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Degree of genetic liability for Alzheimer's disease associated with specific proteomic profiles in cerebrospinal fluid

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ABSTRACT

Genetic factors play a major role in Alzheimer's disease (AD) pathology, but biological mechanisms through which these factors contribute to AD remain elusive. Using a cerebrospinal fluid (CSF) proteomic approach, we examined associations between polygenic risk scores for AD (PGRS) and CSF proteomic profiles in 250 individuals with normal cognition, mild cognitive impairment, and AD-type dementia from the Alzheimer's Disease Neuroimaging Initiative. Out of 412 proteins, 201 were associated with PGRS. Hierarchical clustering analysis on proteins associated with PGRS at different single-nucleotide polymorphism *p*-value inclusion thresholds identified 3 clusters: (1) a protein cluster correlated with highly significant single-nucleotide polymorphisms, associated with amyloid-beta pathology and complement cascades; (2) a protein cluster associated with PGRS additionally including variants contributing to modest risk, involved in neural injury; (3) a protein cluster that also included less strongly associated variants, enriched with cytokine-cytokine interactions and cell adhesion molecules. These findings suggest that CSF protein levels reflect varying degrees of genetic liability for AD and may serve as a tool to investigate biological mechanisms in AD.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that causes dementia (Gaugler, 2019). Genetic factors play an important role in late-onset AD and are estimated to explain between 58% and 79% of the variance in disease (Gatz et al., 2006). The strongest known genetic risk variant for AD is the apolipoprotein E (*APOE*)-ε4 allele, but its presence is not essential for developing AD-type dementia as approximately 30%–50% of all patients with AD do not carry this risk variant (Gatz et al., 2006; Karch et al., 2014; Martiskainen et al., 2015). So far, genome-wide association studies (GWAS) in AD have identified approximately 30 additional susceptibility loci, albeit with more modest effects than *APOE* (Harold et al., 2009; Hollingworth et al., 2011; Jansen et al., 2019; Kunkle et al., 2019; Lambert et al., 2009, 2013; Naj et al., 2011; Seshadri et al., 2010). The cumulative effect of multiple single-nucleotide polymorphisms (SNPs) that are strong, but also modestly and weakly associated with AD, can be combined into polygenic risk scores (PGRS). Such PGRS explain up to 70%–80% (based on area under the curve estimates) of the variance in AD (Escott-Price et al., 2015; Purcell et al., 2009). However, as PGRS are aggregate measures, they are not easy to interpret in terms of biological mechanisms. Nonetheless, such knowledge is essential for the development of therapeutic treatment options.

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Table 1
Demographic and clinical characteristics subjects (n = 250)

Characteristic	All (n = 250)	Controls (n = 73, 29%)	MCI (n = 116, 46%)	AD-type dementia (n = 61, 24%)	Between-group comparisons
Age mean (SD)	75 (7)	76 (5)	75 (8)	75 (8)	NS
Female n (%)	97 (39%)	33 (45%)	37 (31%)	27 (44%)	NS
Education years mean (SD)	15.7 (3.0)	15.9 (2.9)	16.0 (3.0)	15.0 (3.0)	AD < MCI
MMSE mean (SD)	26.7 (2.6)	29.1 (1.0)	27.0 (1.7)	23.5 (1.9)	AD < MCI < controls
APOE ε4 allele ≥1, n (%)	124 (50%)	18 (25%)	62 (53%)	44 (72%)	AD > MCI > controls
Amyloid-β mean pg/mL (SD)	168.4 (55.3)	207.2 (56.7)	158.7 (50.3)	140.4 (34.2)	AD < controls, MCI < controls
Abnormal amyloid-β n (%)	174 (70%)	28 (38%)	93 (80%)	58 (95%)	AD > MCI > controls
Tau mean pg/mL (SD)	99.1 (50.4)	71.43 (28.6)	102.8 (47.2)	125.0 (60.5)	AD > MCI > controls
Abnormal Tau n (%)	111 (44%)	16 (22%)	58 (50%)	37 (61%)	AD > controls, MCI > controls

Key: AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, Mini-mental state examination; NS, not significant ($p > 0.05$); SD, standard deviation. Cutoff for biomarker abnormality is <192 pg/mL for amyloid beta and >93 pg/mL for tau (Shaw et al., 2009).

Changes in cerebrospinal fluid (CSF) protein levels provide unique insight into the pathophysiological processes underlying neurological disorders in vivo. CSF proteomic studies have highlighted the presence of many disrupted biological mechanisms in AD, including amyloid-beta (Aβ) production, neurotoxicity, immune-related processes, and cholesterol metabolism, which are processes also implied by genetic studies (Jansen et al., 2019; Kunkle et al., 2019). The first studies investigating the relationships between PGRS and CSF protein levels suggest that high PGRS (i.e., increased genetic risk for AD), calculated either with or without the *APOE* gene, show a strong association with abnormally low Aβ1-42 and high t-tau, p-tau CSF levels, which are biomarkers for the pathophysiological hallmarks of AD (Darst et al., 2016; Jack et al., 2018; Louwersheimer et al., 2016; Martiskainen et al., 2015; Mormino et al., 2016; Schultz et al., 2015). Other recent research further shows that effects of specific genetic risk loci can be measured in CSF, with the *APOE*-ε4 allele being associated with high levels of *APOE*-ε4–specific peptides (Darst et al., 2016; Spellman et al., 2015). Still, the precise relationship of genetic factors and changes in the CSF proteome remains unclear (Hellwig et al., 2015; Portelius et al., 2015; Represa et al., 1990; Thorsell et al., 2010). Here, we hypothesized that the degree of genetic liability for AD is associated with specific profiles of CSF protein levels.

This study aimed to identify which biological processes that are disrupted in AD are likely to be associated with the genetic liability for AD. We investigated whether PGRS at different SNP *p*-value thresholds show distinct associations with CSF proteomic outcomes across the clinical spectrum of AD, including individuals with varying degrees of AD pathology and genetic risk for AD, clinically presenting with normal cognition, mild cognitive impairment (MCI), or AD-type dementia (Jack et al., 2018).

2. Methods

2.1. Study population

For the present study, we selected from the Alzheimer's disease Neuroimaging Initiative (ADNI) subjects who had baseline CSF proteomic and genetic data available (n = 250; Table 1) (all data are available at http://adni.loni.usc.edu/) (Saykin et al., 2010). ADNI was launched in 2003, under supervision of Michael W. Weiner. ADNI aims to examine whether magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to estimate progression of MCI and AD. All study protocols were approved by the institutional review boards of all 50 participating ADNI centers (http://adni.loni.usc.edu/about/centers-cores/study-sites/). ADNI provided permission to perform current analyses (http://www.adni-info.org/). Written informed consent was obtained from all participants.

2.2. CSF data

CSF samples were collected using lumbar puncture, and samples were stored at the ADNI biomarker core laboratory at the University of Pennsylvania Medical Center. Proteins and peptides were selected based on their previous detection in CSF, relevance to AD, and previous results from the Rules Based Medicine (RBM) multiplex immunoassay analysis of ADNI CSF. In total, 412 proteins and protein fragments were included in this study: 12 proteins with ELISA; 80 proteins with proteomics RBM multiplex; and 320 protein fragments measured with Mass Reaction Monitoring (MRM)-targeted mass spectroscopy.

Protein assessment and quality control has been performed by the ADNI biomarker core team and is described in detail at the ADNI data primer (http://adni.loni.usc.edu/data-samples/biospecimen-data/). CSF proteins measured with ELISA or related essays included Aβ 1-42, t-tau, p-tau, α-Synuclein, YKL-40, beta secretase-1 activity, soluble amyloid precursor protein beta, factor H, neurogranin, neurofilament light (NfL), F(2)-Isoprostanes, and visin-like protein 1, as described in the Supplementary Materials (Mattsson et al., 2011). The xMAP multiplex panel, developed by RBM (Myriad RBM), included 159 proteins. Final analyses included 80 out of 159 RBM proteins that passed data quality control and could be detected in >10% of the samples. RBM proteins were log-transformed if they did not follow a normal distribution

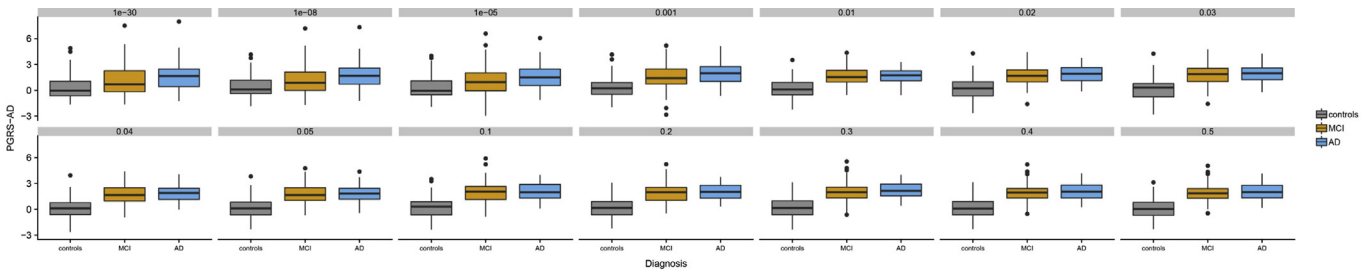

Fig. 1. PGRS in AD-type dementia patients, MCI patients, and controls. PGRS scores were normalized for visualization purposes using controls with normal CSF Aβ (i.e., CSF Aβ1-42 below 192 pg/mL) as reference group. $n_{controls} = 73$, $n_{MCI} = 116$, $n_{AD} = 61$. Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; PGRS, polygenic risk scores.

(Mattsson et al., 2014). Similarly, for MRM, we used only the 320 out of 567 proteins fragments that were of sufficient quality and could be detected in >10% of the samples (Spellman et al., 2015). These protein fragments were preprocessed as listed in the finalized "Normalized Intensity" datasheet downloaded from ADNI (see "Biomarkers Consortium CSF Proteomics MRM data set" in "Data Primer" at http:/adni.loni.ucla.edu). Briefly, each protein fragment was measured at 2 transitions, and protein fragment raw peak area data was normalized to remove variability between samples processed on different days (see Supplementary Materials and (Spellman et al., 2015) for more details on technical quality control).

2.3. Genotyping

Of all 250 subjects with genetic and CSF proteomic data available, DNA was extracted from blood for most subjects (n = 227), and for some subjects, from cell lines (n = 23). ADNI samples were genotyped using the Illumina OmniQuad array (Saykin et al., 2010) and were retrieved online from http://adni.loni.cule.edu/. *APOE* genotype was assessed with 2 single-nucleotide polymorphisms (SNPs; rs429358 and rs7412) that define the epsilon 2, 3, and 4 alleles, using DNA extracted by Cogencis from a 3-mL aliquot of EDTA blood.

The present study used DNA microarray genotype data available from ADNI, including subjects from the ADNI1 subsamples (processed with GenomeStudio v2009.1). In total, 310,221 SNPs were imputed using the 1000 Genomes reference panel (Genomes Project et al., 2015), with the use of the Michigan imputation server (Das et al., 2016) (https://imputationserver.sph.umich.edu/). To avoid strand issues, only SNPs with no AT or CG alleles were included. Genotype data were quality checked for gender mismatch, relatedness, and ancestry. SNPs were excluded before data release if they had a minor allele frequency less than 2%, deviated significantly from Hardy-Weinberg equilibrium ($p < 1 \times 10^{-6}$) in the total sample of founder individuals, or had a call rate of less than 98%. We only used SNPs with no more than 5% genotype missingness and removed samples with excess heterozygosity rate (>5 SD) (Fig. S1). To identify ethnic outliers in the ADNI data, we performed a principal component analysis on imputed ADNI and 1000 Genomes, phase 3 data (including African, Ad Mixed American, East Asian, European, and South Asian ancestries), using the EIGENSOFT package (Patterson et al., 2006). Principal component 1 (PC1) tended to separate African from non-African subjects, and PC2 tended to separate South Asian from non–South Asian subjects (Figs. S2 and S3). ADNI subjects not of European descent (i.e., more than 6 S.D. away from PC1 or PC2) were excluded from the analysis. After imputation, SNPs with an INFO score ≤0.10 and minor allele frequency <0.005 were removed. Subsequently, dosage data were converted into best-guess data with a probability threshold of $p > 0.8$, and resulting SNPs with missing rate <0.02 were removed. Imputed genotype data included n = 766 subjects (n = 250 with and n = 516 without available CSF proteomic data) and 1,496,949 SNPs. To control for population stratification, 20 principal components (PC1-PC20) were computed on a subset of relatively uncorrelated (r2 < 0.2) SNPs (excluding SNPs imputed from the 1000 Genomes reference panel), using the EIGENSOFT package (Patterson et al., 2006). The first 3 PCs explained 27% of variance (PC1: 16%, PC2: 6%, PC3: 5%; Fig. S4).

2.4. Derivation of PGRS

PGRS for AD were calculated using the software package PRSice, by adding the sum of each allele weighted by the strength of its association with AD risk (Euesden et al., 2015). The strength of these associations was calculated previously by the International Genomics of Alzheimer's project (IGAP) GWAS (Lambert et al., 2009). IGAP used genotyped and imputed data on 7,055,881 SNPs to meta-analyze 4 previously published GWAS data sets consisting of 17,008 AD cases and 37,154 controls (i.e., The European Alzheimer's disease Initiative, the Alzheimer Disease Genetics Consortium, the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium, The Genetic and Environmental Risk in AD consortium) (Lambert et al., 2009, 2013). Clumping was performed before calculating PGRS to remove SNPs that are in LD ($r^2 > 0.1$) within a slicing 1M bp window. After clumping, we computed 14 PGRS with varying SNP *p*-value inclusion thresholds, ranging from very strongly associated SNPs (to tease out *APOE*-ε4 effects, $p \leq$ 1e-30) to genome-wide significant SNPs ($p \leq$ 1e-08) and SNPs with weak associations with AD risk: (1) $p \leq$ 1e-30 (6 SNPs), (2) $p \leq$ 1e-08 (27 SNPs), (3) $p \leq$ 1e-05 (68 SNPs); (4) $p \leq 0.001$ (959 SNPs); (5) $p \leq 0.01$ (6184 SNPs); (6) $p \leq 0.02$ (10,544 SNPs); (7) $p \leq 0.03$ (14,595 SNPs); (8) $p \leq 0.04$ (18,123 SNPs); (9) $p \leq 0.05$ (21,402 SNPs); (10) $p \leq 0.1$ (36,125 SNPs); (11) $p \leq 0.2$ (59,537 SNPs); (12) $p \leq 0.3$ (78,564 SNPs); (13) $p \leq 0.4$ (94,189 SNPs); and (14) $p \leq 0.5$ (107,516 SNPs). All PGRS were regressed on PC1-PC3.

2.5. Statistical analysis

All analyses were performed using R (version 3.2.5) (R Development Core Team, 2010). Associations between PGRS (predictor; separate models for each SNP inclusion threshold) and ranked CSF levels (outcome) of 412 protein(s) (fragments) were examined using linear models, adjusted for age and sex. We repeated analyses additionally adjusting for *APOE*-ε4 carrier status, to examine genetic associations unrelated to *APOE*-ε4. Results on 412 PGRS CSF proteins are presented both uncorrected and corrected for multiple comparisons using a 5% false discovery rate procedure.

To identify distinct patterns of CSF proteomic and PGRS associations, we performed hierarchical cluster analysis including all proteins with at least one significant ($p < 0.05$) PGRS association. We used the Euclidean distance of protein-PGRS associations and Ward's minimum variance method to identify clusters. We used 3 approaches to determine the optimal number of clusters *k*: (1) based on the "gap" statistic (R package cluster) (Tibshirani et al., 2001); (2) based on the "elbow" method, that defines the optimal number of clusters as the point where there is a marked curve (i.e., "elbow") of the variance explained (Ketchen and Shook, 1996); and (3) based on the silhouette method, a measure of how similar an object is to its own cluster compared to other clusters (Rousseeuw, 1987).

2.6. Enrichment analyses for Kyoto Encyclopedia of Genes and Genomes pathways and gene ontology biological processes

The online database STRINGv10 (https://string-db.org) (Szklarczyk et al., 2015) was used to create a network diagram of proteins associated with PGRS. To gain more insight into the biological properties of PGRS-associated CSF proteins, proteins were annotated using Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, Reactome pathways, Gene Ontology (GO) biological processes, GO protein class, GO molecular functions, and GO cellular component databases. Analyses were repeated for separate clusters as identified by the hierarchical cluster analysis, to examine whether proteins with different patterns of inheritance were associated with specific biological properties.

3. Results

3.1. Sample description

In total, 250 subjects were selected from ADNI, with an average age of 75 (SD = 7) years and 39% of the participants being female (Table 1). The proportion of individuals with MCI was relatively

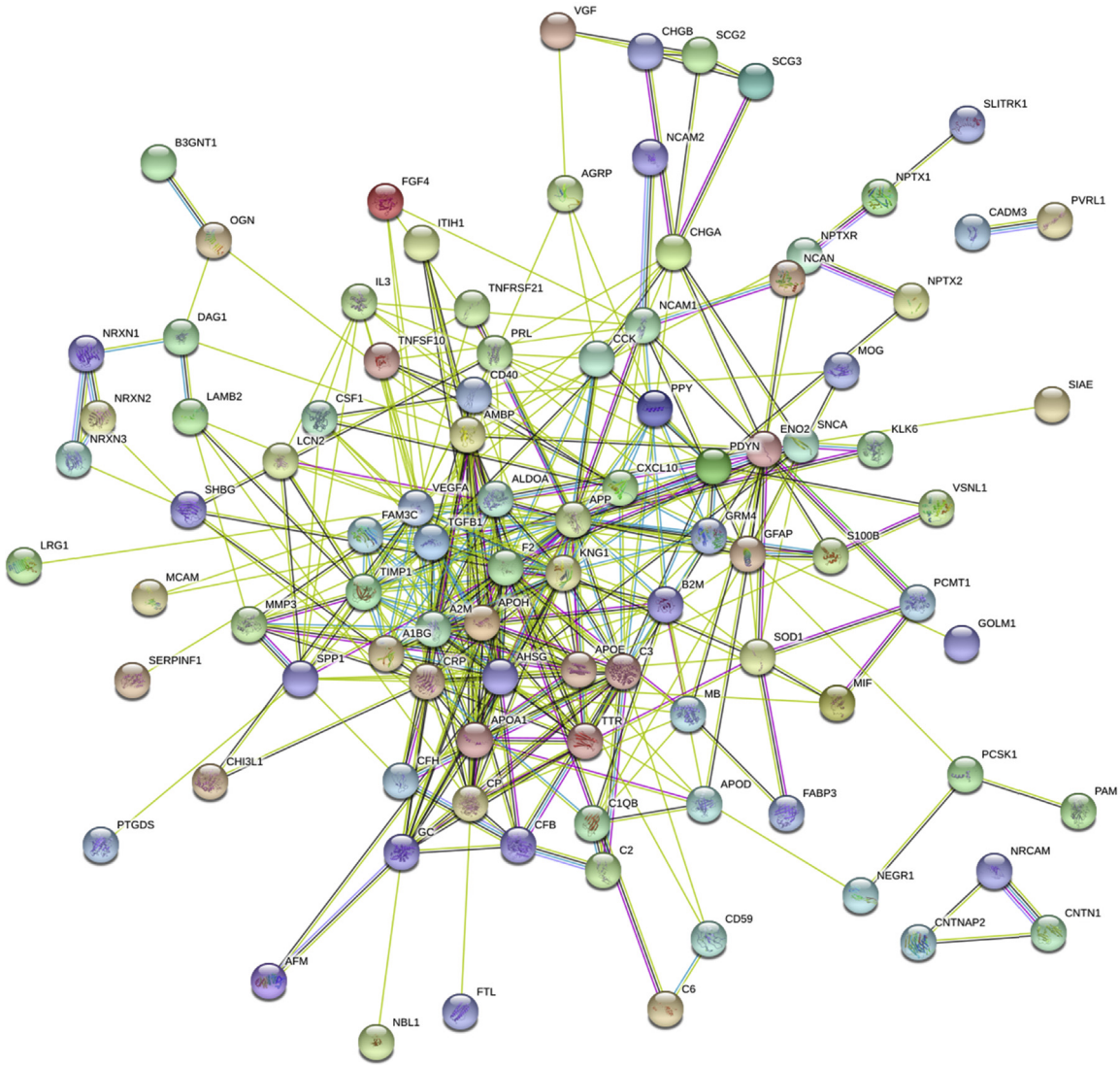

Fig. 2. Network diagram of PGRS-associated proteins, generated using STRING v10. Proteins with at least one PGRS-CSF association with $p_{\text{uncorrected}} < 0.05$ were selected in the network. Disconnected nodes are not shown. $n_{\text{proteins or protein fragments}} = 250$, $n_{\text{nodes}} = 110$, $n_{\text{edges}} = 377$, average node degree = 6.85, average local clustering coefficient = 0.506, expected number of edges = 74, protein-protein interaction (PPI) enrichment p value < 1.0e-16. Proteins were excluded from the STRING network diagram because no uniprot code availability (n = 5), no protein code available in humans (n = 2). Abbreviations: CSF, cerebrospinal fluid; PGRS, polygenic risk scores.

high (46%) compared to controls (29%) and AD-type dementia patients (24%). As expected, PGRS were strongly associated with AD case control status (Fig. S5). For all SNP thresholds, AD-type dementia patients had the highest PGRS scores, followed by MCI patients and controls (all $p < 0.05$) (Fig. 1; Table S1).

3.2. PGRS CSF protein associations

In total, 201 of 412 (48.8%) proteins or protein fragments were associated with at least one of the 14 PGRS scores (n = 201 proteins $p_{\text{uncorrected}} < 0.05$; n = 52 $p_{\text{FDR}} < 0.05$) (Table 2; Table S2). Most of these proteins (n = 163/n = 201, 81%) showed lower levels with higher PGRS. Eighty-six proteins or protein fragments were most strongly associated with PGRS for a SNP threshold of 0.1 (n = 86/n = 201, 43%). When correcting for *APOE*-ε4 status, 120 PGRS-protein associations remained significant (n = 120, 59.7% proteins $p_{\text{uncorrected}} < 0.05$; n = 8, 15.4% proteins $p_{\text{FDR}} < 0.05$) (Table S3). PGRS-associated proteins showed more interactions with each other than what would be expected for a random set of proteins of similar size drawn from the human genome, indicating that the proteins are at least partially biologically connected as a group (enrichment $p <$ 1.0e-16; Figs. 2, and 3, Table S4).

3.3. Hierarchical cluster analysis

Hierarchical clustering analysis on proteins associated with any PGRS (in terms of SNP inclusions thresholds) revealed 3 clusters of CSF protein-PGRS associations, as illustrated in Fig. 4 (Table 2, Figs. S6–8). Cluster 1 included 68 proteins that were associated with PGRS that included SNPs with strong (p_{IGAP} = 1.00e-30–p_{IGAP} = 1.00e-03) associations with AD (PGRS-HR). Cluster 2 consisted of 21 proteins that were associated with PGRS that included SNPs with a strong to moderate (p_{IGAP} = 0.01–p_{IGAP} = 0.05) association with AD risk (PGRS-MR). Cluster 3 included 112 proteins that were associated with PGRS that included SNPs with a strong to low (p_{IGAP} = 0.10–p_{IGAP} = 0.50) association with AD risk (PGRS-LR) (see Fig. S9 for a visualization of the distribution of optimal SNP inclusion thresholds across cluster 1, 2, and 3). For each cluster, protein-protein interaction networks contained more associations than what would be expected for a random set of

Table 2
Association between PGRS and CSF proteins concentrations for optimal SNP threshold, uncorrected and corrected for *APOE*-ε4 status

Protein (fragment)	Including *APOE*		B	*p* uncorrected	*p* FDR	Excluding *APOE*		B	*p* uncorrected	*p* FDR
	Optimal SNP threshold	Adjusted R2				Optimal SNP threshold	Adjusted R2			
Cluster 1										
Afamin_DADPDTFFAK	1.00E-03	0.01	−0.15	2.75E-02	2.38E-01	1.00E-03	0.29	−0.1	7.30E-02	4.85E-01
Afamin_FLVNLVK	1.00E-03	0.01	−0.14	3.05E-02	2.38E-01	1.00E-03	0.29	−0.09	9.66E-02	4.85E-01
Afamin_LPNNVLQEK	1.00E-03	0.01	−0.15	1.98E-02	2.38E-01	1.00E-03	0.29	−0.1	8.13E-02	4.85E-01
Alpha-1B-glycoprotein_NGVAQEPVHLDSPAIK	1.00E-08	0.01	−0.13	4.87E-02	2.57E-01	1.00E-08	0.51	−0.08	9.67E-02	5.58E-01
Alpha-1B-glycoprotein_SGLSTGWTQLSK	1.00E-08	0.01	−0.14	3.24E-02	2.57E-01	1.00E-08	0.51	−0.08	7.21E-02	5.49E-01
Alpha-2-HS-glycoprotein_AHYDLR	1.00E-08	0.01	−0.15	2.76E-02	2.55E-01	1.00E-03	0.29	−0.1	9.56E-02	4.85E-01
Alpha-2-HS-glycoprotein_FSVVYAK	1.00E-08	0.01	−0.16	2.10E-02	2.34E-01	1.00E-08	0.51	−0.11	2.63E-02	5.49E-01
Alpha-2-HS-glycoprotein_HTLNQIDEVK	1.00E-08	0.01	−0.16	1.83E-02	2.29E-01	1.00E-03	0.29	−0.1	7.02E-02	4.85E-01
Alpha-2-macroglobulin	1.00E-08	0.01	−0.16	1.87E-02	2.29E-01	1.00E-08	0.51	−0.11	1.93E-02	5.49E-01
Amyloid beta 1-42	1.00E-08	0.2	−0.46	2.84E-14	**5.91E-12**	0.3	0.15	−0.28	4.40E-05	**9.15E-03**
Apolipoprotein AI	1.00E-08	0.02	−0.18	5.09E-03	1.31E-01	1.00E-08	0.51	−0.08	8.21E-02	5.49E-01
Apolipoprotein E	1.00E-08	0.03	−0.2	1.54E-03	6.52E-02	0.5	0.11	−0.14	2.79E-02	1.73E-01
Apolipoprotein E_CLAVYQAGAR (E2)	1.00E-08	0.05	−0.24	9.53E-05	**9.91E-03**	0.2	0.11	−0.16	8.77E-03	1.90E-01
Apolipoprotein E_LAVYQAGAR	1.00E-05	0.01	0.13	4.41E-02	4.58E-01	0.1	0.11	−0.08	1.97E-01	4.69E-01
Apolipoprotein E_LGADMEDVR (E4)	1.00E-08	0.38	0.62	1.79E-27	**7.43E-25**	0.01	0.2	0.15	1.60E-01	9.94E-01
Apolipoprotein H	1.00E-08	0.01	−0.14	4.70E-02	2.57E-01	1.00E-08	0.51	−0.09	7.28E-02	5.49E-01
Beta-2-microglobulin_VNHVTLSQPK	1.00E-08	0.01	−0.15	3.81E-02	2.57E-01	0.1	0.11	−0.08	2.55E-01	5.49E-01
Biotinidase_SHLIIAQVAK	1.00E-03	0.01	−0.14	4.01E-02	2.38E-01	1.00E-03	0.29	−0.09	9.32E-02	4.85E-01
C-reactive protein	1.00E-03	0.03	−0.2	2.12E-03	1.10E-01	0.2	0.1	−0.11	7.34E-02	3.07E-01
C-reactive protein_ESDTSYVSLK	1.00E-03	0.03	−0.2	1.22E-03	7.66E-02	0.2	0.1	−0.1	9.19E-02	3.60E-01
Cell surface glycoprotein MUC18_EVTVPVFYPTEK	1.00E-03	0.01	−0.15	2.03E-02	2.38E-01	0.1	0.12	−0.11	7.89E-02	2.78E-01
Ceruloplasmin_NNEGTYYSPNYNPQSR	1.00E-08	0.01	−0.15	2.55E-02	2.44E-01	1.00E-08	0.51	−0.1	4.06E-02	5.49E-01
Chromogranin A_EDSLEAGLPLQVR	1.00E-03	0.01	−0.14	2.49E-02	2.38E-01	1.00E-03	0.29	−0.1	6.66E-02	4.85E-01
Complement C1q subcomponent subunit B_LEQGENVFLQATDK	1.00E-30	0.03	−0.22	1.47E-03	6.97E-02	1.00E-05	0.48	−0.11	3.81E-02	9.88E-01
Complement C1q subcomponent subunit B_VPGLYYFTYHASSR	1.00E-08	0.02	−0.2	5.34E-03	1.31E-01	1.00E-08	0.51	−0.09	6.44E-02	5.49E-01
Complement C2_HAIILLTDGK	1.00E-08	0.01	−0.14	4.49E-02	2.57E-01	0.1	0.11	−0.08	2.42E-01	5.33E-01
Complement C3_IHWESASLLR	1.00E-30	0.01	−0.16	1.58E-02	2.86E-01	1.00E-05	0.47	−0.08	1.01E-01	9.88E-01
Complement component C6_SEYGAALAWEK	1.00E-08	0.01	−0.14	3.59E-02	2.57E-01	1.00E-08	0.51	−0.09	4.96E-02	5.49E-01
Complement factor B_DAQYAPGYDK	1.00E-30	0.01	−0.13	4.40E-02	3.40E-01	1.00E-03	0.29	−0.06	2.49E-01	5.72E-01
Complement-C3	1.00E-30	0.01	−0.15	3.30E-02	3.40E-01	1.00E-30	0.51	−0.07	1.36E-01	7.84E-01
Contactin 1_TTKPYPADIVVQFK	1.00E-03	0.01	−0.14	3.93E-02	2.38E-01	1.00E-03	0.29	−0.11	4.75E-02	4.85E-01
Exostosin-like 2_VIVVWNNIGEK	1.00E-08	0.01	−0.14	4.43E-02	2.57E-01	1.00E-08	0.51	−0.1	3.80E-02	5.49E-01
Factor H	1.00E-03	0.01	−0.14	4.99E-02	2.41E-01	1.00E-03	0.29	−0.09	1.32E-01	4.85E-01
Fibroblast Growth Factor 4	1.00E-08	0.13	0.39	1.00E-09	**1.39E-07**	1.00E-08	0.51	0.12	1.76E-02	5.49E-01
Fibulin-1_IIEVEEEQEDPYLNDR	1.00E-30	0.01	−0.15	1.87E-02	2.89E-01	1.00E-03	0.28	−0.05	3.47E-01	6.35E-01
Fibulin-1_TGYYFDGISR	1.00E-30	0.01	−0.13	4.78E-02	3.40E-01	1.00E-30	0.51	−0.06	1.76E-01	7.84E-01
Glial fibrillary acidic protein_ALAAELNQLR	0.02	0.03	0.18	1.03E-02	1.87E-01	0.02	0.17	0.11	9.29E-02	8.65E-01
Immunoglobulin alpha	1.00E-03	0.01	−0.14	3.76E-02	2.38E-01	1.00E-03	0.29	−0.1	7.08E-02	4.85E-01
Inter-alpha-trypsin inhibitor heavy chain H1_EVAFDLEIPK	1.00E-08	0.01	−0.15	2.49E-02	2.44E-01	1.00E-08	0.51	−0.12	8.59E-03	5.49E-01
Inter-alpha-trypsin inhibitor heavy chain H1_QYYEGSEIVVAGR	1.00E-08	0.02	−0.17	9.01E-03	1.45E-01	1.00E-08	0.51	−0.12	1.17E-02	5.49E-01
Interferon gamma Induced Protein-10	1.00E-05	0.03	−0.2	1.63E-03	1.14E-01	1.00E-05	0.47	−0.06	2.30E-01	9.88E-01
Interleukin 3	1.00E-08	0.04	−0.22	5.98E-04	**4.15E-02**	1.00E-08	0.51	−0.09	5.09E-02	5.49E-01
Isoprostane 8,12-iso-isoprostane F2_-VI-d11	1.00E-08	0.02	−0.17	7.03E-03	1.44E-01	1.00E-08	0.5	−0.06	2.29E-01	5.90E-01
Kininogen 1_DIPTNSPELEETLTHTITK	1.00E-08	0.01	−0.13	4.17E-02	2.57E-01	1.00E-08	0.51	−0.09	5.02E-02	5.49E-01
Kininogen 1_QVVAGLNFR	1.00E-30	0.01	−0.14	3.71E-02	3.40E-01	1.00E-30	0.51	−0.08	8.45E-02	7.74E-01
Laminin subunit beta-2_AQGIAQGAIR	1.00E-03	0.01	−0.14	3.51E-02	2.38E-01	1.00E-03	0.3	−0.12	3.29E-02	4.85E-01
Leucine-rich alpha-2-glycoprotein_DLLLPQPDLR	1.00E-08	0.01	−0.15	2.48E-02	2.44E-01	1.00E-08	0.5	−0.06	2.03E-01	5.89E-01
Leucine-rich alpha-2-glycoprotein_VAAGAFQGLR	1.00E-08	0.01	−0.14	3.49E-02	2.57E-01	1.00E-08	0.5	−0.06	1.95E-01	5.89E-01
Metalloproteinase inhibitor 1_SEEFLIAGK	1.00E-03	0.01	−0.14	4.58E-02	2.41E-01	1.00E-03	0.29	−0.08	1.86E-01	5.04E-01
Mimecan, osteoglycin_ESAYLYAR	1.00E-03	0.02	−0.18	8.66E-03	2.00E-01	1.00E-03	0.29	−0.08	1.84E-01	5.04E-01
Mimecan, osteoglycin_ETVIIPNEK	1.00E-30	0.01	−0.16	2.32E-02	3.12E-01	1.00E-03	0.28	−0.06	3.53E-01	6.35E-01
Mimecan, osteoglycin_LEGNPIVLGK	1.00E-30	0.03	−0.2	3.42E-03	1.29E-01	1.00E-30	0.51	−0.07	1.77E-01	7.84E-01

(*continued on next page*)

Table 2 (*continued*)

Protein (fragment)	Including *APOE*		B	*p* uncorrected	*p* FDR	Excluding *APOE*		B	*p* uncorrected	*p* FDR
	Optimal SNP threshold	Adjusted R2				Optimal SNP threshold	Adjusted R2			
Myelin-oligodendrocyte glycoprotein	1.00E-03	0.01	−0.14	3.26E-02	2.38E-01	1.00E-03	0.29	−0.1	6.61E-02	4.85E-01
Myoglobin	1.00E-30	0.01	−0.14	3.50E-02	3.40E-01	1.00E-03	0.29	−0.06	2.71E-01	5.84E-01
N-acetylmuramoyl-L-alanine amidase_AGLLRPDYALLGHR	1.00E-08	0.01	−0.14	4.28E-02	2.57E-01	1.00E-08	0.51	−0.09	7.97E-02	5.49E-01
Neural cell adhesion molecule 2_IIELSQTTAK	1.00E-03	0.01	−0.14	3.11E-02	2.38E-01	1.00E-03	0.29	−0.1	6.13E-02	4.85E-01
Neutrophil Gelatinase Associated Lipocal	1.00E-08	0.02	−0.18	1.58E-02	2.12E-01	1.00E-08	0.51	−0.09	9.88E-02	5.61E-01
Osteopontin	1.00E-08	0.03	0.18	3.46E-03	1.11E-01	0.01	0.2	0.07	2.40E-01	9.94E-01
Prostaglandin F2 alpha isoform 8	1.00E-08	0.02	−0.17	6.02E-03	1.39E-01	1.00E-08	0.51	−0.08	6.36E-02	5.49E-01
Protein-AMBP	1.00E-30	0.02	−0.2	7.39E-03	2.05E-01	1.00E-30	0.51	−0.1	4.78E-02	7.74E-01
Protein-AMBP_AFIQLWAFDAVK	1.00E-08	0.02	−0.18	7.94E-03	1.44E-01	1.00E-08	0.51	−0.12	1.77E-02	5.49E-01
Protein-AMBP_ETLLQDFR	1.00E-30	0.03	−0.23	1.51E-03	6.97E-02	1.00E-30	0.52	−0.12	1.88E-02	7.74E-01
Protein-AMBP_FLYHK	1.00E-30	0.04	−0.25	5.81E-04	5.70E-02	1.00E-30	0.52	−0.13	9.78E-03	7.74E-01
Prothrombin_ETAASLLQAGYK	1.00E-30	0.01	−0.14	3.45E-02	3.40E-01	1.00E-30	0.51	−0.09	5.70E-02	7.74E-01
Prothrombin_YGFYTHVFR	1.00E-30	0.01	−0.14	4.63E-02	3.40E-01	1.00E-30	0.51	−0.1	4.11E-02	7.74E-01
Sex hormone binding globulin	1.00E-08	0.01	−0.14	3.73E-02	2.57E-01	0.02	0.17	0.09	1.28E-01	8.65E-01
Visinin-like protein 1	1.00E-03	0.01	0.15	1.66E-02	2.38E-01	0.4	0.1	0.07	2.35E-01	5.62E-01
Vitamin D-binding protein_VPTADLEDVLPLAEDITNILSK	1.00E-30	0.01	−0.14	3.98E-02	3.40E-01	1.00E-30	0.51	−0.09	5.65E-02	7.74E-01
Cluster 2										
Agouti-related protein	0.01	0.02	0.13	4.79E-02	6.51E-01	1.00E-03	0.29	−0.07	2.30E-01	5.49E-01
Alpha synuclein	0.01	0.02	0.14	3.04E-02	5.05E-01	0.3	0.1	0.09	1.55E-01	4.63E-01
Chitinase-3-like protein 1_ILGQQVPYATK	0.05	0.05	0.23	8.08E-04	6.72E-02	0.05	0.14	0.17	1.08E-02	5.63E-01
Chitinase-3-like protein 1_SFTLASSETGVGAPISGPGIPGR	0.05	0.04	0.21	1.89E-03	9.33E-02	0.05	0.14	0.15	2.08E-02	6.47E-01
Chitinase-3-like protein 1_VTIDSSYDIAK	0.05	0.04	0.2	3.85E-03	1.23E-01	0.05	0.14	0.15	2.77E-02	6.47E-01
Contactin-associated protein-like 2_YSSSDWVTQYR	0.01	0.02	0.12	4.85E-02	6.51E-01	0.01	0.21	0.11	6.46E-02	9.94E-01
Fatty acid−binding protein, heart	0.04	0.03	0.19	3.45E-03	1.11E-01	0.04	0.15	0.13	3.10E-02	7.78E-01
Fatty acid−binding protein, heart_SIVTLDGGK	0.01	0.04	0.22	8.52E-04	5.06E-02	0.01	0.21	0.13	3.00E-02	9.94E-01
Fatty acid−binding protein, heart_SLGVGFATR	0.03	0.04	0.2	1.45E-03	7.52E-02	0.04	0.15	0.13	3.62E-02	7.78E-01
Ferritin	0.01	0.03	0.16	1.15E-02	2.56E-01	0.01	0.2	0.09	1.17E-01	9.94E-01
Fructose-bisphosphate aldolase A _ALDOA_ALQASALK	1.00E-05	0.01	0.14	2.48E-02	3.55E-01	0.01	0.2	0.05	4.15E-01	9.94E-01
Fructose-bisphosphate aldolase A _ALDOA_QLLLTADDR	1.00E-05	0.02	0.16	1.31E-02	2.60E-01	1.00E-05	0.47	0.05	2.81E-01	9.88E-01
Gamma-enolase_GNPTVEVDLYTAK	0.01	0.05	0.22	5.10E-04	**3.54E-02**	0.01	0.22	0.16	6.49E-03	8.71E-01
Gamma-enolase_LGAEVYHTLK	0.05	0.03	0.16	1.18E-02	2.47E-01	0.05	0.13	0.12	4.65E-02	6.47E-01
Macrophage colony stimulating factor 1	0.02	0.02	0.15	2.46E-02	3.11E-01	0.02	0.18	0.15	1.06E-02	5.92E-01
Matrix metalloproteinase 3	0.01	0.02	0.15	1.96E-02	3.55E-01	0.01	0.21	0.12	3.71E-02	9.94E-01
Neurogranin	0.01	0.1	0.32	3.91E-07	**5.42E-05**	0.01	0.24	0.22	3.63E-04	1.51E-01
Osteopontin_AIPVAQDLNAPSDWDSR	0.01	0.02	0.13	4.63E-02	6.51E-01	0.01	0.2	0.08	1.81E-01	9.94E-01
S100 calcium-binding protein B	1.00E-05	0.02	0.17	8.61E-03	1.99E-01	0.02	0.16	0.07	2.32E-01	8.65E-01
Total tau	0.01	0.11	0.33	1.32E-07	**1.11E-05**	0.40	0.14	0.24	1.43E-04	**2.00E-02**
Phosphorylated tau	0.01	0.13	0.36	6.43E-09	**1.35E-06**	0.20	0.13	0.23	5.60E-04	5.87E-02
Cluster 3										
Alpha-dystroglycan_GVHYISVSATR	0.1	0.03	−0.17	1.16E-02	6.63E-02	0.1	0.13	−0.15	1.56E-02	9.96E-02
Alpha-dystroglycan_LVPVVNNR	0.1	0.02	−0.13	4.83E-02	1.72E-01	0.1	0.12	−0.1	1.01E-01	3.24E-01
Amyloid beta A4 protein _LVFFAEDVGSNK	0.1	0.03	−0.17	8.05E-03	5.58E-02	0.1	0.12	−0.12	4.01E-02	1.74E-01
Apolipoprotein D_VLNQELR	1.00E-03	0.01	0.13	4.37E-02	2.39E-01	1.00E-03	0.3	0.14	1.05E-02	4.85E-01
Beta-2-microglobulin_VEHSDLSFSK	0.1	0.02	−0.16	2.21E-02	9.92E-02	0.1	0.12	−0.11	8.97E-02	3.04E-01
CD40 antigen	1.00E-03	0.03	−0.2	2.39E-03	1.10E-01	0.1	0.13	−0.17	6.56E-03	7.70E-02
CD59 glycoprotein	0.1	0.04	−0.2	2.39E-03	**3.32E-02**	0.1	0.13	−0.17	8.22E-03	7.81E-02
Cadherin-13_INENTGSVSVTR	0.1	0.03	−0.17	7.06E-03	5.15E-02	0.1	0.13	−0.16	7.74E-03	7.70E-02
Cadherin-13_YEVSSPYFK	0.1	0.03	−0.16	1.09E-02	6.52E-02	0.1	0.13	−0.15	1.15E-02	8.99E-02
Calsyntenin 3_ATGEGLIR	0.1	0.02	−0.14	2.26E-02	9.92E-02	0.1	0.13	−0.15	1.05E-02	8.81E-02
Cell adhesion molecule 3_EGSVPPLK	0.1	0.04	−0.2	1.84E-03	**2.95E-02**	0.1	0.14	−0.19	1.90E-03	6.42E-02
Cell adhesion molecule 3_GNPVPQQYLWEK	0.1	0.03	−0.18	6.38E-03	**4.91E-02**	0.1	0.13	−0.16	8.89E-03	7.87E-02
Cell adhesion molecule 3_SLVTVLGIPQKPIITGYK	0.1	0.02	−0.15	2.26E-02	9.92E-02	0.1	0.12	−0.12	4.34E-02	1.82E-01
Cell surface glycoprotein MUC18_GATLALTQVTPQDER	0.1	0.02	−0.15	2.11E-02	9.66E-02	0.1	0.12	−0.12	5.54E-02	2.13E-01
Cholecystokinin_AHLGALLAR	0.5	0.05	−0.2	1.49E-03	**4.43E-02**	0.5	0.13	−0.17	4.14E-03	1.15E-01
Cholecystokinin_NLQNLDPSHR	0.1	0.02	−0.14	3.18E-02	1.27E-01	0.1	0.12	−0.12	4.39E-02	1.82E-01

Chromogranin A	0.1	0.03	−0.17	6.00E-03	**4.91E-02**	0.1	0.14	−0.17	4.01E-03	6.74E-02
Chromogranin A_SEALAVDGAGKPGAEEAQDPEGK	0.1	0.06	−0.25	5.78E-05	**4.81E-03**	0.1	0.15	−0.22	3.56E-04	**3.71E-02**
Chromogranin A_SGEATDGARPQALPEPMQESK	0.1	0.03	−0.16	1.18E-02	6.63E-02	0.1	0.13	−0.14	1.99E-02	1.17E-01
Chromogranin A_SGELEQEEER	0.1	0.03	−0.18	4.41E-03	**4.43E-02**	0.1	0.13	−0.16	8.80E-03	7.87E-02
Chromogranin A_YPGPQAEGDSEGLSQGLVDR	0.1	0.04	−0.19	2.56E-03	**3.33E-02**	0.1	0.13	−0.17	6.08E-03	7.67E-02
Contactin 1_DGEYVVEVR	0.3	0.03	−0.17	8.67E-03	7.67E-02	0.3	0.11	−0.16	7.67E-03	1.28E-01
Glutamate receptor 4_LQNILEQIVSVGK	0.1	0.02	−0.13	4.06E-02	1.47E-01	0.1	0.13	−0.14	1.71E-02	1.06E-01
Glutamate receptor 4_NTDQEYTAFR	0.1	0.03	−0.17	7.33E-03	5.26E-02	0.1	0.13	−0.17	5.49E-03	7.37E-02
Golgi membrane protein 1_QQLQALSEPQPR	0.1	0.03	−0.18	6.79E-03	5.13E-02	0.1	0.13	−0.15	1.23E-02	8.99E-02
Immunoglobulin superfamily member 8_DTQFSYAVFK	1.00E-03	0.01	−0.13	4.49E-02	2.41E-01	1.00E-03	0.29	−0.1	8.43E-02	4.85E-01
Immunoglobulin superfamily member 8_LQGDAVVLK	0.1	0.02	−0.14	4.02E-02	1.47E-01	0.1	0.12	−0.11	7.88E-02	2.78E-01
Immunoglobulin superfamily member 8_VVAGEVQVQR	0.1	0.03	−0.17	1.04E-02	6.39E-02	0.1	0.13	−0.14	2.49E-02	1.29E-01
Kallikrein 6_LSELIQPLPLER	1.00E-03	0.01	−0.13	4.65E-02	2.41E-01	1.00E-03	0.29	−0.1	5.98E-02	4.85E-01
Latrophilin 1_LVVSQLNPYTLR	0.5	0.03	−0.14	3.29E-02	1.47E-01	0.5	0.11	−0.12	5.71E-02	2.48E-01
Macrophage Migration Inhibitory Factor	0.2	0.04	0.2	1.55E-03	5.85E-02	0.2	0.12	0.18	2.93E-03	1.90E-01
N-acetyllactosaminide beta-1,3-N-acetylglucosaminyltransferase_YEAAVPDPR	0.1	0.02	−0.13	3.73E-02	1.41E-01	0.1	0.12	−0.12	5.28E-02	2.09E-01
N-terminal prohormone of brain natriuretic peptide	0.4	0.03	0.15	2.95E-02	1.46E-01	0.4	0.1	0.13	4.56E-02	2.31E-01
Neural cell adhesion molecule 1_AGEQDATIHLK	0.1	0.03	−0.18	4.42E-03	**4.43E-02**	0.1	0.13	−0.16	9.52E-03	8.25E-02
Neural cell adhesion molecule 1_GLGEISAASEFK	0.1	0.02	−0.14	2.69E-02	1.12E-01	0.1	0.12	−0.12	4.27E-02	1.81E-01
Neural epidermal growth factor-like like 2_AFLFQDTPR	0.5	0.03	−0.15	1.74E-02	1.01E-01	0.5	0.11	−0.14	2.52E-02	1.69E-01
Neural epidermal growth factor-like like 2_FTGSSWIK	0.1	0.03	−0.17	7.99E-03	5.58E-02	0.1	0.13	−0.15	1.23E-02	8.99E-02
Neural epidermal growth factor-like like 2_SALAYVDGK	0.1	0.02	−0.15	1.64E-02	8.11E-02	0.1	0.13	−0.14	2.24E-02	1.22E-01
Neurexin 1_DLFIDGQSK	0.1	0.03	−0.17	8.93E-03	5.78E-02	0.1	0.13	−0.16	7.34E-03	7.70E-02
Neurexin 1_ITTQITAGAR	0.1	0.03	−0.18	5.76E-03	**4.89E-02**	0.1	0.14	−0.18	3.28E-03	6.55E-02
Neurexin 1_SDLYIGGVAK	0.1	0.03	−0.18	3.55E-03	**3.99E-02**	0.1	0.14	−0.18	2.62E-03	6.42E-02
Neurexin 2_AIVADPVTFK	0.1	0.02	−0.13	3.76E-02	1.41E-01	0.1	0.12	−0.13	3.57E-02	1.58E-01
Neurexin 2_LGERPPALLGSQGLR	0.3	0.02	−0.12	4.84E-02	1.92E-01	0.3	0.1	−0.12	5.32E-02	2.33E-01
Neurexin 3_IYGEVVFK	0.1	0.02	−0.15	1.61E-02	8.09E-02	0.1	0.13	−0.15	1.45E-02	9.82E-02
Neuroblastoma suppressor of tumorigenicity 1	0.1	0.04	−0.2	2.38E-03	**3.32E-02**	0.1	0.13	−0.16	1.33E-02	9.21E-02
Neurocan core protein_APVLELEK	0.1	0.03	−0.18	3.76E-03	**4.12E-02**	0.1	0.14	−0.17	3.88E-03	6.74E-02
Neurocan core protein_LSSAIIAAPR	0.1	0.02	−0.16	1.60E-02	8.09E-02	0.1	0.13	−0.14	2.20E-02	1.22E-01
Neuroendocrine convertase 1_ALAHLLEAER	0.1	0.03	−0.18	5.69E-03	**4.89E-02**	0.1	0.13	−0.15	1.22E-02	8.99E-02
Neuroendocrine convertase 1_GEAAGAVQELAR	0.1	0.04	−0.19	2.97E-03	**3.62E-02**	0.1	0.13	−0.17	5.67E-03	7.37E-02
Neuroendocrine convertase 1_NSDPALGLDDDPDAPAAQLAR	0.1	0.03	−0.18	4.47E-03	**4.43E-02**	0.1	0.13	−0.16	7.48E-03	7.70E-02
Neurofilament light	0.3	0.11	0.34	2.57E-07	**5.34E-05**	0.3	0.17	0.31	2.18E-06	**9.08E-04**
Neuronal cell adhesion molecule_SLPSEASEQYLTK	0.1	0.03	−0.16	1.13E-02	6.60E-02	0.1	0.13	−0.14	1.94E-02	1.16E-01
Neuronal cell adhesion molecule_VFNTPEGVPSAPSSLK	0.1	0.03	−0.17	6.25E-03	**4.91E-02**	0.1	0.13	−0.16	8.44E-03	7.81E-02
Neuronal cell adhesion molecule_YIVSGTPTFVPYLIK	0.1	0.02	−0.14	3.26E-02	1.28E-01	0.1	0.12	−0.12	5.50E-02	2.13E-01
Neuronal growth regulator 1_SSIIFAGGDK	0.1	0.03	−0.18	4.78E-03	**4.48E-02**	0.1	0.13	−0.16	7.35E-03	7.70E-02
Neuronal pentraxin 1_FQLTFPLR	0.1	0.02	−0.16	1.47E-02	7.55E-02	0.1	0.12	−0.13	2.69E-02	1.36E-01
Neuronal pentraxin 1_LENLEQYSR	0.1	0.03	−0.16	1.28E-02	7.01E-02	0.1	0.13	−0.15	1.28E-02	9.05E-02
Neuronal pentraxin 2_LESLEHQLR	0.5	0.04	−0.17	8.07E-03	7.31E-02	0.5	0.12	−0.15	1.59E-02	1.36E-01
Neuronal pentraxin 2_TESTLNALLQR	0.5	0.05	−0.2	1.12E-03	**3.94E-02**	0.3	0.12	−0.18	3.14E-03	1.19E-01
Neuronal pentraxin receptor_ELDVLQGR	0.1	0.04	−0.21	8.09E-04	**2.33E-02**	0.3	0.12	−0.18	2.37E-03	1.19E-01
Neuronal pentraxin receptor_LVEAFGGATK	0.1	0.04	−0.2	1.82E-03	**2.95E-02**	0.1	0.13	−0.17	5.66E-03	7.37E-02
Neurosecretory protein VGF_AYQGVAAPFPK	0.1	0.04	−0.21	8.03E-04	**2.33E-02**	0.1	0.14	−0.18	2.62E-03	6.42E-02
Neurosecretory protein VGF_NSEPQDEGELFQGVDPR	0.1	0.05	−0.23	3.85E-04	**1.79E-02**	0.5	0.14	−0.2	1.01E-03	7.99E-02
Neurosecretory protein VGF_THLGEALAPLSK	0.1	0.04	−0.21	1.07E-03	**2.79E-02**	0.1	0.14	−0.18	3.02E-03	6.55E-02
Pancreatic Polypeptide	0.03	0.02	0.17	1.32E-02	2.46E-01	0.03	0.17	0.18	4.62E-03	3.84E-01
Peptidyl-glycine alpha-amidating monooxygenase_IPVDEEAFVIDFKPR	0.1	0.04	−0.2	1.60E-03	**2.95E-02**	0.1	0.14	−0.18	4.05E-03	6.74E-02
Peptidyl-glycine alpha-amidating monooxygenase_IVQFSPSGK	0.1	0.05	−0.23	3.00E-04	**1.78E-02**	0.1	0.15	−0.2	9.03E-04	**5.00E-02**
Peptidyl-glycine alpha-amidating monooxygenase_NGQWTLIGR	0.1	0.04	−0.21	1.50E-03	**2.95E-02**	0.1	0.14	−0.18	3.31E-03	6.55E-02
Pigment epithelium-derived factor_SSFVAPLEK	0.1	0.02	−0.15	2.60E-02	1.09E-01	0.1	0.12	−0.12	5.36E-02	2.11E-01
Poliovirus receptor-related protein 1_ITQVTWQK	0.1	0.04	−0.2	1.35E-03	**2.95E-02**	0.1	0.14	−0.19	1.10E-03	5.07E-02
Proenkephalin-B_FLPSISTK	0.1	0.03	−0.17	6.28E-03	**4.91E-02**	0.1	0.13	−0.15	1.54E-02	9.96E-02
Proenkephalin-B_LSGSFLK	0.1	0.03	−0.16	1.18E-02	6.63E-02	0.1	0.12	−0.14	2.52E-02	1.29E-01
Proenkephalin-B_SVGEGPYSELAK	0.1	0.02	−0.14	3.05E-02	1.23E-01	0.1	0.12	−0.12	4.85E-02	1.97E-01
Prolactin	0.04	0.04	0.21	8.47E-04	5.47E-02	0.04	0.17	0.19	1.51E-03	2.09E-01

(*continued on next page*)

Table 2 (*continued*)

Protein (fragment)	Including *APOE*		B	*p* uncorrected	*p* FDR	Excluding *APOE*		B	*p* uncorrected	*p* FDR
	Optimal SNP threshold	Adjusted R2				Optimal SNP threshold	Adjusted R2			
Prostaglandin-H2 D-isomerase_WFSAGLASNSSWLR	0.1	0.02	−0.14	3.53E-02	1.35E-01	0.1	0.12	−0.1	1.12E-01	3.42E-01
Protein CutA_TQSSLVPALTDFVR	0.1	0.03	−0.17	8.62E-03	5.78E-02	0.1	0.13	−0.16	1.06E-02	8.81E-02
Protein family with sequence similarity 3C_GINVALANGK	0.1	0.03	−0.19	3.44E-03	**3.97E-02**	0.1	0.14	−0.17	4.70E-03	7.24E-02
Protein family with sequence similarity 3C_SALDTAAR	0.1	0.04	−0.2	1.97E-03	**3.04E-02**	0.1	0.14	−0.18	3.06E-03	6.55E-02
Protein family with sequence similarity 3C_SPFEQHIK	0.1	0.03	−0.18	4.60E-03	**4.45E-02**	0.1	0.13	−0.16	7.29E-03	7.70E-02
Protein family with sequence similarity 3C_TGEVLDTK	0.1	0.02	−0.14	2.58E-02	1.09E-01	0.1	0.12	−0.13	3.84E-02	1.68E-01
Protein-L-isoaspartate(D-aspartate) O-methyltransferase_VQLVVGDGR	0.1	0.02	−0.14	2.97E-02	1.22E-01	0.1	0.13	−0.14	2.07E-02	1.20E-01
Receptor-type tyrosine-protein phosphatase-like N_AEAPALFSR	0.1	0.05	−0.22	4.72E-04	**1.79E-02**	0.1	0.15	−0.2	7.56E-04	5.07E-02
Receptor-type tyrosine-protein phosphatase-like N_LAAVLAGYGVELR	0.1	0.03	−0.17	9.02E-03	5.78E-02	0.1	0.13	−0.15	1.53E-02	9.96E-02
Receptor-type tyrosine-protein phosphatase-like N_SELEAQTGLQILQTGVGQR	0.5	0.04	−0.18	4.26E-03	6.19E-02	0.3	0.12	−0.17	6.36E-03	1.28E-01
SLIT and NTRK-like protein 1_SLPVDVFAGVSLSK	0.1	0.03	−0.16	9.41E-03	5.93E-02	0.1	0.13	−0.15	1.08E-02	8.81E-02
SPARC-like protein 1_HIQETEWQSQEGK	0.1	0.03	−0.18	4.36E-03	**4.43E-02**	0.1	0.13	−0.16	6.46E-03	7.70E-02
SPARC-like protein 1_HSASDDYFIPSQAFLEAER	0.1	0.02	−0.14	2.35E-02	1.02E-01	0.1	0.12	−0.13	3.39E-02	1.54E-01
Secretogranin 1_GEAGAPGEEDIQGPTK	0.1	0.06	−0.24	1.90E-04	**1.31E-02**	0.1	0.15	−0.2	7.52E-04	**5.00E-02**
Secretogranin 1_HLEEPGETQNAFLNER	0.1	0.04	−0.2	2.36E-03	**3.32E-02**	0.1	0.14	−0.19	2.25E-03	6.42E-02
Secretogranin 1_NYLNYGEEGAPGK	0.1	0.07	−0.26	3.00E-05	**3.12E-03**	0.1	0.16	−0.23	1.41E-04	**2.81E-02**
Secretogranin 1_SSQGGSLPSEEK	0.1	0.04	−0.21	8.42E-04	**2.33E-02**	0.1	0.14	−0.18	4.00E-03	6.74E-02
Secretogranin 2_ALEYIENLR	0.1	0.02	−0.15	2.23E-02	9.92E-02	0.1	0.13	−0.14	1.79E-02	1.09E-01
Secretogranin 2_IILEALR	0.1	0.02	−0.16	1.40E-02	7.38E-02	0.1	0.13	−0.16	7.74E-03	7.70E-02
Secretogranin 2_VLEYLNQEK	0.1	0.04	−0.2	1.82E-03	**2.95E-02**	0.1	0.13	−0.17	5.26E-03	7.37E-02
Secretogranin 3_ELSAERPLNEQIAEAEEDK	0.1	0.05	−0.22	6.15E-04	**2.13E-02**	0.1	0.14	−0.19	1.92E-03	6.42E-02
Secretogranin 3_FQDDPDGLHQLDGTPLTAEDIVHK	0.1	0.03	−0.18	5.49E-03	**4.87E-02**	0.1	0.13	−0.15	1.46E-02	9.82E-02
Secretogranin 3_LNVEDVDSTK	0.1	0.05	−0.22	4.64E-04	**1.79E-02**	0.1	0.14	−0.19	1.99E-03	6.42E-02
Seizure 6-like protein 1_ETGTPIWTSR	0.1	0.03	−0.17	9.04E-03	5.78E-02	0.1	0.13	−0.15	1.18E-02	8.99E-02
Seizure 6-like protein 1_SPTNTISVYFR	0.1	0.02	−0.14	2.60E-02	1.09E-01	0.1	0.12	−0.13	3.56E-02	1.58E-01
Sialate O-acetylesterase_ELSNTAAYQSVR	0.5	0.03	0.14	3.32E-02	1.47E-01	0.5	0.11	0.11	6.85E-02	2.75E-01
Superoxide dismutase [Cu-Zn]_GDGPVQGIINFEQK	0.1	0.02	−0.13	3.95E-02	1.47E-01	0.1	0.13	−0.14	2.19E-02	1.22E-01
Superoxide dismutase [Cu-Zn]_HVGDLGNVTADK	0.1	0.02	−0.15	1.45E-02	7.52E-02	0.1	0.13	−0.14	1.96E-02	1.16E-01
Superoxide dismutase [Cu-Zn]_TLVVHEK	0.1	0.02	−0.14	2.99E-02	1.22E-01	0.1	0.13	−0.14	1.63E-02	1.02E-01
TNF-Related Apoptosis-Inducing Ligand	0.03	0.02	0.14	4.01E-02	4.64E-01	0.03	0.16	0.14	2.29E-02	8.68E-01
Tranforming growth factor beta 1	0.05	0.03	0.18	5.17E-03	1.34E-01	0.05	0.14	0.15	1.38E-02	5.63E-01
Transthyretin_TSESGELHGLTTEEEFVEGIYK	0.3	0.03	0.15	1.44E-02	9.33E-02	0.3	0.11	0.16	9.67E-03	1.28E-01
Transthyretin_VEIDTK	0.3	0.02	0.13	4.71E-02	1.88E-01	0.3	0.11	0.14	1.85E-02	1.41E-01
Tumor necrosis factor receptor superfamily member_ASNLIGTYR	0.1	0.02	−0.15	1.80E-02	8.52E-02	0.1	0.13	−0.14	2.47E-02	1.29E-01
Vascular endothelial growth factor	1.00E-03	0.02	−0.19	4.74E-03	1.51E-01	0.3	0.1	−0.13	4.09E-02	2.06E-01
Voltage-dependent calcium channel subunit alpha-2 delta-1_FVVTDGGITR	0.5	0.04	−0.18	4.31E-03	6.19E-02	0.3	0.11	−0.16	1.01E-02	1.28E-01
Voltage-dependent calcium channel subunit alpha-2 delta-1_IKPVFIEDANFGR	0.3	0.03	−0.16	1.21E-02	8.67E-02	0.3	0.11	−0.14	2.13E-02	1.48E-01
Voltage-dependent calcium channel subunit alpha-2 delta-1_TASGVNQLVDIYEK	0.3	0.04	−0.18	4.73E-03	6.17E-02	0.3	0.11	−0.16	9.43E-03	1.28E-01

Significant associations (i.e., $p_{FDR} < 0.05$) are depicted in bold.

Key: APOE, apolipoprotein E; CSF, cerebrospinal fluid; FDR, false discovery rate; PGRS, polygenic risk scores; SNP, single-nucleotide polymorphism.

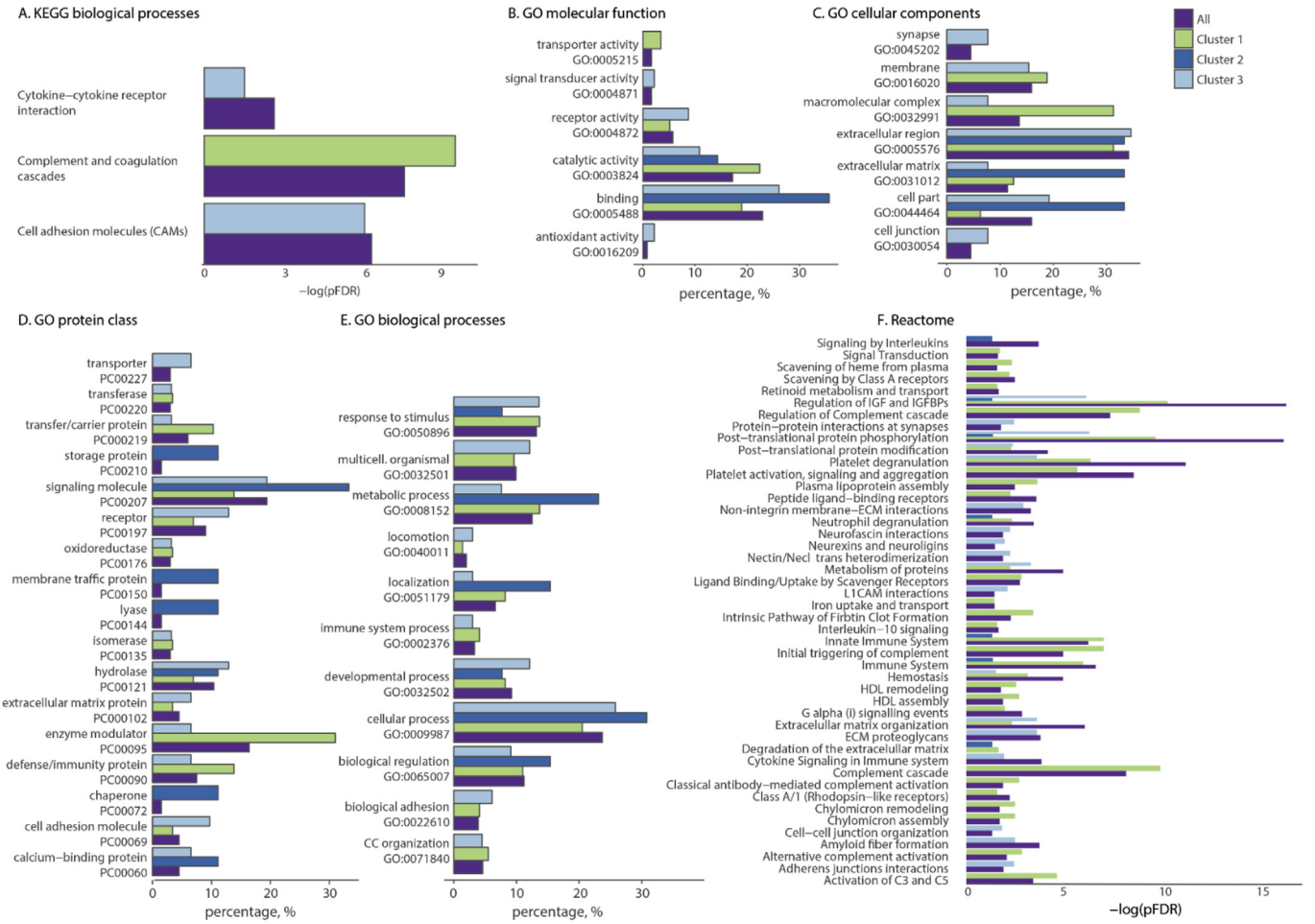

Fig. 3. Horizontal bar graph of KEGG biological processes (A), GO molecular function (B), GO cellular components (C), GO protein class (D), GO biological processes (E), and Reactome pathways (F) of PGRS-associated CSF proteins. Abbreviations: CSF, cerebrospinal fluid; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PGRS, polygenic risk scores.

proteins of similar size drawn from the human genome (all $p_{FDR} < 0.05$; Fig. 3A–F).

Proteins in cluster 1 included among others APOE protein fragments (APOE_LGADMEDVR [APOE-ε4], APOE_CLAVYQAGAR [APOE-ε2]), Aβ1-42, alpha-1-microglobulin (AMBP) protein fragments (AMBP_AFIQLWAFDAVK, AMBP_ETLLQDFR, AMBP_FLYHK), complement protein fragments (C1q subunit B_LEQGENVFLQATDK, C1q subunit B_VPGLYYFTYHASSR, C2_HAIILLTDGK, C3_IHWESASLLR, C6_SEYGAALAWEK, factor B_DAQYAPGYDK). Cluster 1 proteins were enriched for "complement and coagulation cascades" (KEGG $p_{FDR} = 4.23e\text{-}12$, Table S5).

Cluster 2 proteins included neurogranin, total tau (t-tau), phosphorylated tau (p-tau), chitinase-3-like protein 1 (CHI3L1/YKL-40) fragments (CHI3L1_ILGQQVPYATK, CHI3L1_SFTLASSETGVGAPISGPGIPGR, CHI3L1_VTIDSSYDIAK), and fatty acid–binding protein (FABP) fragments (FABP_SIVTLDGGK, FABP_SLGVGFATR), proteins supposed to reflect neural injury and astrocyte (dys)function. Cluster 2 proteins were not enriched for specific KEGG biological processes (Table S6).

Cluster 3 proteins (n = 112) included NfL, secretogranin (SCG)-1, -2, and -3 fragments (SCG-1_GEAGAPGEEDIQGPTK, SCG-1_HLEEPGETQNAFLNER, SCG-1_NYLNYGEEGAPGK, SCG-1_SSQGGSLPSEEK, SCG-2_ALEYIENLR, SCG-2_IILEALR, SCG-2_VLEYLNQEK, SCG-3_ELSAERPLNEQIAEAEEDK, SCG-3_FQDDPDGLHQLDGTPLTAEDIVHK, SCG-3_LNVEDVDSTK), chromogranin-A (CgA) fragments (CgA_SEALAVDGAGKPGAEEAQDPEGK, CgA_SGEATDGARPQALPEPMQESK, CgA_SGELEQEEER, CgA_YPGPQAEGDSEGLSQGLVDR), and neurosecretory protein VGF (non-acronymic) (VGF_AYQGVAAPFPK, VGF_NSEPQDEGELFQGVDPR, VGF_THLGEALAPLSK) fragments. Proteins in cluster 3 were enriched for cytokine-cytokine receptor interaction (KEGG $p_{FDR} = 0.0146$) and cell adhesion molecules (KEGG $p_{FDR} = 5.28e\text{-}08$) (Table S7).

When repeating analyses adjusting for *APOE*-ε4 status, most PGRS-HR cluster 1 protein associations (n = 49, 72%) lost significance, indicating that the associations of those proteins were mostly dependent of *APOE*-ε4, possibly reflecting downstream effects of *APOE*-ε4 on those proteins. The association of PGRS-HR with Aβ1-42 remained significant after controlling for *APOE*-ε4 status. Of all proteins in cluster 2, levels of 13 (62%) proteins (e.g., neurogranin, total tau, phosphorylated tau, CHI3L1/YKL-40 fragments, and FABP fragments) were independent of *APOE*-ε4 status ($p < 0.05$). Most cluster 3 proteins (88%), including NfL, SCG 1 fragments, and CgA, remained significantly associated ($p < 0.05$) with the corresponding PGRS-LR after controlling for *APOE*-ε4 carrier status (Table 2, Table S3). We further repeated clustering analysis including only proteins that survived correction for multiple testing (n = 52 proteins with $p_{FDR} < 0.05$) and observed largely similar clusters (Figs. S10–S12).

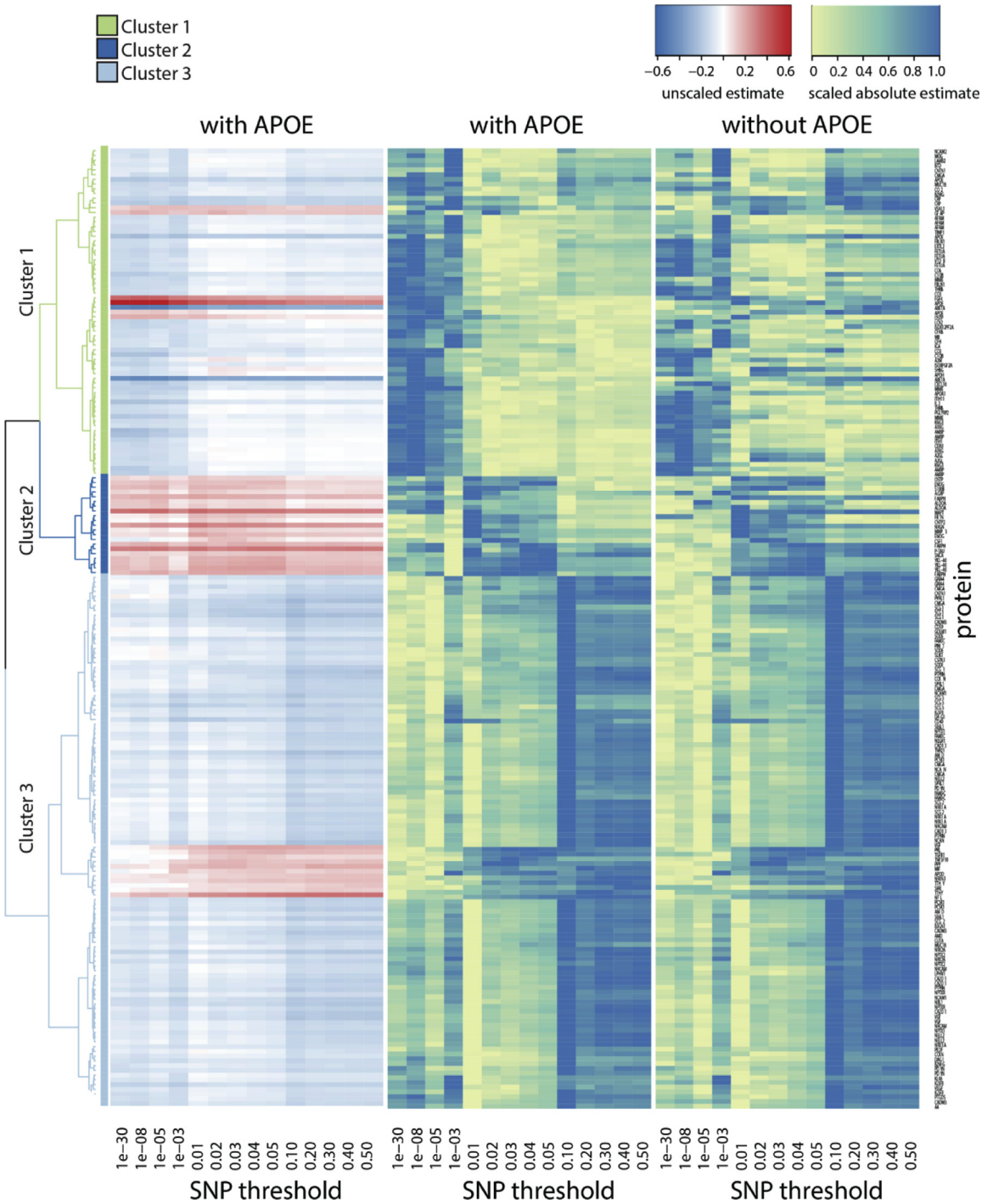

Fig. 4. Heatmap of associations between PGRS and in vivo levels of protein levels in CSF with (left, middle) and without (right) including *APOE*-ε4 status. Proteins with at least one PGRS-CSF association with $p_{\text{uncorrected}} < 0.05$ (n = 201) were selected in this heatmap. Abbreviations: APOE, apolipoprotein E; CSF, cerebrospinal fluid; PGRS, polygenic risk scores; SNP, single-nucleotide polymorphisms.

4. Discussion

In this study, we observed that differential patterns of inheritance for AD were associated with 3 distinct CSF proteomic profiles. Our findings show that it is possible to dissect heritability in biological processes underlying AD pathogenesis in vivo by studying associations with CSF proteomic levels.

Previous studies reported that high PGRS, calculated with genome-wide significant susceptibility loci only and thus indicating a strong genetic risk for AD, were associated with low CSF Aβ1-42 and high CSF t-tau and p-tau levels (Darst et al., 2016; Louwersheimer et al., 2016; Martiskainen et al., 2015; Mormino et al., 2016; Schultz et al., 2015). We replicate those findings and extend on those by showing the genetic risk for AD is also associated with CSF protein levels that are related to other biological processes than Aβ pathology, including inflammatory processes, synaptic degeneration, and dyslipidemia. Furthermore, we observed that the degree of genetic risk for AD (i.e., very strong to weak genetic effects) was associated with 3 distinct subsets of proteins.

When controlling for *APOE*-ε4 status, 40.3% PGRS-protein associations lost significance, highlighting the crucial role of the *APOE*-ε4 allele in AD pathogenesis. Most cluster 1 proteins lost significance after *APOE*-ε4 correction, followed by cluster 2 and cluster 3 proteins. Still, PGRS associations with Aβ1-42, t-tau, chromogranin A, NfL, peptidyl-glycine alpha-amidating monooxygenase and secretogranin 1 CSF levels remained significant after correction for *APOE*-ε4 status, suggesting that other genes next to *APOE* are associated with key AD pathogenic processes, such as Aβ aggregation, neural injury, and inflammatory responses.

Cluster 1 contained proteins related to Aβ pathology and complement and coagulation cascades (Lambert et al., 2009). The closely linked complement and coagulation systems play a major role in the primary immune response to pathogens, primarily lead via the innate immune response and hemostasis (i.e., cessation of blood loss from a damaged vessel), respectively (Yasojima et al., 1999). An explanation for the observed genetic association with these pathways could be that multiple variants conferring genetic risk to AD such as the genome-wide significant SNP rs4844610 on complement receptor 1 (*CR1*) or the long isoform of *CR1* (CR1-S) were included in the PGRS, which may directly influence levels of complement protein(s) (fragments) (Hazrati et al., 2012; Lambert et al., 2009). Aβ has shown to activate the complement system, potentially explaining the genetic association between AD and complement-related proteins (Rogers et al., 1992).

Cluster 2 proteins were related to synaptic degeneration, neuroinflammatory processes, and dyslipidemia. Proteins included t-tau and p-tau, neurogranin, CHI3L1/YKL-40, and FABP protein(s) (fragments), all known to be increased in AD and also in other neurodegenerative disorders (Blennow et al., 2001; Chiasserini et al., 2010; Hellwig et al., 2015). This suggests that multiple causes (e.g., multiple common genetic variants) exist for higher levels of these proteins, highlighting the importance of precision medicine when developing potential therapeutic interventions for AD.

Cluster 3 consisted of proteins that correlated with PGRS that also included SNPs with weak associations with AD. These were enriched for cytokine-cytokine interactions. Cytokines play a major role in inflammatory and anti-inflammatory processes and are dysregulated in AD (Kauwe et al., 2014; Rubio-Perez and Morillas-Ruiz, 2012; Tarkowski et al., 2000; Togo et al., 2000; Zetterberg et al., 2004). The notion that these proteins were associated with PGRS that included the weakest SNPs suggests that many different SNPs may lead to inflammatory processes as observed in AD. There is some evidence that dysfunctional inflammatory and anti-inflammatory processes could be upstream to Aβ pathology. For example, transforming growth factor β1 (TGFβ1) has shown to stimulate amyloid precursor protein production and subsequent Aβ1-42 generation in rodent and human astrocytes (Gray and Patel, 1993; Lesne et al., 2003). However, inflammatory responses may also be a downstream consequence of Aβ1-42 aggregation (Luedecking et al., 2000; Wyss-Coray et al., 2001). Our results suggest that the cumulative effect of many genes with weak effects on AD risk may contribute to subtle abnormalities in the inflammatory response, possibly making the brain at higher risk for developing Aβ pathology and eventually AD-type dementia. Cluster 3 proteins further showed enrichment for cell adhesion molecules, proteins expressed on the cell surface which are particularly important for synapse structure and function (Bot et al., 2011). Synaptic loss has been observed in a variety of neurodegenerative disorders and is directly linked to cognitive decline (Bereczki et al., 2018). Furthermore, NfL was part of this cluster, of which higher levels indicate axonal injury (Yuan et al., 2015). Previous studies have reported elevated CSF NfL levels in a variety of neurological disorders, including AD (Bridel et al., 2019; Khalil et al., 2018). Together with our observation that NfL strongly relates to the cumulative effects of SNPs with weak effects for AD, this suggests that CSF NfL levels reflect a generic neuropathological mechanism, rather than AD-specific mechanisms.

A potential limitation of this study is that PGRS including SNPs with weak effects may include more noise, making it difficult to differentiate between true risk alleles and unassociated variants. Still, we think that the PGRS approach is an elegant method for resembling polygenicity, as it captures many SNPs that collectively contribute to disease risk that would have been missed when using a genome-wide threshold (Purcell et al., 2009). In addition, sample overlap between ADNI and IGAP could have inflated the PGRS, as we were not able to identify the exact (potential) overlap between the 2 samples. However, as the potential contribution of ADNI subjects to IGAP is relatively small ($<$1.04% for patients with AD-type dementia, $<$0.20% for control subjects) and because we examined PGRS associations with independently measured CSF proteomic data, potential influence of inflation is likely to be minimal. Another limitation of our study is that we are unable to make strong inferences on the strength of causality, that is, whether the genetic liability for AD is directly or indirectly associated with CSF protein levels because we performed analyses cross-sectionally. Repeated CSF proteomic analyses need to be performed to further investigate this question. We also do not know the degree to which these analyses extend to individuals from non-European descent. Furthermore, we show that the degree of genetic risk for AD associates with distinct CSF patterns, suggesting that these patterns may help in patient stratification. Where the objective of our study was to examine PGRS-CSF associations, it is essential that our efforts will be extended to the classification of diagnostic groups (e.g., AD case-control status) using CSF protein patterns as predictors. Finally, we did not stratify analyses on diagnostic groups. However, we see this as a strength of the present study as continuous PGRS may more precisely reflect underlying pathogenic processes. As such, examining CSF protein levels provides unique insights into pathophysiological processes underlying AD along the clinical spectrum of the disease.

Results presented in this study demonstrate that a high genetic liability for AD is associated with distinct biological mechanisms that are measurable using a CSF proteomic approach. CSF protein levels seemed to reflect varying degrees of genetic liability for AD, suggesting that the CSF proteome is influenced by multiple distinct patterns of inheritance. Identifying how CSF protein levels are genetically influenced by AD may be of importance for the development of treatments, especially when using CSF protein levels as outcome measure for drug trials.

CRediT authorship contribution statement

Lianne M. Reus: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Visualization. **Sven Stringer:** Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Danielle Posthuma:** Writing - review & editing. **Charlotte E. Teunissen:** Writing - review & editing. **Philip Scheltens:** Writing - review & editing. **Yolande A.L. Pijnenburg:** Conceptualization, Supervision, Writing - review & editing. **Pieter Jelle Visser:** Conceptualization, Supervision, Writing - review & editing. **Betty M. Tijms:** Conceptualization, Methodology, Supervision, Writing - review & editing.

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Appendix A. Supplementary data

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