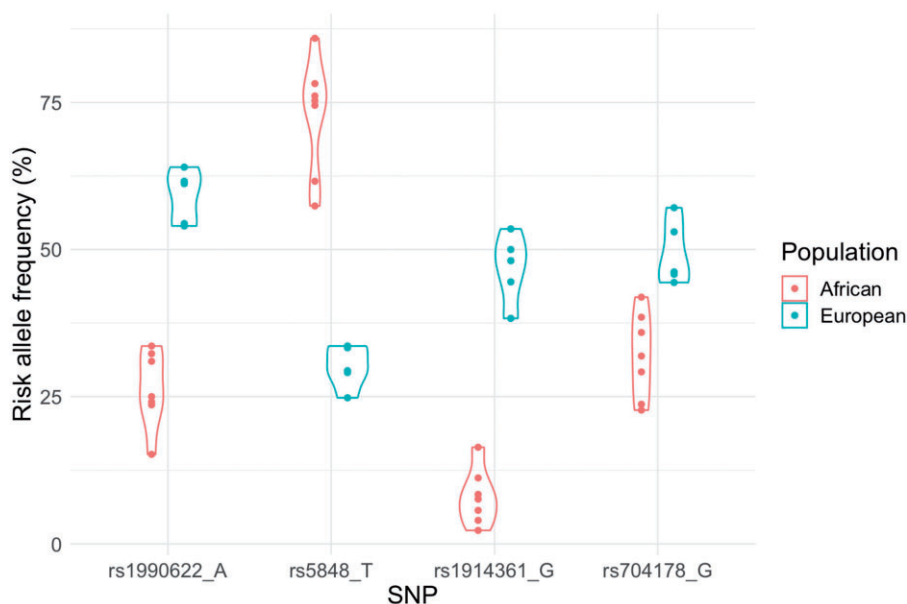*Data derive from publicly available website: https://ldlink.nih.gov/.

Figure 1. Allele frequencies for single nucleotide variants (SNVs) associated with LATE-NC phenotype(s) in persons of European (blue) or African (orange) ancestry. For the identity of the specific increased risk-associated allele, see Table 1. Risk alleles are rs1990622 (*TMEM106B*), rs5848 (*GRN*), rs1914361 (*ABCC9*), and rs704178 (*ABCC9*). As the plots and Table 1 indicate, there were n = 5 cohorts for European ancestry and n = 7 cohorts for African ancestry.

error bars in Fig. 1) was relatively small, indicating that the findings were robust within continental ancestry groups.

Association between selected SNVs and LATE-NC pathologic phenotypes in a cohort of African-Americans

A total of n = 166 genetically identified African-Americans from US ADRCs (with neuropathology data and SNV genotyping available) met inclusion criteria. We also assessed a larger group of participants of European ancestry (n = 3178). Demographic and neuropathologic summary data on these subjects are displayed in Table 2. This is a highly educated cohort (average years of education for African-Americans = 15.6). Note that among both African and European ancestry groups, most of the included participants had severe ADNC at autopsy, and approximately one-third had LATE-NC.

In these convenience samples, we tested the associations between selected SNVs and LATE-NC phenotypes. Principal components analyses (PCA) results and UMAP plots are shown in Figure 2. The results of the genotype-phenotype association tests (with ethnoracial parameters according to the PCA/UMAP results) are shown in Table 3 for participants of African ancestry, and Table 4 for a larger cohort of European ancestry. Among the various tests performed in individuals of African ancestry, only the *ABCC9* genotype (rs1914361) was associated with HS pathology in this small sample.

The *GRN* genetic variant rs5848 is considered to be a likely disease-driving 3'UTR genetic variant as it changes gene expression via a miRNA binding site (35). However, both *TMEM106B* (36) and *ABCC9* (37) have shown evidence that the disease-associated allele may be a proxy for larger

Table 2. Demographic and neuropathologic characteristics of included subjects for genotype/phenotype correlation

| Characteristics	African Ancestries n = 166	European Ancestries n = 3178
Age at death, mean ± SD	80.6 ± 11.6	82.3 ± 10.6
Years in education, mean ± SD	15.6 ± 9.9	16.4 ± 8.5
Sex, n (%)		
Male	61 (36.7)	1671 (52.6)
Female	105 (63.3)	1507 (47.4)
Thal phase, n (%)		
0	7 (7.4)	113 (6.9)
1–2	13 (13.7)	145 (8.9)
3	9 (9.5)	184 (11.3)
4–5	66 (69.5)	1190 (72.9)
Braak NFT stage, n (%)		
0	2 (1.2)	54 (1.7)
I–II	21 (12.7)	433 (13.7)
III–IV	35 (21.2)	778 (24.6)
V–VI	107 (64.8)	1902 (60.1)
Neuritic plaques, n (%)		
No	29 (17.5)	457 (14.4)
Sparse	12 (7.2)	412 (13.0)
Moderate	27 (16.3)	651 (20.5)
Frequent	98 (59.0)	1653 (52.1)
TDP-43 in any region, n (%)		
No	54 (70.1)	799 (67.6)
Yes	23 (29.9)	383 (32.4)
LATE-NC Stage >1, n (%)		
No	48 (70.6)	726 (71.2)
Yes	20 (29.4)	293 (28.8)
Hippocampal sclerosis, n (%)		
No	74 (81.3)	1389 (87)
Yes	17 (18.7)	208 (13)

SD, standard deviation.
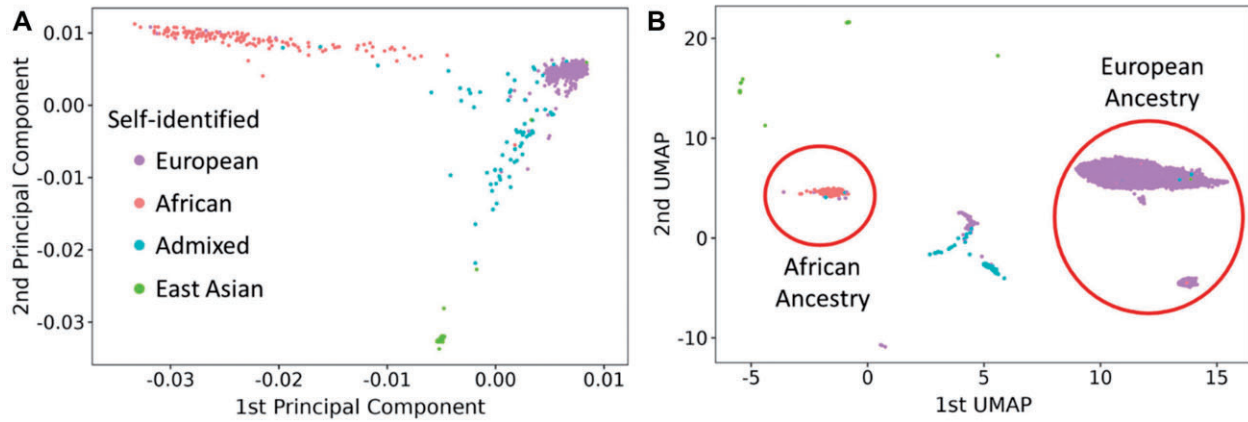
Figure 2. Principal components (**A**) and Uniform Manifold Approximation and Projection (UMAP) plots (**B**) for participants in the present study (Table 1), colored by self-identified race. African and European ancestries were identified based on UMAP plot.

Table 3. Genotype/phenotype correlation for SNVs linked with LATE-NC phenotypes (n = 166 African ancestries)

Pathology	Gene	SNV	Allele	AF	OR	95% CI		p-value
LATE-NC (any)	TMEM106B	rs1990622	A	0.34	0.78	0.31	1.91	0.59
	GRN	rs5848	T	0.66	0.65	0.24	1.65	0.37
	ABCC9	rs1914361	G	0.17	1.57	0.54	4.62	0.40
	ABCC9	rs704178	G	0.39	0.56	0.21	1.36	0.21
LATE-NC (Stage >1)	TMEM106B	rs1990622	A	0.34	0.58	0.20	1.60	0.31
	GRN	rs5848	T	0.66	0.50	0.15	1.43	0.21
	ABCC9	rs1914361	G	0.17	1.53	0.48	4.94	0.46
	ABCC9	rs704178	G	0.39	0.71	0.27	1.77	0.47
Hippocampal sclerosis	TMEM106B	rs1990622	A	0.34	0.38	0.12	1.02	0.071
	GRN	rs5848	T	0.66	1.67	0.64	4.64	0.30
	ABCC9	rs1914361	G	0.17	4.60	1.62	14.69	**0.0059**
	ABCC9	rs704178	G	0.39	2.03	0.81	5.41	0.14

SNV, simple nucleotide variant; AF, allele frequency (risk allele); OR, odds ratio; CI, confidence interval. **Bold** = p<0.05.

Table 4. Genotype/phenotype correlation for SNVs linked with LATE-NC phenotypes (n = 3178 European ancestries)

Pathology	Gene	SNV	Allele	AF	OR	95% CI		p-value
LATE-NC (any)	TMEM106B	rs1990622	A	0.58	1.47	1.23	1.77	3.3×10^{-5}
	GRN	rs5848	T	0.30	1.13	0.94	1.37	0.19
	ABCC9	rs1914361	G	0.44	0.94	0.79	1.12	0.49
	ABCC9	rs704178	G	0.50	0.85	0.71	1.01	0.071
LATE-NC (Stage >1)	TMEM106B	rs1990622	A	0.58	1.48	1.21	1.82	1.8×10^{-4}
	GRN	rs5848	T	0.30	1.03	0.83	1.27	0.81
	ABCC9	rs1914361	G	0.44	0.88	0.73	1.07	0.21
	ABCC9	rs704178	G	0.50	0.82	0.67	1.00	**0.047**
Hippocampal sclerosis	TMEM106B	rs1990622	A	0.58	1.72	1.38	2.16	1.7×10^{-6}
	GRN	rs5848	T	0.30	1.47	1.18	1.83	5.1×10^{-4}
	ABCC9	rs1914361	G	0.44	1.12	0.91	1.38	0.29
	ABCC9	rs704178	G	0.50	0.99	0.80	1.22	0.92

SNV, simple nucleotide variant; AF, allele frequency (risk allele); OR, odds ratio; CI, confidence interval. **Bold** = p<0.05.
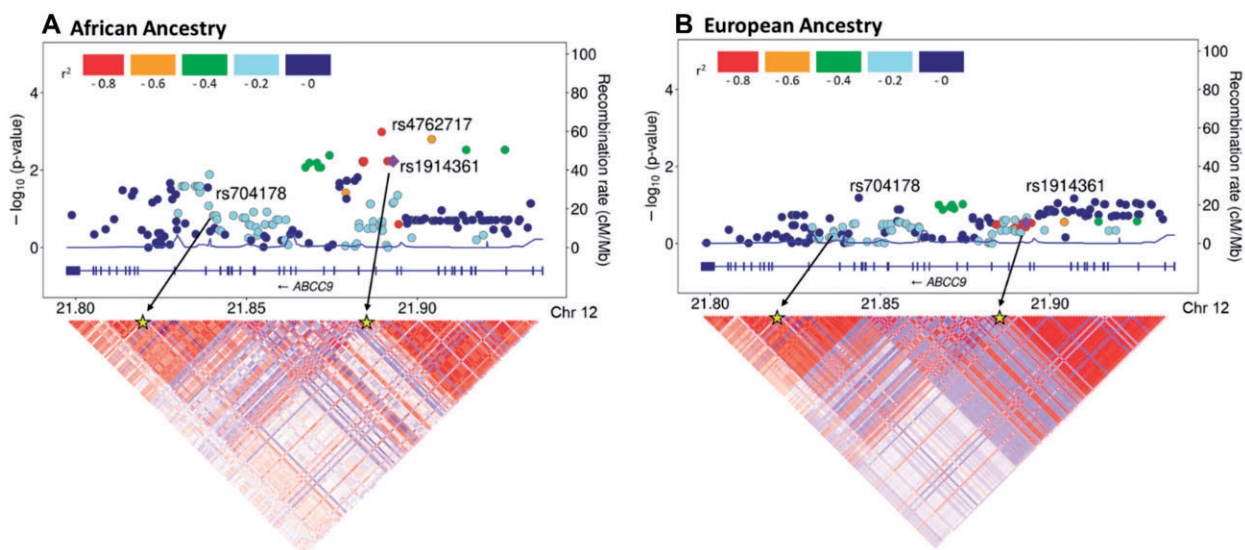
Figure 3. In persons of African ancestry (**A**) and European ancestry (**B**), LocusZoom plots shown for associations between single nucleotide polymorphisms in *ABCC9* and hippocampal sclerosis with linkage disequilibrium (LD) depicted below in heatmap plots. A signal at rs1914361 was evident in the participants of African ancestry, whereas in this sample of European ancestry participants, ABCC9 genetic variation was not associated with HS risk.
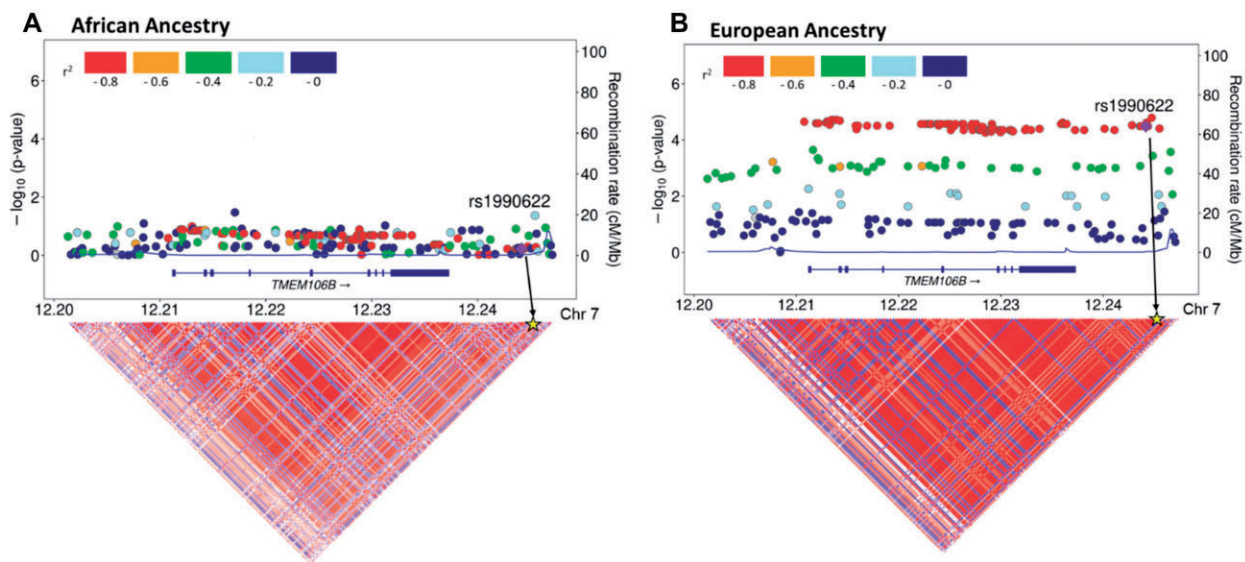

Figure 4. In persons of African ancestry (**A**) and European ancestry (**B**), LocusZoom plots shown for associations between single nucleotide polymorphisms in *TMEM106B* and limbic predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC), with linkage disequilibrium (LD) depicted below in heatmap plots. In this sample of participants of African ancestry, *TMEM106B* variants were not associated with risk for LATE-NC.

haplotypes. For more detailed presentation of the genotype/phenotype associations and genetic architectures in and nearby *TMEM106B* and *ABCC9* genes, in samples of African and European ancestry, see Figures 3 and 4. Notably, with caveats related to sample size, there does not seem to be a clear signal of *TMEM106B* gene variation association with LATE-NC in persons of African ancestry.

Results are presented in Supplementary Data Tables S1–S3 for *KCNMB2* SNV (rs9637454) that was found to be associated with HS (19). We did not find compelling reasons to

indicate that *KCNMB2* genetic variation would explain ethno-racial differences in LATE-NC/HS.

DISCUSSION

We evaluated SNVs (referent to *TMEM106B*, *GRN*, and *ABCC9* genes) in persons of African ancestry. Among the cohorts we evaluated, the allele frequencies of the LATE-associated genetic variants were different in relation to the geographical region of ancestry: In persons of African ancestry,

the LATE-NC-linked risk alleles for *TMEM106B* and *ABCC9* were less frequent, whereas the HS risk allele in *GRN* was more common than in persons of European ancestry. In an exploratory analysis of data on African-American subjects from the ADGC, only the *ABCC9*/rs1914361 SNV was associated with HS pathology.

There are notable limitations to the present study. Ethnoracial groupings are partly a sociocultural construct and the history of biased research should be factored in to any scientific study related to race/ethnicity (38). Although beyond the purview of the present manuscript, structural racism (inside and outside of scientific institutions) tends to have insidious influences that should be considered. Culture-defined groups can also be differentially recruited into research studies, even within the same research center. The genetic and cultural aspects can be intertwined; for example, self-described "Blacks" in 1 US state can have very different genetic patterns than those in another (even nearby) state (39). These are only some of the relevant considerations in the study of the impact of ancestry in genetic research (40).

In addition to the inherent challenges of dealing with racial identity as an experimental parameter, another challenge related to the current study was that the sample sizes of the gene-pathology association analyses were small, limiting statistical power. The lack of associations (in terms of statistical testing results) between *TMEM106B* and *GRN* SNVs with LATE-NC pathology in persons with African ancestry should be considered in light of that limitation due to the high likelihood of type II (false-negative) error. However, we note that relatively small European-predominant cohorts have seen evidence of *TMEM106B* association with LATE-NC/HS (41, 42). In the present study, even in the larger analyses of participants of European ancestry, some but not all of the previously replicated genotype-phenotype association signals were not seen. Such (presumably type II error) results are not unusual in genetic studies with these sample sizes for various reasons (43, 44). Nonetheless, in the present study, there was a statistically significant association between the *ABCC9* risk allele rs1914361 and HS pathology in persons of African ancestry.

Keeping the abovementioned notes of caution in mind, it is notable that Blacks/African-Americans have been hypothesized to be at higher risk for dementia than other ethnoracial groups (38, 45). This phenomenon has not been fully explained but there are some indications that non-AD pathways may be important (38, 46). Further, there is precedence for impactful differences in genotype/phenotype correlations in different ethnoracial groups. A given genetic variant may signal different things in persons with differing genetic background. For example, while *APOE* ε4 is a driving factor in AD neuropathology, that allele appears to have an attenuated impact in persons of African ancestry (relative to those of European ancestry), whereas the correlative impact of *ABCA7* gene variants is relatively stronger in persons of African ancestry (47–52).

Thus, it is not necessarily true that differences in the frequency of a specific allele in one population (versus another) will have a predictable correlative association with a given phe-

notype: It remains to be seen if the relatively low frequencies in Blacks/African ancestry individuals, of SNVs (rs1990622 in *TMEM106B*, and *ABCC9* alleles) that have been associated with increased risk in White-predominant cohorts, are predictive of a lower vulnerability of LATE-NC in persons of African ancestry. Nor can we predict whether Blacks/African ancestry persons are at increased risk given the relatively higher frequency of *GRN* risk variant rs5848 in persons of African heritage.

In summary, our findings indicate intriguing phenomenology in terms of LATE-NC-associated genetic variants in persons of African ancestry. The findings in the present study are mostly exploratory and they are part of an emerging understanding of the commonalities and differences between ethnoracial groups in terms of the pathobiology of dementia-related diseases. It is acknowledged that these observations raise more questions than they answer. Additional work is required on genomics underlying dementia-related brain pathology, such as LATE-NC, in diverse populations.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The authors have no duality or conflicts of interest to declare.

SUPPLEMENTARY DATA

Supplementary Data can be found at academic.oup.com/jnen.

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