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RESEARCH ARTICLE

Genetic associations with dementia-related proteinopathy: Application of item response theory

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Abstract

INTRODUCTION: Although dementia-related proteinopathy has a strong negative impact on public health, and is highly heritable, understanding of the related genetic architecture is incomplete.

METHODS: We applied multidimensional generalized partial credit modeling (GPCM) to test genetic associations with dementia-related proteinopathies. Data were analyzed to identify candidate single nucleotide variants for the following proteinopathies: Aβ, tau, α-synuclein, and TDP-43.

RESULTS: Final included data comprised 966 participants with neuropathologic and WGS data. Three continuous latent outcomes were constructed, corresponding to TDP-43-, Aβ/Tau-, and α-synuclein-related neuropathology endophenotype scores. This approach helped validate known genotype/phenotype associations: for example, *TMEM106B* and *GRN* were risk alleles for TDP-43 pathology; and *GBA* for α-synuclein/Lewy bodies. Novel suggestive proteinopathy-linked alleles were also discovered, including several (*SDHAF1*, *TMEM68*, and *ARHGEF28*) with colocalization analyses and/or high degrees of biologic credibility.

DISCUSSION: A novel methodology using GPCM enabled insights into gene candidates for driving misfolded proteinopathies.

KEYWORDS
Alzheimer's Coordinating Center, Alzheimer's Disease Neuroimaging Initiative, Alzheimer's disease neuropathologic changes (ADNC), Alzheimer's Disease Sequencing Project, ARHGEF28, Item response theory, Lewy, neuropathology, Religious Orders Study, RGNEF, Rush Memory and Aging Project (MAP), SDHAF1, TMEM68

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Highlights

- Latent factor scores for proteinopathies were estimated using a generalized partial credit model.
- The three latent continuous scores corresponded well with proteinopathy severity.
- Novel genes associated with proteinopathies were identified.
- Several genes had high degrees of biologic credibility for dementia risk factors.

1 | BACKGROUND

Many older persons' brains harbor multiple comorbid misfolded protein aggregates,[1–4] termed "multi-proteinopathy," which is a complex spectrum of abnormally aggregated proteins. Indeed, neuropathology (NP) in the aged brain is rarely "pure" but instead tends to occur in combination.[5–17] We reported that at least three of four pathologically misfolded dementia-related proteins (Aβ, tau, α-synuclein, and TDP-43) were observed in 50% of brains with any tau pathology in the University of Kentucky Alzheimer's Disease Research Center (UK-ADRC) cohort.[12] To address the complicated challenges of "mixed" NP-based genetic association studies, a new toolkit is required, which accomplishes at least two goals: (1) the use of proteinopathy (as opposed to less specific clinical features) as the endophenotype of genetic association studies, and (2) optimal classification criteria and statistical methods to systematically analyze the complex combinations of pathologies.

Dimensionality reduction techniques are often employed to facilitate the analysis of multiple phenotypes. Item response theory (IRT), one such technique, is widely used for estimating latent traits in educational testing and psychometrics.[18] IRT was initially developed for dichotomous item responses in the context of an exam with questions correctly or incorrectly answered.[19] Over the past decades, it has been extended from dichotomous to polytomous, nominal, or graded data; from parametric to non-parametric models; and, from unidimensional to multidimensional models. The generalized partial credit model (GPCM)[20] is a two-parameter model (discrimination and difficulty parameters) for two or more ordered item responses that are not necessarily spaced evenly and do not necessarily have the same number of response options among items. As such, GPCM is a potentially ideal approach to analyze multi-proteinopathy data because: (1) neuropathological features are often measured as a mixture of dichotomous and ordered polytomous variables; (2) each specific NP subtype theoretically contributes differentially to overall disease severity; (3) stages of different neuropathologies do not progress in parallel, as a brain may have a severe burden of one NP subtype but a mild burden of another. Further, GPCM produces continuous unobserved latent traits, which can theoretically increase statistical power (over categorical outcome data) even in a small sample study.[21–23]

In the present study, we investigated the potential of multidimensional GPCM to address the complexities of analyzing genetic associations with multi-proteinopathies by creating latent, continuous, and aggregated proteinopathy measures, thus yielding an overall measure of both the presence and severity of individual brain proteinopathies. We used a combined set of resources that included detailed neuropathologic data from the National Alzheimer's Coordinating Center (NACC), the Alzheimer's Disease Neuroimaging Initiative (ADNI), and the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP) [together referred to as ROSMAP], and genetic data from the Alzheimer's Disease Sequencing Project (ADSP).

2 | METHODS

2.1 | Study cohorts and participants

We obtained NP data from three different cohorts. The NACC NP data https://www.naccdata.org/ were derived from the September 2022 data freeze and measured via the NACC NP v10-11 forms; this included data from 37 different National Institute on Aging-funded Alzheimer's Disease Research Centers (ADRCs). Brain autopsies were performed on site at each of the contributory ADRCs. The second set of NP data comprised ADNI. Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). The third source of NP data was a harmonized dataset from the ROSMAP study.[24] Since all NP data in ROSMAP came from those who died aged 65 years or older, we excluded participants who were younger than 65 years old at death in the NACC and ADNI NP data. We also excluded participants who were diagnosed with at least one of 19 rare brain diseases at autopsy (see Figure 1 and ref.[25]) from the NACC and ADNI NP data. The excluded conditions included frontotemporal lobar degeneration (FTLD), chronic traumatic encephalopathy, multiple sclerosis, multiple system atrophy, amyotrophic lateral sclerosis (ALS), triplet repeat (e.g., Huntington's and other) diseases, and prion diseases. Similar exclusion criteria were not applied to ROSMAP due to a lack of data availability. Finally,

we removed participants who had missing data in any NP variables described below. ADRCs obtained written informed consent from their participants and maintained their own separate IRB review and approval from their institution prior to submitting data to NACC.

2.2 | NP data

The NP features included in this study are listed in Supplementary Table 1. AD neuropathologic changes (ADNC) include amyloid plaques, neocortical neuritic plaques, and tau neurofibrillary tangles (NFTs), all of which were specified as ordinal variables. Regional progression of amyloid plaques was represented by modified Thal Aβ phase ratings (A score: Thal Aβ phase A0–A3)[26] in NACC and ADNI. In ROSMAP, where Thal Aβ phase was not available, diffuse plaque burden across regions (plaq_d = 0, plaq_d $\leq$ 0.5, plaq_d $\leq$ 1, and plaq_d > 1), which was calculated as the average of scaled counts determined by microscopic examination from five brain regions (middle frontal gyrus cortex, middle temporal gyrus cortex, inferior parietal cortex, entorhinal cortex, and hippocampus), was included instead of Thal Aβ phase ratings. Regional progression of tau NFTs was operationalized by modified Braak NFT stage (B score: Stage 0 (B0), Stage I or II (B1), Stage III or IV (B2), and Stage V or VI (B3)),[27] and density of neocortical neuritic plaques by Consortium to Establish a Registry for Alzheimer's Disease (CERAD) ratings (C score: none (C0), sparse (C1), moderate (C2), and frequent (C3)).[28,29] TDP-43 immunoreactive inclusions were specified as indicators for the presence of inclusions in three brain regions: amygdala, entorhinal/inferior temporal cortex and/or hippocampus, and neocortex. Lewy body pathology (LBP) data were categorized into three levels: 0 = none, 1 = present in non-neocortical regions, and 2 = present in neocortical regions. Hippocampal sclerosis (HS) was determined by bilateral or unilateral HS of the CA1 region. Since NACC and ADNI NP data were collected using the "NACC NEUROPATHOLOGY DATA FORM" but ROSMAP NP data were not, we combined the NACC and ADNI NP data (hereafter referred as NACC/ADNI) and created two completed NP datasets (i.e., NACC/ADNI and ROSMAP) for the multidimensional GPCM analyses (Figure 1).

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using various sources including PubMed, meeting abstracts, and conference presentations. While the scientific problems regarding proteinopathy are increasingly recognized, we currently lack key instruments to augment efforts to understand the genetic architecture underlying dementia-related proteinopathy. Relevant citations are appropriately cited.
2. **Interpretation**: Our approach discovered novel suggestive genes associated with limbic-predominant age-related TDP-43 encephalopathy neuropathologic change, Alzheimer's disease neuropathologic changes, and Lewy body pathology.
3. **Future directions**: Future research will examine the functionalities of those genes using omics data analyses and elucidate the roles of biological pathways.

2.3 | Whole genome sequencing data

ADSP whole genome sequencing (WGS) variant calling data (NG00067.v9) formatted with Variant Call Format (VCF)[30,31] were downloaded from DSS NIAGADS (https://dss.niagads.org/). The data consisted of biallelic/multiallelic single nucleotide variants (SNVs) and short insertions/deletions (INDELs) mapped to Genome Reference Consortium Human Build 38 (GRCh38). The ADSP WGS data were linked to the NACC/ADNI and ROSMAP NP data by ADSP sample IDs. Primary quality control (QC) was performed using bcftools version 1.10.2[32] based on the VCF's INFO field for each variant and the VCF's FORMAT for individual genotype calling. The filtering criteria and bcftools command lines are described in Supplementary Table 2. After the primary QC, the VCF format files were converted to PLINK format files pruned for each of the two NP datasets using PLINK v1.90a.[33,34] Hardy-Weinberg equilibrium (HWE) was tested for AD cases and AD controls in the whole ADSP WGS data (the clinically diagnosed AD status data were available in DSS NIAGADS https://dss.niagads.org/ for NACC/ADNI and in SYNAPSE https://www.synapse.org/ for ROSMAP) using PLINK with the "--hardy" option to evaluate excess homozygosity and heterozygosity. Variants with minor allele count < 5, or missing call rate > 5%, or p-value $< 5 \times 10^{-8}$ in the HWE test for the AD control group were removed. To derive orthogonal principal components (PCs), which were used as covariates in the genetic association analyses, PC analyses (PCA) were performed using PLINK with the "--pca" option using a linkage disequilibrium (LD) pruned subset of markers (pairwise $r^2 < 0.2$) in NACC/ADNI and ROSMAP, separately. We determined the appropriate number of PCs for covariate adjustment based on the screen plots shown in Supplementary Figure 1.

2.4 | Statistical analysis

The multidimensional GPCM analyses were conducted using R version 4.2.1.[35] The two-parameter models were run by specifying a normal distribution (dentype = "Gaussian") with z-score constraints (mean = 0 and standard deviation (SD) = 1) and quasi-Monte Carlo EM estimation (method = "QMCEM") in the "mirt" function from the "mirt" R package version 1.37.1.[36] To determine the best fitting number of dimensions, or factors, we first performed leave-one-out cross-validation for the responses to a set of the eight NPs and compared standardized root mean square residual (SRMSR) and comparative fit index (CFI) values among two to four dimensions models. Supplementary Figures 2A and 2B for NACC/ADNI show the evidence that three-dimensional GPCMs were more appropriate than two- and

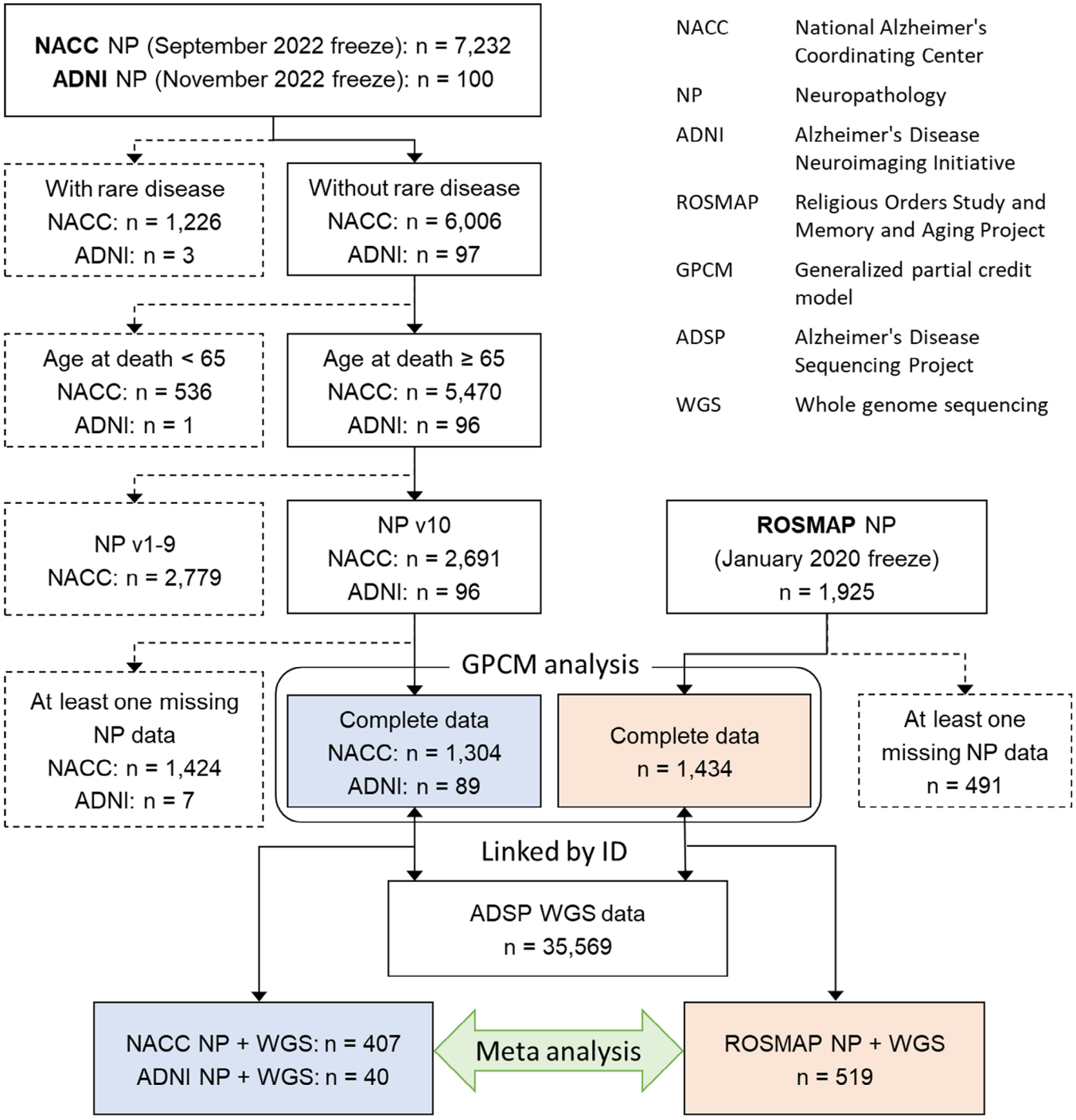


FIGURE 1 Work flow diagram of the present study.

four-dimensional models. As shown in Supplementary Figures 2C and 2D, although four-dimensional model had larger CFI values in ROSMAP, the model seemed unstable according to the SRMSR distribution (Supplementary Figures 2C). From this assessment, we specified model = 3 as a number of dimensions (i.e., three factors) in the "mirt" function. We then estimated three factor scores with 10,000 plausible value imputations (i.e., plausible.draws = 10000 in the "fscores" function from the "mirt" package) and then computed the means of the 10,000 plausible value imputations as individual factor score estimates.

For each of the three factor scores, we performed SNV association tests under an additive mode of inheritance. We ran two linear mixed effects models, which incorporated the kinship matrix: (1) model adjusted for age at death, sex, and the top three PCs; and (2) additionally adjusted for the other two factor score estimates. These analyses were implemented by GEMMA (https://github.com/genetics-statistics/GEMMA)[37] in NACC/ADNI and ROSMAP, separately. Then we conducted meta-analyses along with the heterogeneity tests using METAL (released 3/25/2011).[38] We included SNVs which were contained in both the NACC/ADNI and ROSMAP, and excluded SNVs

with $p < 1\times10^{-5}$ in the heterogeneity tests. Because genetic effects may be attenuated for those with genetic risks but dying before a NP feature develops, we also focused on participants who died aged 80 years or older as a sensitivity analysis. We set genome-wide significance at $p < 5\times10^{-8}$ and "suggestive" significance at $p < 1\times10^{-5}$. We explored annotation (coding, intron, splice site, promoter, 5′ or 3′ untranslated region [UTR], or intergenic region) of significant and suggestively significant SNVs using the "locateVariants" function in the VariantAnnotation Bioconductor R package v1.44.1[39] and the "TxDb.Hsapiens.UCSC.hg38.knownGene" annotation R package v3.16.0.[40] Region association plots were created by LocusZoom software.[41]

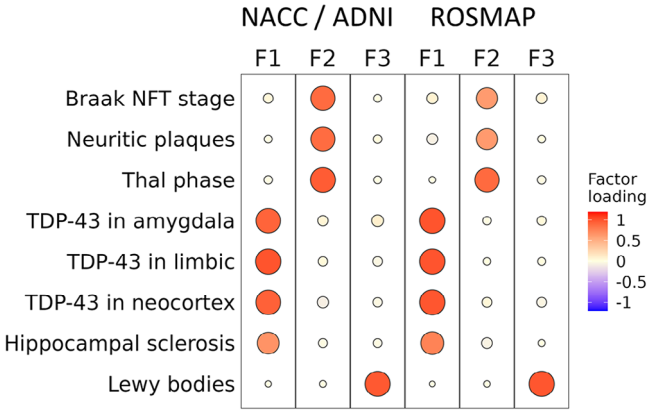
To examine whether any candidate loci were possibly functional, we performed Bayesian colocalization analyses[42,43] developed by Giambartolomei et al., in which only summary statistics are required from two independent association studies. We obtained publicly available summary statistics on gene expression quantitative trait loci (eQTL) from the Genotype-Tissue Expression Project (GTEx),[44] ROSMAP[45] downloaded from https://mostafavilab.stat.ubc.ca/xqtl/,[45] and the Trans-Omics for Precision Medicine (TOPMed) Program (https://topmeddemo.wesdemo.com/). We ran the "coloc.abf" function in the "coloc" R package v5.1.0.1[42] with three prior probabilities of 10^{-4}, 10^{-5}, and 10^{-6} that a SNV is associated with both traits. We evaluated the loci and ± 500 kbp flanking regions for each of the SNVs that had significant or suggestively significant associations with proteinopathy in participants who died aged 65 years or older. We then identified eQTL based on posterior probability of 0.9 or more for each of the three prior probabilities.

3 | RESULTS

Of 2,691 NACC participants, more than half of the participants (n = 1,387) were excluded due to at least one missing data element (Figure 1). The comparison between included and excluded participant groups is displayed in Supplementary Table 3. The excluded participants were older at death, less severe Aβ and neuritic plaques, less TDP-43 pathology in amygdala and more TDP-43 pathology in hippocampus and/or entorhinal/inferior temporal cortex, and less LBP.

The numbers of participants included in the multidimensional GPCM analyses were 1,304 in NACC, 89 in ADNI, and 1,413 in ROSMAP (Figure 1). The mean age at death was 83.0 (standard deviation (SD) = 9.1), the mean of years in education was 16.5 (SD = 8.5), and 50.8% were females in NACC; the mean age at death was 83.0 (SD = 6.6), the mean of years in education was 16.3 (SD = 2.7), and 25.8% were females in ADNI; and the mean age at death was 89.7 (SD = 6.5), the mean of years in education was 16.2 (SD = 3.6), and 68.2% were females in ROSMAP. The NACC and ADNI cohorts included more severe AD patients and fewer people with TDP-43 pathology than ROSMAP (Table 1).

Figure 2 and Supplementary Table 4 show the rotated factor loadings (rotate = "oblimin") representing a strength of the association between each of the eight NPs and each of the latent factor scores (F1 to F3) estimated by three-dimensional GPCMs. The predominant NPs were TDP-43 pathology and HS for the factor 1 (F1), ADNC-related NPs for the factor 2 (F2), and LBP for the factor 3 (F3). The factor correlations were 0.225 between factors 1 and 2, 0.165 between factors 1 and 3, 0.204 between factors 2 and 3 in NACC/ADNI, and 0.303 between factors 1 and 2, 0.104 between factors 1 and 3, 0.115 between factors 2 and 3 in ROSMAP (Figure 2). Supplementary Figures 3-10 display the density plots in each estimated factor score by the eight NP outcomes, indicating that the factor scores reflected well the NP presence and absence as well as the severities.



Pearson correlations of factor loadings

NACC / ADNI

	F1	F2
F2	0.225	-
F3	0.165	0.204

ROSMAP

	F1	F2
F2	0.303	-
F3	0.104	0.115

FIGURE 2 Rotated factor loadings with the oblimin rotation in NACC/ADNI and ROSMAP. ADNI = Alzheimer's Disease Neuroimaging Initiative; NFT, neurofibrillary tangle; NACC, National Alzheimer's Coordinating Center; ROSMAP, Religious Orders Study and Rush Memory and Aging Project.

After linking the NP data to ADSP genotype data, 447 (NACC/ADNI) and 519 (ROSMAP) participants were included in the subsequent SNV association tests (Figure 1). Most participants have predominantly European ancestry in both NACC/ADNI (Supplementary Figure 11A) and ROSMAP (Supplementary Figure 11B). We confirmed that known proteinopathy loci could be detected in our novel NP scoring: SNVs in *TMEM106B* and *GRN*, which are known as TDP-43 pathology and HS related genes;[46–50] the SNVs in the *BIN1* and *APOE* loci, which are strongly associated with ADNC;[51,52] and, the SNVs in *GBA*, which is a risk gene for dementia with LBP[53,54] (Table 2 and Supplementary Table 5 show the number of missing data for each SNV). Although the *GBA* and *BIN1* did not reach the suggestive significance level, rs10950392 in *TMEM106B* and rs429358 in *APOE* were associated with the estimated factor 1 (TDP-43 and HS related) score and factor 2 (ADNC related) score, respectively. Interestingly, the associations of rs429358 in *APOE* with each of the factor scores were attenuated after adjusting for the other factor scores (Supplementary Figures 12-14).

TABLE 1 Characteristics in subjects of National Alzheimer's Coordinating Center (NACC), Alzheimer's Disease Neuroimaging Initiative (ADNI), and Religious Orders Study and Memory and Aging Project (ROSMAP).

Characteristics	NACC ($n = 1,304$)	ADNI ($n = 89$)	ROSMAP ($n = 1,413$)
Age at death (years), mean ± SD	83.0 ± 9.1	83.0 ± 6.6	89.7 ± 6.5
Years in education, mean ± SD	16.5 ± 8.5	16.3 ± 2.7	16.2 ± 3.6
Sex, n (%)			
Male	641 (49.2)	66 (74.2)	450 (31.8)
Female	663 (50.8)	23 (25.8)	963 (68.2)
Thal phase/diffuse plaques[a], n (%)			
0/0	102 (7.8)	5 (5.6)	253 (17.9)
1-2/≤0.5	115 (8.8)	6 (6.7)	440 (31.1)
3/≤1	114 (8.7)	10 (11.2)	338 (23.9)
4-5/> 1	973 (74.6)	68 (76.4)	382 (27.1)
Braak NFT stage, *n* (%)			
0	25 (1.9)	1 (1.1)	14 (1.0)
I-II	177 (13.6)	19 (21.3)	221 (15.6)
III-IV	266 (20.4)	7 (7.9)	802 (56.8)
V-VI	836 (64.1)	62 (69.7)	376 (26.6)
Neuritic plaques, *n* (%)			
No	196 (15.0)	18 (20.2)	319 (22.6)
Sparse	140 (10.7)	9 (10.1)	126 (8.9)
Moderate	222 (17.0)	9 (10.1)	507 (35.9)
Frequent	746 (57.2)	53 (59.6)	461 (32.6)
TDP-43 in amygdala, *n* (%)			
No	860 (66.0)	52 (58.4)	681 (48.2)
Yes	444 (34.0)	37 (41.6)	732 (51.8)
TDP-43 in hippocampus and/or entorhinal/inferior temporal cortex, *n* (%)			
No	884 (67.8)	51 (57.3)	943 (66.7)
Yes	420 (32.2)	38 (42.7)	470 (33.3)
TDP-43 in neocortex, *n* (%)			
No	1240 (95.1)	76 (85.4)	1,085 (76.8)
Yes	64 (4.9)	13 (14.6)	328 (23.2)
Lewy bodies, *n* (%)			
No	713 (54.7)	44 (49.4)	1078 (76.3)
Other regions	384 (29.4)	25 (28.1)	142 (10.0)
Neocortex	207 (15.9)	20 (22.5)	193 (13.7)
Hippocampal sclerosis, *n* (%)			
No	1109 (85.0)	80 (89.9)	1,281 (90.7)
Yes	195 (15.0)	9 (10.1)	132 (9.3)

Abbreviations: NFT, neurofibrillary tangle; SD, standard deviation.
[a]Thal phase and diffuse plaques across regions were used in NACC and ROSMAP, respectively.

Next, we performed the whole genome SNV analyses on each of the estimated factor scores without (Supplementary Figures 15 and 16) and with the adjustment of the other two scores (Supplementary Figures 17 and 18). The top significant and suggestive significant SNVs from the model additionally adjusted for the other factor scores for the three factor scores are shown in Supplementary Tables 6-8 along with the individual quality values including RMS mapping quality (MQ), Phred-scaled *p*-value using Fisher's exact test to detect strand bias

TABLE 2 Top single nucleotide variants in genes associated with proteinopathy.

CHR	Gene	SNV	Position	Effect/ reference	Model[a]	F1[b]		F2[b]		F3[b]	
						$\hat{\beta}$	Q-value[c]	$\hat{\beta}$	Q-value[c]	$\hat{\beta}$	Q-value[c]
1	*GBA*	rs140335079	155237596	A/T	1	0.26	0.28	−0.02	0.93	−0.68	0.015
					2	0.38	0.12	0.01	0.98	−0.69	0.017
2	*BIN1*	rs6733839	127135234	T/C	1	0.06	0.28	0.15	0.018	0.12	0.040
					2	0.00	0.99	0.11	0.064	0.08	0.19
7	*TMEM106B*	rs10950392	12223912	T/C	1	0.18	0.0017	−0.11	0.084	−0.10	0.098
					2	0.22	3.6×10^{-5}	−0.15	0.0097	−0.10	0.14
17	*GRN*	rs5848[d]	44352876	T/C	1	0.19	0.0018	−0.05	0.48	−0.06	0.30
					2	0.21	2.2×10^{-4}	−0.10	0.081	−0.08	0.22
19	*APOE*	rs429358	44908684	C/T	1	0.36	5.1×10^{-8}	0.64	1.1×10^{-23}	0.22	0.0028
					2	0.14	0.037	0.50	4.5×10^{-16}	0.06	0.38

Abbreviations: CHR, chromosome; SNV, single nucleotide variant.

[a]Model 1 = adjusted for age at death, sex, and top three principal components; Model 2 = adjusted for age at death, sex, top three principal components, and other scores.

[b]F1 = TDP-43 and hippocampal sclerosis related score; F2 = Alzheimer's disease neuropathologic change related score; F3 = Lewy body pathology related score.

[c]Q-value indicates that false discovery rate (FDR) adjusted *p*-value in each score and model.

[d]The *p*-value of Hardy-Weinberg equilibrium test for rs5848 in AD controls was 1.2×10^{-61}; however, we displayed the results because rs5848 is well-known as TDP-43 related single nucleotide variant.

TABLE 3 Significant and suggestive significant single nucleotide variants associated with each factor score both in subjects aged 65 years or older at death and in subjects aged 80 years or older at death.

CHR	Gene	SNV	Position	Effect/ reference	≥ 65 at death		≥ 80 at death	
					$\hat{\beta}$	*p*-Value	$\hat{\beta}$	*p*-Value
Factor 1 (TDP-43 pathology and hippocampal sclerosis) score								
1	*KAZN*	rs72643142	14148707	T/C	−0.40	7.1×10^{-7}	−0.48	5.6×10^{-7}
5	*ARHGEF28*	rs80190672	73973002	G/A	**−0.64**	**4.7×10^{-8}**	−0.76	5.8×10^{-8}
15	*UNC13C*	rs141108370	54631819	G/A	−1.06	5.7×10^{-7}	−1.25	2.8×10^{-7}
Factor 2 (Alzheimer's disease neuropathologic change related) score								
1	*C1orf185*	rs72692278	51129361	A/G	−0.50	6.6×10^{-6}	−0.58	7.2×10^{-6}
1	*ZNF281*	rs188482877	200431363	T/A	−1.00	3.2×10^{-6}	−1.12	3.3×10^{-6}
12	*GRIN2B*	rs71457202	13748154	A/G	0.81	3.8×10^{-6}	0.99	1.1×10^{-6}
13	*LINC00559*	rs145442832	89883465	T/C	−0.39	4.6×10^{-6}	−0.52	2.2×10^{-7}
14	*TTLL5*	rs745536628	75760859	A/AT	−1.04	5.4×10^{-6}	−1.21	6.3×10^{-6}
Factor 3 (Lewy body pathology related) score								
6	*TNFRSF21*	rs78794444	47311493	T/G	−0.71	3.0×10^{-6}	−0.87	1.5×10^{-6}

Notes: Bolded result indicates statistical significance.

Abbreviations: CHR, chromosome; SNV, single nucleotide variant.

(FS), symmetric odds ratio of 2×2 contingency table to detect strand bias (SOR), variant confidence/quality by depth (QD), and *p*-value from HWE test (Supplementary Tables 9-11). We here highlighted some intriguing SNVs that reached to the significance (i.e., $p < 5\times10^{-8}$) or suggestive significance level (i.e., $p < 1\times10^{-5}$) in both people who died after 65 years or older (≥ 65 at death) and people who died after 80 years or older (≥ 80 at death) in the sensitivity analyses in Table 3 (Supplementary Table 5 displays the number of missing data for each SNV). The G allele of rs80190672 in *ARHGEF28* on chromosome 5 was significantly associated with decreased factor 1 (TDP-43 and HS related) score ($\hat{\beta} = -0.64$ and *p*-value = 4.7×10^{-8}) in ≥ 65 at death, and the association remained in ≥ 80 at death at suggestive significance ($\hat{\beta} = -0.76$ and *p*-value = 5.8×10^{-8}). rs141108370 in *UNC13C* on chromosome 15 was the second top SNV suggestively associated with the factor 1 score ($\hat{\beta} = -1.06$ and *p*-value = 5.7×10^{-7} in ≥ 65 at death and $\hat{\beta} = -1.25$ and *p*-value = 2.8×10^{-7} in ≥ 80 at death). The T allele of rs72643142 in *KAZN* on chromosome 1 was also suggestively significant with the factor 1 score ($\hat{\beta} = -0.40$ and *p*-value = 7.1×10^{-7} in ≥ 65

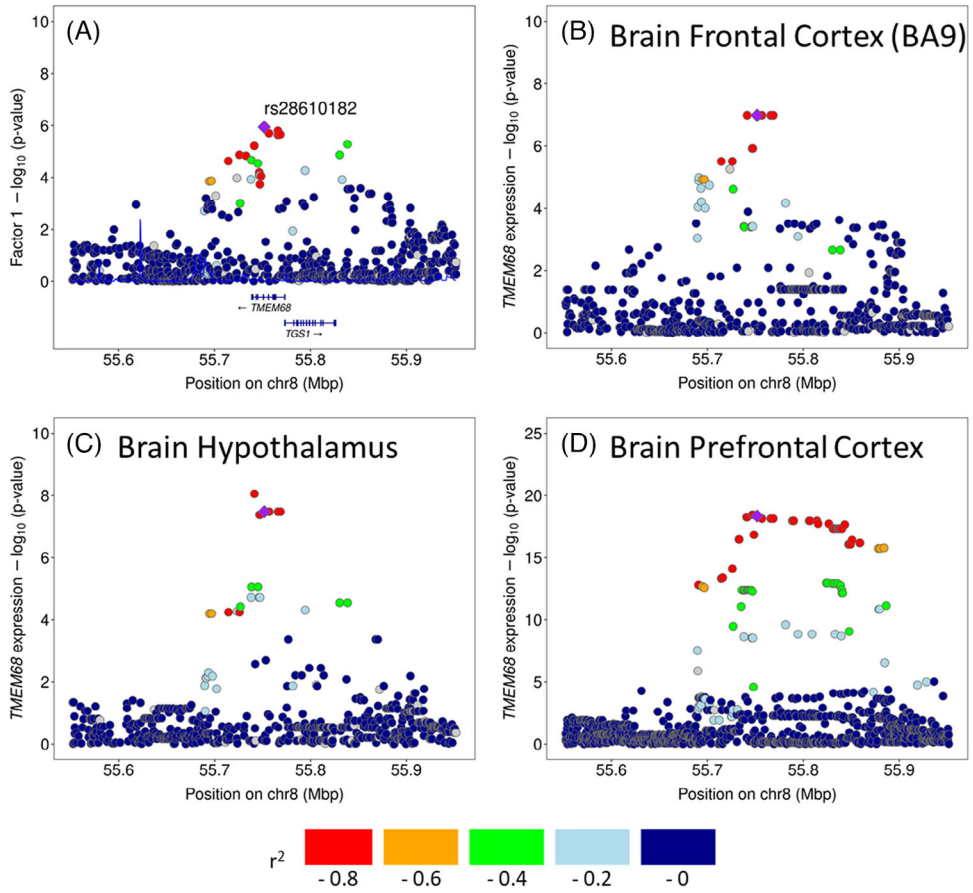


FIGURE 3 LocusZoom plots for the association of single nucleotide variants with the estimated factor 1 (TDP-43 and hippocampal sclerosis) score in *TMEM68* (A) and with the *TMEM68* expressions in brain prefrontal cortex BA9 (B) and brain hypothalamus (C) from GTEx, and in brain prefrontal cortex (D) from ROSMAP. GTEx = Genotype-tissue expression project; ROSMAP = Religious Orders Study and Rush Memory and Aging Project.

at death and $\hat{\beta} = -0.48$ and p-value $= 5.6\times10^{-7}$ in ≥ 80 at death). Other than *APOE* loci on chromosome 19, there were five loci that reached the suggestive significance level for the factor 2 (ADNC related) score and were confirmed in the sensitivity analysis for ≥ 80 at death. For the factor 3 (LBP related) score, we observed one locus that reached the suggestive significance level, and the associations retained even in ≥ 80 at death.

Some of the putative risk alleles also showed evidence of biological significance in eQTL (i.e., colocalization). Supplementary Tables 12-14 show the full results of colocalization analyses with eQTL p-value $< 1\times10^{-5}$. Figure 3 and Supplementary Figures 19-22 highlighted the colocalization PPH4 > 0.9 for the prior probability of 10^{-5}. The SNVs in *TMEM68* on chromosome 8 (the top SNV rs28610182 was located in the promoter region shown in Supplementary Table 9) suggestively associated with the factor 1 (TDP-43 and HS) score ($\hat{\beta} = -0.29$ and p-value $= 1.1\times10^{-6}$ for the A allele in ≥ 65 at death shown in Supplementary Table 6 and Figure 3A) colocalized with the *TMEM68* expression in brain prefrontal cortex BA9 (Figure 3B) and brain hypothalamus (Figure 3C) in GTEx, and the colocalization of the *TMEM68* expression in prefrontal cortex was replicated in ROSMAP (Figure 3D). This locus also colocalized with the *TMEM68* expression in other tissues (Supplementary Table 12 and Supplementary Figure 20). We did not observe colocalization between the *TMEM106B* SNVs and gene expression in any brain region, but the *TMEM106B* locus colocalized with *TMEM106B* expression in several tissues (Supplementary Table 12 and Supplementary Figure 19). The *SDHAF1* locus (the top SNV rs17706479 was located in the promoter region (Supplementary Table 9)) colocalized with *SDHAF1* expression in lung and whole blood (Supplementary Table 12 and Supplementary Figure 21). The *BMS1* locus suggestively associated with the factor 2 (ADNC related) score colocalized with the ENSG00000259869 in artery tibial and *BMS1* expression in brain cerebellum (Supplementary Table 13 and Supplementary Figure 22). We did not observe a colocalization with PPH4 > 0.9 for the prior probability of 10^{-5} in the factor 3 (Lewy body pathology related) score (Supplementary Table 14).

4 | DISCUSSION

Multidimensional GPCM methods were used to generate new insights into dementia-related proteinopathies. By applying this novel methodology, genetic analyses of WGS data were used to identify candidate risk-associated SNVs for complex proteinopathies. Using data from multiple large autopsy studies with a meta-analytic study design, our

findings included the replication of prior studies' results, as well as some novel findings. More specifically, our analyses helped validate known genotype/phenotype associations: *APOE* is a risk allele for ADNC; *TMEM106B* and *GRN* for LATE-NC; and *GBA* for LBP. These findings also provided assurance about the validity of our approach (analogous to positive internal controls) and its potential to be applied to elucidate previously undiscovered genotype/phenotype associations. Indeed, novel risk allele candidates were identified and a subset of these are discussed below.

We demonstrated that NP phenotypes could be integrated via the IRT which provided three-dimensional factor scores representing different severities on NP spectrums. The continuous factor scores allowed us to adjust the models for scores other than the outcome, that is, the adjustment removed the effect of other proteinopathies. For example, *APOE* is a well-known risk gene of ADNC. Previous studies reported that *APOE* was also associated with TDP-43 proteinopathy.[55,56] In our approach, the C allele of rs429358 was associated with increased burden of TDP-43 without the adjustment of other scores; however, the association was greatly attenuated after adjustment for the ADNC and LBP related scores (Supplementary Figure 12). This implies that although TDP-43 pathology commonly co-exists with ADNC, *APOE* would primarily affect ADNC rather than directly promoting TDP-43 pathology.

The three factors that we identified were predominantly associated with either LATE-NC, ADNC, or LBP. As we expected, Braak NFT stage, neuritic plaques, and Thal Aβ phase/diffuse amyloid plaques had larger contributions to the same factor (i.e., factor 2 related to ADNC) which indicates that these measurements were involved in the same latent trait. We observed the similar structure in TDP-43 pathology and HS (factor 1 related LATE-NC). On the other hand, LBP was projected into the different latent space from ADNC, which was seen in both NACC/ADNI and ROSMAP. Previous studies reported that LBP was highly correlated and co-existed with ADNC.[57–59] However, our study indicated that LBP had a different NP spectrum from ADNC and thus could be analyzed as a separate latent trait (termed factor 3).

At least several of the new potential risk alleles have compelling bases of biological credibility. Included are some novel and intriguing loci for ADNC (factor 2 in our study). However, because the genetic architecture of AD/ADNC has been exhaustively studied, we here focus on three putative novel genes that were linked in the current study to non-ADNC dementia-driving neuropathologies: *ARHGEF28*, *TMEM68*, and *SDHAF1* as risk allele candidates for factor 1 (LATE-NC).

The SNV rs80190672, which was significantly associated with TDP-43 pathology and HS score (LATE-NC) in participants with age at death $\geq$ 65 years, is located downstream of *ARHGEF28* encoding rho guanine nucleotide exchange factor 28 (the cognate polypeptide is referred to as RGNEF). Of all the novel loci identified, this was the one with the lowest *p*-value. *ARHGEF28* has been reported as a putative ALS gene.[60,61] The large majority of ALS cases have TDP-43 pathology in affected cells (i.e., motor neurons).[62] RGNEF has been found to localize to hallmark TDP-43 immunoreactive inclusion bodies in ALS patient spinal cord motor neurons.[63,64] Although the SNVs located near *ARHGEF28* are downstream of the transcript-encoding gene sequences, they may be involved in pathogenesis through modulating the splicing or translation of the gene transcript.

Some of the genetic associations that were not statistically significant at the whole-genome level were nonetheless intriguing, and follow-up analyses indicated credible biological impacts. For example, rs28610182 in the *TMEM68* gene had a nominal *p*-value = 1.1×10^{-6} with TDP-43 and HS pathologies (factor 1 score). The *TMEM68* locus colocalized with the *TMEM68* expression in brain frontal cortex in two independent datasets (i.e., GTEx and ROSMAP, PPH4 > 90%). *TMEM68* encodes a protein named transmembrane protein 68, which is a putative "brain-specific" acyltransferase involved in glycerolipid metabolism.[65,66] Recent studies showed that the deregulated metabolism of glycerolipid was associated with ALS risk.[67,68] Given that the A allele of rs28610182 had a protective effect (shown in Supplementary Table 6) and was associated with upregulated *TMEM68* expression in human brain (shown in Supplementary Table 12), our findings may indicate a protective influence of this protein product and/or the glycerolipid metabolism pathway, in LATE-NC.

Another SNV suggestively associated with Factor 1/LATE-NC in the present study was rs17706479, which is in the *SDHAF1* gene. *SDHAF1* encodes a protein that serves as an assembly factor in mitochondrial complex II.[69,70] Mitochondrial dynamics have been implicated in numerous ways with TDP-43 pathology.[71,72] We found colocalization between the strongest pathology-associated allele and methylation at the *SDHAF1* locus. Intriguingly, the *SDHAF1* gene has previously been linked to neurological disease phenotypes, in addition to mitochondrial deficits with clinical impact.[69,73] Methylation of the *SDHAF1* locus was specifically implicated in fetal alcohol syndrome, and mutations in the *SDHAF1* gene were linked to the phenotype of white matter disease (specifically, pediatric leukoencephalopathy).[73–76] More work is required to ascertain if the association between *SDHAF1* genetic variation and TDP-43 pathology is robust in aging individuals.

There were limitations to the present study. Most importantly, most of the genotype-NP phenotype associations identified (including the previously described ones, e.g., *TMEM106B* with LATE-NC) did not reach the threshold for genome-wide statistical significance, indicating that statistical power was only marginally capable of testing the null hypothesis. However, we were encouraged by the validation of prior pathology-linked SNPs. Further, the pathologic data constitutes semiquantitative (ordinal, rather than quantitative) parameters according to consensus-based rubrics, and these were generated in a manner that probably differs—even if subtly—from research center to research center. The NP phenotypes "pure" or "mixed" constitute the gold standard for disease presence and severity and the IRT methods we applied were meant to render these phenotypes testable with the quantitative genetic data. Nonetheless, the pathological phenotypes are still evolving as new clinical-pathological relationships are elucidated. Although we showed that our NP scoring could detect known proteinopathy-linked loci, some important SNVs that are associated with single proteinopathy may have been missed. For example, our scoring method aggregated Aβ and tau pathologies; thus, it may not be able to detect Aβ specific SNPs. We also note that the majority of the included research participants were people with European

ancestry. In future research, we will need many sources to validate our findings, including different race/ethnicity sample groups and independent study cohorts of NACC, ADNI, and ROSMAP, and we will expand our scoring approach to multivariate outcomes representing more complicated patterns of mixed proteinopathies. In this study, we excluded participants who had at least one missing NP data element. The excluded participants had different NP characteristics, and thus our findings may be biased. In future studies, we will take into account the missing value issue using some techniques such as imputing missing data and handling missing data as a non-answer (i.e., no contribution to any factor score) within an IRT framework.

Despite the significant caveats, we conclude that our novel application of multidimensional GPCM and human WGS data, combined with relatively sharp NP-based endophenotype data from multiple high-quality autopsy series, enabled novel insights into the genetic architecture of dementia-associated brain pathologies. These findings require validation/corroboration from other data sets. However, they help underscore once again that, as with the clinical and pathological phenotypes involved, the underlying genetic factors that influence amnestic dementia are highly complex.

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CONFLICT OF INTEREST STATEMENT

The authors report no competing interests. The authors have no conflicts of interest (see supporting information).

CONSENT STATEMENT

Alzheimer's Disease Research Centers obtained written informed consent from their participants and maintain their own separate IRB review and approval from their institution prior to submitting data to NACC.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

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