RESEARCH

Multiplex proteomics identifies novel CSF and plasma biomarkers of early Alzheimer's disease

Christopher D. Whelan¹⁺, Niklas Mattsson^{2,3+}, Michael W. Nagle⁴⁺, Swetha Vijayaraghavan⁵, Craig Hyde⁴, Shorena Janelidze², Erik Stomrud², Julie Lee⁴, Lori Fitz⁴, Tarek A. Samad⁶, Gayathri Ramaswamy¹, Richard A. Margolin⁷, Anders Malarstig^{4,5*} and Oskar Hansson^{2,8*}

Abstract

To date, the development of disease-modifying therapies for Alzheimer's disease (AD) has largely focused on the removal of amyloid beta $A\beta$ fragments from the CNS. Proteomic profiling of patient fluids may help identify novel therapeutic targets and biomarkers associated with AD pathology. Here, we applied the Olink™ ProSeek immunoassay to measure 270 CSF and plasma proteins across 415 Aβ- negative cognitively normal individuals (Aβ-CN), 142 AB-positive CN (AB+ CN), 50 AB- mild cognitive impairment (MCI) patients, 75 AB+ MCI patients, and 161 A β + AD patients from the Swedish BioFINDER study. A validation cohort included 59 A β - CN, 23 A β - + CN, 44 A β -MCI and 53 A β + MCI. To compare protein concentrations in patients versus controls, we applied multiple linear regressions adjusting for age, gender, medications, smoking and mean subject-level protein concentration, and corrected findings for false discovery rate (FDR, q < 0.05). We identified, and replicated, altered levels of ten CSF proteins in Aβ+ individuals, including CHIT1, SMOC2, MMP-10, LDLR, CD200, EIF4EBP1, ALCAM, RGMB, tPA and STAMBP (-0.14 < d < 1.16; q < 0.05). We also identified and replicated alterations of six plasma proteins in A β + individuals OSM, MMP-9, HAGH, CD200, AXIN1, and uPA (-0.77 < d < 1.28; q < 0.05). Multiple analytes associated with cognitive performance and cortical thickness (q < 0.05). Plasma biomarkers could distinguish AD dementia (AUC = 0.94, 95% CI = 0.87-0.98) and prodromal AD (AUC = 0.78, 95% CI = 0.68-0.87) from CN. These findings reemphasize the contributions of immune markers, phospholipids, angiogenic proteins and other biomarkers downstream of, and potentially orthogonal to, Aβ- and tau in AD, and identify candidate biomarkers for earlier detection of neurodegeneration.

Keywords: Alzheimer's disease, Mild cognitive impairment, Biomarker, Proteomics, Inflammation, Apoptosis, Angiogenesis

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, affecting one in 10 people aged 65 years or older [3]. To date, the development of diseasemodifying treatments for AD has largely targeted one of its pathological hallmarks, amyloid beta ($A\beta$), and to a lesser extent tau, with notably high failure rates

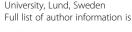
* Correspondence: Anders.Malarstig@pfizer.com; Hansson@med.lu.se [†]Christopher D. Whelan, Niklas Mattsson and Michael W. Nagle contributed equally to this work.

⁴Pfizer Worldwide Research & Development, Cambridge, MA 02139, USA ²Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Lund, Sweden

Full list of author information is available at the end of the article

in clinical trials [12]. Molecular markers such as amyloid PET, cerebrospinal fluid (CSF) A β , and CSF tau are frequently employed in the clinical diagnosis of AD, and biomarkers are increasingly recognized as integral components of the drug development pipeline [10]. However, recent evidence from human genetics [45, 52], neuroimaging [14], and in-vivo modeling [9] has strongly implicated additional disease mechanisms in AD, not reflected by the established A β and tau biomarkers. These potential pathophysiological processes, such as inflammation [14, 52], membrane phospholipid dysregulation [62], and neurovascular

© The Author(s). 2019 **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.





Open Access

Whelan et al. Acta Neuropathologica Communications(2019) 7:169https://doi.org/10.1186/s40478-019-0795-2

disruption [45], are less frequently targeted, and remain less well understood [22].

Proteomics, the analysis of proteins in different bodily tissues and fluids, can be used to study myriad pathways putatively affected in AD in-vivo, before the onset of overt neurodegeneration, thus potentially elucidating important disease mechanisms and informing future pharmacotherapeutic trials. In CSF, certain proteomic assays can reflect underlying brain pathology [48], and thus, may be useful for pharmacokinetic monitoring, diagnosis, and stratification [5]. However, lumbar puncture is invasive. Blood may serve as a more accessible body fluid; however, many blood-based molecular profiling studies of AD have been restricted by small sample sizes, methodological variability, and suboptimal diagnostic sensitivity [28, 38]. Additionally, with the exception of certain blood biomarkers, such as plasma A β [39] and plasma tau [28], few studies have directly explored the relationship between CSF proteins and their blood-based analogs in the same cohort; thus, the extent to which peripheral molecular changes accurately reflect CNS dynamics has yet to be characterized at large scale.

Here, we sought to understand the contributions of proteins downstream of, and potentially orthogonal to, $A\beta$ and tau across the preclinical, prodromal, and dementia stages of AD. We measured a diverse panel of 270 proteins in the CSF and plasma of up to 1022 individuals, using a validated, highly sensitive and specific immunoassay [4]. We identified, and replicated, evidence of differential regulation in proteins related to innate and adaptive immunity (CD200, CHIT1, MMP-9, MMP-10, oncostatin-M, STAMBP), membrane phospholipids (LDLR), axon guidance, cell adhesion and differentiation (ALCAM, RGMB, ROBO2), ischemic injury (uPA, tPA, SMOC2), mTOR and Wnt/β-catenin signaling (AXIN1, EIF4EBP1), and glucose metabolism (HAGH) in early and later-stage AD. Multiple proteins associated with baseline cortical thickness and cognitive performance. Approximately half of all assayed proteins in CSF showed modest correlations with their analogs in plasma, and a combination of plasma analytes could differentiate AD from non-AD with high accuracy. Thus, our findings reemphasize the importance of targeting pathways beyond A β and tau in AD, and identify several candidate biomarkers for early detection of brain pathology, pending additional validation.

Materials and methods

Standard protocol approvals, registrations, and patient consents

The study was approved by the Regional Ethics Committee in Lund, Sweden. Written informed consent was collected from all participants.

Study participants

Participants were recruited from southern Sweden between 2009 and 2014 as part of the prospective and longitudinal BioFINDER study (www.biofinder.se). A total of 872 participants assessed at the Memory Clinic in Malmö were recruited to the discovery cohort, including 565 cognitively normal elderly participants (CN), 131 patients with mild cognitive impairment (MCI), and 176 patients with dementia due to AD (see Table 1). An additional 179 participants assessed at the Memory Clinic in Lund were recruited to the replication cohort, including 82 elderly participants who presented with memory complaints but were clinically determined to be cognitively normal, and 97 MCI patients (see Additional file 1: Table S6).

Cognitively normal elderly participants were included as study controls if they (i) were aged 60–80 years, (ii) had Mini-mental State Examination (MMSE) scores of 28–30 at their initial screening visit, (iii) lacked symptoms of cognitive impairment, as assessed by a physician, and (iv) did not fulfill the criteria for MCI or dementia. Participants were excluded from the control group if they (i) refused lumbar puncture, or if they presented with (i) a significant neurological or psychiatric disease (iii) current alcohol or substance misuse, or (iv) a systematic illness preventing them from participating in the study.

Patients with MCI were recruited from a larger cohort of non-demented outpatients with cognitive symptoms; the inclusion criteria for this cohort included (i) age 60-80 years, (ii) initial presentation with a complaint related to memory, executive, visuo-spatial, language praxis, or psychomotor function, (iii) an MMSE score between 24 and 30, (iv) significant impairment in at least one cognitive domain (most often memory) according to an assessment by an experienced neuropsychologist [26] and (iv) essentially preserved activities of daily living. Exclusion criteria included (i) fulfillment of the criteria for any dementia disorder, (ii) cognitive impairment that could be definitively explained by another condition, (iii) a systemic illness preventing them from participating in the study, and (iv) refusal to undergo lumbar puncture or neuropsychological assessment.

AD dementia patients were classified using the criteria for probable AD, as defined by NINCDS-ADRDA [29].

Participants were grouped based on a combination of their clinical diagnosis (AD, MCI, or CN) and CSF Aβ pattern, based on combined Aβ40 and Aβ40 assays (Eurimmun, Germany). Individuals with a CSF Aβ42/Aβ40 ratio ≥ 0.1 were considered amyloid-negative controls (Aβ- CN) or patients with MCI not due to AD (Aβ-MCI), and individuals with a ratio ≤ 0.1 were considered amyloid-positive cognitively normal participants (Aβ+ CN), or patients with MCI due to AD (Aβ+MCI) [20,

Table 1 Demographic and clinical data for the Memory Malmö 'discovery' cohort

	Control Aβ-	Control Aβ+	MCI- Aβ-	MCI- Aβ+	AD (Aβ+)	P-value ^a (group differences)
Sample size (n)	415	142	50	75	161	
Sex (F/M)	256/159	100/42	20/30	33/42	104/57	0.000061
Mean age in years (SD)	71.7 (5.21)	72.99 (4.78)	68.8 (5.12)	72.29 (4.93)	74.58 (7.37)	1.676 × 10–10
MMSE mean (SD)	29.11 (0.9)	29.02 (0.83)	27.3 (1.68)	26.56 (1.79)	21.47 (3.9)	9.4022 × 10-213
APOE (1 or 2 ϵ 4 alleles)	22.89%	57.75%	20%	74.67%	66.46%	7.0724 × 10-32
Anti-inflammatory drugs	9.64%	7.75%	4.00%	9.33%	6.21%	0.52
Platelet inhibitor drugs	16.39%	17.61%	38.00%	33.33%	29.19%	0.000016
Antidepressive drugs	6.75%	7.04%	32.00%	16.00%	22.98%	1.3371 × 10–10
Lipid-lowering drugs	26.02%	30.99%	42.00%	37.33%	29.81%	0.07
Antihypertensive/cardioprotective drugs	41.69%	49.30%	54%	52%	54.04%	0.04
Current smoker	9.4%	2.82%	8%	5.33%	9.94%	0.08
Mean Aβ42 in pg/ml (SD)	752 (253)	423 (175)	628 (223)	280 (90)	305 (132)	6.3545 × 10- 119
Mean Aβ40 in pg/ml (SD)	5847 (2042)	6566 (2373)	4956 (2045)	5057 (1612)	5470 (2179)	4.9837 × 10-8
A β 42/40 ratio - log2 transformed (SD)	2.05 (0.17)	2.75 (0.28)	2.05 (0.17)	2.89 (0.28)	2.9 (0.29)	7.8397 × 10–253
Mean total tau (SD)	292 (89)	432 (163)	295 (110)	515 (181)	649 (221)	
Mean phospho-tau (SD)	37 (13)	66 (35)	40 (17)	105 (46)	123 (47)	

Demographics are provided for participants who were included in the final proteomics analysis after quality assessment (see Methods) ^aTo assess group differences we used a test of independence (Chi-square) for categorical variables and ANOVA for continuous variables

41]. All patients with dementia due to AD had pathological CSF ratios ≥ 0.1 . The CSF A β 42/A β 40 ratio was used instead of CSF A β 42 alone, as this ratio has a greater concordance with amyloid PET findings [20, 41]. A β - MCI patients were included in the study for comparison with A β + patients, since proteins showing evidence of differential regulation across Ab-positive and Ab-negative groups could potentially implicate processes orthogonal to A β deposition.

Following quality control, the Memory Malmö discovery cohort consisted of 415 A β - CN participants, 142 A β + CN participants, 50 A β - MCI patients, 75 A β + MCI patients, and 161 AD patients (see Table 1 for participant demographics). The Memory Lund replication cohort consisted of 59 A β - CN participants, 23 A β + CN participants, 44 A β - MCI patients, and 53 A β + MCI patients (see Additional file 1: Table S6 for participant demographics).

Magnetic resonance imaging

MRI data were collected from 303 healthy elderly controls and 112 MCI patients from the Memory Malmö cohort, using a 3 Tesla Siemens[®] Trio scanner equipped with a standard 12-channel head coil. Hippocampal volume and cortical thickness estimates were measured using FreeSurfer v5.3 (https://surfer/nmr.mgh.harvard.edu). A composite AD 'signature cortical thickness' measurement was constructed by calculating mean surface-area adjusted thickness across the entorhinal, inferior temporal, middle temporal, and fusiform cortices bilaterally [17]. Hippocampal volume measures were adjusted for total intracranial volume. Full details of MRI processing are described elsewhere [40].

Plasma and CSF sampling

Plasma and lumbar CSF samples were collected from non-fasting participants during the 'subjects' baseline BioFINDER visit. and analyzed following a standardized protocol [40]. After collection, samples were centrifuged (2000 g, +4 °C, 10 min), aliquoted into 1 ml polypropylene tubes (Sarstedt AG & Co., Nümbrecht, Germany), and stored at -80 °C. Prior to proteomic screening, all plasma and CSF samples underwent one freeze-thaw cycle, and were further aliquoted into 200L Lobind tubes (Eppendorf Nordic A/S, Denmark).

Protein quantification

Protein concentrations were quantified using the validated, highly sensitive and specific ProSeek multiplex immunoassay, developed by Olink Proteomics (Uppsala, Sweden) [4]. Three commercially available ProSeek[®] Multiplex panels were used to measure the concentrations of 270 proteins in human plasma and CSF (Additional file 1: Table S1). Protein measurements were conducted using Proximity Extension Assay (PEA) technology, following the manufacturer's protocol [4]. Briefly, antigens were incubated with pairs of antibodies containing DNA oligonucleotides bound to each of the 270 proteins to be measured. A template for hybridization and extension was generated bv oligonucleotides in close proximity, and preamplification was performed using polymerase chain reaction (PCR). Following digestion of residual primers, specific primers were digested on a quantitative realtime PCR chip (Dynamic Array IFC; Fluidigm Biomark) using a Biomark HD Instrument. Protein quantities were produced as normalized protein expression (NPX) values on the log_2 scale.

Patient-level quality control

Samples from 1051 participants (872 discovery samples, 179 replication samples) were randomized and assayed in parallel on 54 ProSeek plates in plasma and 55 Pro-Seek plates in CSF. Four internal controls were added to each sample to monitor assay performance and the quality of individual samples, and intensity normalization was implemented to minimize technical variation between plates. The quality of each sample was assessed by evaluating deviation from the median value of its internal control; samples that deviated less than 0.3 NPX from the median passed quality assessment.

Protein-level quality control

Proteins detected in more than 70% of samples were considered sufficient to allow statistical analysis using standard regression models. Only proteins with less than 20% of values below the reported lower limit of quantification (LLQ) were analyzed quantitatively. In these instances, we used the actual raw extended values (under LLQ), provided by OLINK, to impute best-guess values. A histogram was made of each such protein to verify a continuous distribution of values across the LLQ threshold when using these extended values.

Principal component analyses (PCAs) were generated on the NPX values and visually inspected to identify possible outliers and to evaluate the consistency of plasma and CSF data.

Statistical analysis

All statistical analyses and data processing were conducted using R version 3.4.4 and IBM SPSS Statistics for Windows 22.0. All univariate linear regressions and mixed-effects models conducted in the discovery cohort were adjusted for False Discovery Rate (FDR) at an FDRadjusted *p*-value (i.e. *q* value) threshold of 0.05, using the *p.adjust* function in R. For proteins surviving FDR adjustment in the discovery cohort, unadjusted *p*-values were inspected in the replication cohort.

Univariate linear regressions

Differential regulation of proteins was assessed between the cognitively normal, $A\beta$ - elderly CN and; (i) cognitively normal, $A\beta$ + elderly individuals, (ii) $A\beta$ - MCI patients, (iii) $A\beta$ + MCI patients, and (iv) patients with dementia due to AD, using multiple linear regressions via the *lm* function in R, where clinical grouping was the predictor of interest, and protein concentration in plasma or CSF was the outcome measure. Age, gender, current smoking status, medications (including platelet inhibitors, antidepressants, anti-inflammatory, lipidlowering, antihypertensive, and cardioprotective drugs), and cross-subject mean protein concentration, collectively referred to as 'standard covariates', were included in all models. For brevity, comparisons between clinical groups (AD versus A β + MCI, A β + MCI versus A β + CN, AD versus A β + CN) were omitted from the main text, but included in the Additional file 1: (see Additional file 1: Note 1 and Tables S23-S28).

Multivariate LASSO regression

We employed multivariable modeling to identify subsets of proteins that could accurately discriminate cognitively normal healthy individuals from cognitively normal AB+ individuals, MCI, and AD-dementia. Our model evaluated several different proteins simultaneously, using the least absolute shrinkage and selection operator method (LASSO; [55], implemented via the *glmnet* package in R. We separately tested models to predict A β - MCI, A β + MCI, and AD-dementia patients, versus Aβ- controls, adjusting for age and gender. The LASSO regularization parameter lambda was selected by 10-fold crossvalidation using the *cv.glmnet* function, to protect against overfitting. Results from the LASSO models are presented as the mean and 95% CI of the cross-validated area under the receiver operating characteristics curves (AUC). In a supplementary analysis, we employed a more complex LASSO model which adjusted for the standard covariates (Additional file 1: Note 2).

Associations with clinical and neuroimaging endpoints

Associations between circulating proteins and Mini-Mental State Examination (MMSE; collected for all participants) and Clinical Dementia Rating Scale Sum of Boxes (CDR-SB; collected for healthy elderly and MCI) were assessed using multiple linear regressions in R, where baseline MMSE or CDR-SB score was the determinant of interest, and protein concentration was the outcome measure, adjusting for the standard covariates.

Associations between circulating proteins, hippocampal volume, and signature cortical thickness were assessed using multiple linear regressions in *R*, again adjusting for the standard covariates.

Within- and between-fluid correlations

Within-fluid correlations (CSF-to-CSF, plasma-toplasma) and between-fluid correlations (CSF-to-plasma) were assessed across all proteins using a simple Pearson correlation test in R.

Results

190 CSF proteins and 250 plasma proteins were analyzed across 843 discovery samples and 179 replication samples

Due to technical issues, no data were recorded from the BDNF and CCL22 assays. An additional 68 CSF proteins and 18 plasma proteins were excluded due to low detection rates (< 70%; Additional file 1: Table S1). Thus, our final statistical analyses included 190 proteins that were detected in > 70% of CSF samples, and 250 proteins that were detected in > 70% of plasma samples.

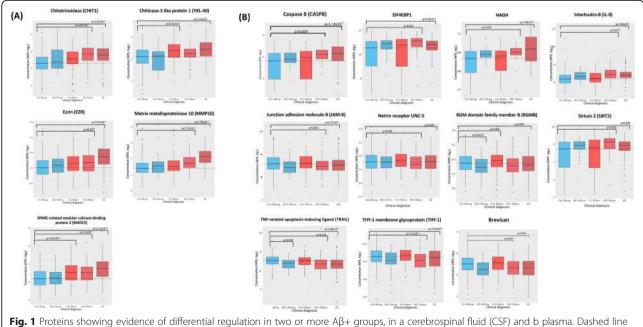
Of the 1051 samples, 29 failed due to missingness of 10% or more analytes in CSF. 31 samples (including the aforementioned 29 samples) had missingness rates of 10% or more in plasma. The remaining samples had no more than five missing values (representing 1.8% of all analytes). A single healthy elderly participant was identified as an outlier in plasma, due to a covariate-adjusted PCA value more than 3.5 standard deviations from the centroid (Additional file 1: Figs. S1-S8). Thus, of the initial 1051 participants, 1022 were eligible for plasma analysis, and 1019 were eligible for CSF analysis.

CSF levels of CHIT1, MMP-10, SMOC2, and ezrin were increased in AD and A β -positive MCI

Compared to Aβ- cognitively normal (CN) elderly controls, AD-dementia and Aβ+ MCI patients both showed significant increases of four proteins in CSF, including chitinase 1 (CHIT1; d = 0.95 in Aβ+ MCI; d = 0.76 in AD; $q < 6.07 \times 10^{-7}$), matrix metalloproteinase 10 (MMP-10; d = 0.32 in Aβ+ MCI; d = 0.54 in AD; $q < 1.16 \times 10^{-5}$), SMOC2 (d = 0.29 in Aβ+ MCI; d = 0.28 in AD; $q < 1.16 \times 10^{-5}$), and ezrin (d = 0.13 in Aβ+ MCI; d = 0.24 q < 0.05; see Fig. 1a and Table 2). An additional five CSF proteins were increased, and 13 CSF proteins were decreased, in AD-dementia patients only, while an additional three proteins were increased in Aβ+ MCI patients only, when compared to controls (see Fig. 2a and Table 2).

CSF levels of SMOC2 and YKL-40 were increased in A β -positive, cognitively normal individuals

Two proteins were increased in the CSF of A β + cognitively normal (CN) individuals, including SMOC2 (d = 0.19; $q = 9.01 \times 10^{-5}$), which was also increased in the CSF of A β + MCI patients (d = 0.29; $q = 1.16 \times 10^{-5}$) and AD-dementia patients (d = 0.28; $q = 1.09 \times 10^{-10}$), and YKL-40 (d = 0.13; q = 0.007), which was also increased in the CSF of AD-dementia patients (d = 0.17; $q = 1.19 \times 10^{-5}$; see Fig. 1a and Table 2).



represents the average protein concentration of the A β - cognitively normal group (i.e. study controls). A β - groups are coloured in blue; A β + groups are coloured in red. Ctrl-ABneg = A β - controls; MCl-ABneg = A β - MCl patients; Ctrl-ABpos = A β + cognitively normal individuals, MCl-ABpos = A β + MCl patients; AD = Dementia due to Alzheimer's disease; q = false discovery rate adjusted p-value. Image generated using the ggplot package in R

Table 2 Demographic and	clinical data f	or the Memory	/ Malmö 'discov	very' cohort

	Alzheimer's deme						
Protein name	Protein abbreviation	CSF Fold change	CSF Std. error	CSF q-value	Plasma Fold change	Plasma Std. error	Plasma q-value
Chitinase 1 (chitotriosidase) ²	CHIT12	0.76	0.12	1.26x10 ⁻⁸	-0.26	0.16	1
Matrix metalloproteinase 10 ²	MMP-10 ²	0.54	0.04	5.2x10 ⁻³¹	-0.04	0.05	1
Disintegrin and metalloproteinase							
domain- containing protein 22	ADAM22	0.32	0.03	9.24x10 ⁻²⁰	-0.07	0.05	1
SPARC-related modular calcium- binding protein 2 ^{2,4}	SMOC2*2.4	0.28	0.04	1.09x10 ⁻¹⁰	-0.18	0.04	0.002
Ezrin ²	EZR ²	0.24	0.03	6.34x10 ⁻¹⁷	0.00	0.03	1
Osteoprotegerin ^a	OPG ³	0.20	0.03	3.75x10 ⁻⁰	0.05	0.03	1
Eukaryotic translation initiation factor	0.4	010	0.00	0.70010	0.05	0.00	
4E- binding protein 1	EIF4EBP1*	0.19	0.03	9.07x10 ⁻⁸	0.39	0.09	0.009
Chitinase-3-like protein 14	CHI3L1 (YKL-40)4	0.17	0.03	1.19x10 ⁻⁵	0.12	0.09	1
C-C motif chemokine 3	CCL3	0.17	0.03	3.8x10 ⁻⁵	-0.03	0.06	1
Caspase 8	CASP8*	0.16	0.02	2.2x10 ⁻¹⁴	0.67	0.11	1.1x10 ⁻⁷
STAM-binding protein	STAMBP	0.13	0.02	2.38x10 ⁻¹¹	-0.09	0.12	1
Tumor necrosis factor receptor							
superfamily member 12A	TNFRSF12A	0.12	0.02	3.7x10 ⁻⁵	0.05	0.04	1
Tissue factor pathway inhibitor	TFPI	0.12	0.03	0.002	0.02	0.03	1
Junction adhesion molecule B	JAM-B*	-0.05	0.01	0.044	-0.17	0.03	4.11x10 ⁻⁵
Epidermal growth factor receptor	EGFR	-0.06	0.02	0.04	-0.07	0.03	1
Matrix metalloproteinase 2	MMP-2	-0.07	0.02	0.038	-0.07	0.04	1
CD166 antigen	ALCAM	-0.07	0.02	0.027	-0.05	0.03	1
Netrin receptor UNC5C	UNC5C*	-0.09	0.02	0.026	-0.11	0.03	0.043
LDL receptor	LDLreceptor*	-0.09	0.02	0.025	-0.22	0.06	0.016
RGM domain family member B ³	RGMB*3	-0.10	0.02	5.74x10 ⁻⁵	-0.12	0.03	0.045
Interlukin 17 receptor alpha	IL-17RA	-0.12	0.03	0.024	-0.14	0.05	1
Cadherin-6	CDH6	-0.12	0.03	0.0027	0.04	0.02	1
Tissue-type plasminogen activator	tPA*	-0.12	0.02	0.0001	-0.56	0.09	1.94x10 ⁻⁷
TNF-related apoptosis-inducing ligand	TRAIL*	-0.13	0.02	3.64x10 ⁻⁷	-0.17	0.03	1.81x10 ⁻⁵
Vascular endothelial growth factor A	VEGFA	-0.13	0.02	3.99x10 ⁻⁶	-0.12	0.07	1
OX-2 membrane glycoprotein	CD200	-0.14	0.03	6.82x10 ⁻⁸	-0.04	0.04	1
Insulin-like growth factor-binding				0.009	-0.06	0.04	
protein 7 Fibroblast growth factor 19	IGFBP-7	-0.18	0.04	0.000	0.00	0.04	1
Kynureninase	FGF-19	-0.18	0.05	0.009	-0.04	0.09	1
Tyrosine-protein phosphatase non-	KYNU*	-0.19	0.04	0.0007	-0.22	0.06	0.034
receptor type substrate 1	SHPS-1	-0.20	0.05	0.017	-0.08	0.05	1
C-C motif chemokine 19	CCL19	-0.30	0.06	5.86x10 ⁻⁶	-0.06	0.07	1
NKG2D ligand 2	N2DL2	-0.34	0.05	1.74x10 ⁻⁸	-0.09	0.04	1
Aβ+ MCI patients vs. Aβ- controls							
Protein name	Protein abbreviation	CSF Fold change	CSF Std. error	CSF q-value	Plasma Fold change	Plasma Std. error	Plasma
Chitinase 1 (chitotriosidase)1	CHIT11	0.95	0.16		· · · · · · · · · · · · · · · · · · ·		a-value.
Matrix metalloproteinase 10 ²		0.95		0.00-40-7	0.04	0.00	q-value
		0.22		6.08x10 ⁻⁷	-0.04	0.22	1
SPARC-related modular calcium-	MMP10 ²	0.32	0.06	6.08x10 ⁻⁷ 1.16x10 ⁻⁵	-0.04	0.22	
SPARC-related modular calcium- binding protein 2 1.4	MMP10 ² SMOC2 ^{1,4}	0.32					1
binding protein 2 1/4 Turnor necrosis factor receptor 2			0.06	1.16x10 ⁻⁵	-0.02	0.08	1
binding protein 2 ^{1,4} Tumor necrosis factor receptor 2 Ezrin ¹	SMOC21.4	0.29	0.06	1.16x10 ⁻⁵	-0.02	0.08	1 1 0.35
binding protein 2 1/4 Turnor necrosis factor receptor 2	SMOC21.4 TNF-R2	0.29 0.19	0.06 0.05 0.04	1.16x10 ⁻⁵ 1.16x10 ⁻⁵ 3.03x10 ⁻⁵	-0.02 -0.17 -0.15	0.08 0.05 0.07	1 1 0.35 1
binding protein 2 ^{1,4} Turnor necrosis factor receptor 2 Ezrin ¹ Osteopontin GDNF family receptor alpha-1	SMOC2 ^{1,4} TNF-R2 EZR ¹	0.29 0.19 0.13	0.06 0.05 0.04 0.04	1.16x10 ⁻⁵ 1.16x10 ⁻⁵ 3.03x10 ⁻⁵ 0.042	-0.02 -0.17 -0.15 0.03	0.08 0.05 0.07 0.04	1 1 0.35 1 1
binding protein 2 ^{1,4} Tumor necrosis factor receptor 2 Ezrin ¹ Osteopontin	SMOC2 ^{1,4} TNF-R2 EZR ¹ OPN	0.29 0.19 0.13 0.11	0.06 0.05 0.04 0.04 0.03	1.16x10 ⁻⁵ 1.16x10 ⁻⁵ 3.03x10 ⁻⁵ 0.042 0.028	-0.02 -0.17 -0.15 0.03 0.01	0.08 0.05 0.07 0.04 0.07	1 1 0.35 1 1 1 1
binding protein 2 ^{1,4} Turnor necrosis factor receptor 2 Ezrin ¹ Osteopontin GDNF family receptor alpha-1	SMOC214 TNF-R2 EZR1 OPN GFR-alpha-1 Protein	0.29 0.19 0.13 0.11 0.10 CSF	0.06 0.05 0.04 0.04 0.03 0.03 CSF	1.16x10 ⁻⁵ 1.16x10 ⁻⁵ 3.03x10 ⁻⁵ 0.042 0.028 0.034 <i>CSF</i>	-0.02 -0.17 -0.15 0.03 0.01 -0.04 Plasma	0.08 0.05 0.07 0.04 0.07 0.05 Plasma	1 1 0.35 1 1 1 1 1 <i>Plasma</i>
binding protein 2 ^{1,4} Tumor mecrosis factor receptor 2 Ezrin ¹ Osteopontin GDNF family receptor alpha-1 <i>Aft-Mcl patients vs. Aft-controls</i> Protein name	SMOC2 ^{1,4} TNF-R2 EZR ¹ OPN GFR-alpha-1 Protein abbreviation	0.29 0.19 0.13 0.11 0.10 <i>CSF</i> Fold change	0.06 0.05 0.04 0.04 0.03 0.03 CSF Std. error	1.16x10 ⁻⁵ 1.16x10 ⁻⁵ 3.03x10 ⁻⁵ 0.042 0.028 0.034 <i>CSF</i> q-value	-0.02 -0.17 -0.15 0.03 0.01 -0.04 Plasma Fold change	0.08 0.05 0.07 0.04 0.07 0.05 Plasma Std. error	1 1 0.35 1 1 1 1 Plasma q-value
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin ¹ Costeopontin GDNF family receptor alpha-1 <i>Af-: Mol patients vs. Af-controls</i> Protein name Plasminogen activator inhibitor	SMOC2 ¹⁴ TNF-R2 EZR ¹ OPN GFR-alpha-1 Protein abbreviation PAI	0.29 0.19 0.13 0.11 0.10 CSF Fold change 0.24	0.06 0.05 0.04 0.04 0.03 0.03 CSF Std. error 0.05	1.16x10 ⁻⁵ 1.16x10 ⁻⁵ 3.03x10 ⁻⁵ 0.042 0.028 0.034 <i>CSF</i> q-value 0.002	-0.02 -0.17 -0.15 0.03 0.01 0.01 Plasma Fold change 0.36	0.08 0.05 0.07 0.04 0.07 0.05 Plasma Std. error 0.13	1 1 0.35 1 1 1 1 1 <i>Plasma</i> q-value 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezin' Osteopontin GDNF family receptor alpha-1 <i>Afr: MCI patients vs. Afr:</i> controls Protein name Plasminogen activator inhibitor Osteoprotegerin'	SMOC2 ^{1,4} TNF-R2 EZR ¹ OPN GFR-alpha-1 Protein abbreviation PAI OPG ¹	0.29 0.19 0.13 0.11 0.10 CSF Fold change 0.24 0.18	0.06 0.05 0.04 0.03 0.03 0.03 CSF Skt. error 0.05	1.16x10 ⁻⁵ 1.16x10 ⁻⁵ 3.03x10 ⁻⁵ 0.042 0.028 0.028 0.002 0.002 0.004	-0.02 -0.17 -0.15 0.03 0.01 -0.04 Patama Fold change 0.36 0.05	0.08 0.05 0.07 0.04 0.07 0.04 0.07 0.05 Plasma Skt.error 0.13 0.05	1 0.35 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin' Osteopontin GDNF lamily receptor alpha-1 Ap-Mc/ patients vs. Ap- controls Protein name Plasminogen activator inhibitor Osteoprotegerin' NT-5 growth factor receptor	SMOC2 ^{1,4} TNF-R2 EZR ¹ OPN GFR-alpha-1 Protein abbreviation PAI OPG ¹ NTRK3	0.29 0.19 0.13 0.11 0.10 CSF Fold change 0.24 0.18 -0.14	0.06 0.05 0.04 0.04 0.03 0.03 CSF Std. error 0.05 0.05 0.04	1.16x10 ⁻⁵ 1.16x10 ⁻⁵ 3.03x10 ⁻⁵ 0.042 0.028 0.028 0.002 0.002 0.004 0.028	-0.02 -0.17 -0.15 -0.03 -0.04 -0.04 -0.04 -0.04 -0.05 -0.09	0.08 0.05 0.07 0.04 0.07 0.05 Plasma Std. error 0.13 0.05 0.05	1 0.35 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin ¹ Osteopontin GDNF family receptor alpha-1 <i>AB-MCP patients vs. AB-controls</i> Protein name Plasminogen activator inhibitor Osteoprotegarin ¹ NT-3 growth factor receptor RGM domain family member B ¹	SMOC214 TNF-R2 EZR ¹ OPN GFR-alpha-1 Protein abbreviation PAI OPG ¹ NTRK3 RGMB ⁻¹	0.29 0.19 0.13 0.11 0.10 CSF Fold change 0.24 0.18 -0.14 -0.16	0.06 0.05 0.04 0.04 0.03 0.03 0.03 CSF SkL error 0.05 0.05 0.04 0.03	1.16x10* 1.16x10* 3.03x10* 0.042 0.028 0.034 CSF q-value 0.002 0.002 0.004 0.028 0.004 0.028	-0.02 -0.17 -0.15 0.03 0.01 -0.04 Plasma Fold change 0.36 0.05 -0.09 -0.25	0.08 0.05 0.07 0.04 0.05 0.05 0.05 0.05 0.05 0.05	1 1 0.35 1 1 1 1 1 1 1 Pasma Pasma 1 1 1 2 1 1 2 1 1 2 1 1 1 1 2 1 1 1 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin ¹ Obsepontin GDNF family receptor alpha-1 <i>Ag-MCI patients vs. Ag-controls</i> Protein name Plasmingen activator inhibitor Osteoprotegerin ¹ NT-3 growth factor receptor RM domain family member B ¹ Contactin-5	SMOC2 ^{1/4} TNF-R2 EZR ¹ OPN GFR-alpha-1 Protein abbreviation PAI OPG ¹ NTRK3 RGMB ^{1/1} CNTN5	0.29 0.19 0.13 0.11 0.10 CSF Fold change 0.24 0.24 0.18 -0.14 -0.16 -0.17	0.06 0.05 0.04 0.04 0.03 0.03 0.05 0.05 0.05 0.04 0.03	1.16x10* 1.16x10* 3.03x10* 0.042 0.028 0.028 0.028 0.028 0.024 0.022 0.024 0.022 0.024 0.022 0.024 0.026	-0.02 -0.17 -0.15 0.03 0.01 -0.04 Plasma Fold change 0.36 0.05 -0.09 -0.25 -0.14	0.08 0.05 0.07 0.04 0.05 8ds.error 0.13 0.05 0.05 0.05 0.05	1 1 0.35 1 1 1 1 1 Plasma qvalue 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin' Costeopontin GDNF family receptor alpha-1 <i>Af: MCI patients vs. Afg-controlic</i> Protein name Plasminogen activator inhibitor Osteoprotegerin' NT-3 growth factor receptor RGM domain family member B' Contactin-5	SMOC2 ^{1,4} TNF-R2 EZR ¹ OPN GFR-alpha-1 PAI OPG ¹ NTRK3 RGM8 ⁻¹ CNTN5 GCP5	0.29 0.19 0.13 0.11 0.10 0.10 0.10 0.24 0.24 0.18 0.18 0.18 0.16 0.17 0.17	0.06 0.05 0.04 0.04 0.03 0.03 0.05 0.05 0.05 0.05 0.05	1.16x10 ⁴ 1.16x10 ⁴ 3.03x10 ⁴ 0.042 0.034 0.034 0.002 0.004 0.002 0.004 0.0000 0.000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.000	-0.02 -0.17 -0.15 0.03 0.01 -0.04 -0.04 0.36 0.05 0.05 -0.09 -0.25 -0.14 -0.08	0.08 0.05 0.07 0.04 0.07 0.05 81d.error 0.13 0.05 0.05 0.05 0.05 0.07 0.16	1 1 0.35 1 1 1 1 1 Plasma qvalue 1 1 1 2.16x10 ⁴ 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin' Cateoportin GDNF family receptor alpha-1 Af- MCI patients vs. Af-controls Protein name Plasminogen activator inhibitor Costeoprotegerin' NT-3 growth factor receptor RGM domain family member B' Contactin-5 Diraxin	SMOC2 ¹⁴ TNF-R2 EZR ¹ OPN GFR-alpha-1 Protein abbroviation PAI OPG ¹ NTRK3 RGMB ⁴¹ CNTN5 GCP5 DRAXIN	0.29 0.19 0.13 0.11 0.10 CSF Fold change 0.24 0.24 0.18 -0.14 -0.16 -0.17	0.06 0.05 0.04 0.04 0.03 0.03 0.05 0.05 0.05 0.04 0.03	1.16x10* 1.16x10* 3.03x10* 0.042 0.028 0.028 0.028 0.028 0.024 0.022 0.024 0.022 0.024 0.022 0.024 0.026	-0.02 -0.17 -0.15 0.03 0.01 -0.04 Plasma Fold change 0.36 0.05 -0.09 -0.25 -0.14	0.08 0.05 0.07 0.04 0.05 8ds.error 0.13 0.05 0.05 0.05 0.05	1 1 0.35 1 1 1 1 1 Plasma qvalue 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin ¹ Osteopontin GDNF family receptor alpha-1 <i>Als</i> - <i>BdC patients vs. Als</i> -controls Protein name Prasminogen activator inhibitor Osteoportegamin ¹ NT-3 growth factor receptor RGM domain family member B ¹ Contactin-5 Gilypican-5 Drawin Roundabout homolog 2	SMOC2 ^{1,4} TNF-R2 EZR ¹ OPN GFR-alpha-1 PAI OPG ¹ NTRK3 RGM8 ⁻¹ CNTN5 GCP5	0.29 0.19 0.13 0.11 0.10 0.10 0.10 0.24 0.24 0.18 0.18 0.18 0.16 0.17 0.17	0.06 0.05 0.04 0.04 0.03 0.03 0.05 0.05 0.05 0.05 0.05	1.16x10 ⁴ 1.16x10 ⁴ 3.03x10 ⁴ 0.042 0.034 0.034 0.002 0.004 0.002 0.004 0.0000 0.000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.000	-0.02 -0.17 -0.15 0.03 0.01 -0.04 -0.04 0.36 0.05 0.05 -0.09 -0.25 -0.14 -0.08	0.08 0.05 0.07 0.04 0.07 0.05 81d.error 0.13 0.05 0.05 0.05 0.05 0.07 0.16	1 1 0.35 1 1 1 1 1 1 1 Plasma qvalue 1 1 1 2.16x10*6 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin ¹ Osteopontin GDNF family receptor alpha-1 <i>Af-MCI patients vs. Aβ-controls</i> Protein name Plasmingen activator inhibitor Osteoportegorin ¹ NF-3 growth factor receptor RGM domain family member B ¹ Contractin-5 Diraxin Roundabout homolog 2 <i>Af+ controls</i> vs. <i>Af+controls</i>	SMOC2 ¹⁴ TINF-R2 EZR1 OPN GFR-alipha-1 Protein abbreviation PAI OP01 NTRKS RGMB*1 CNTNS GOP5 DRAXIN ROB02	0.29 0.19 0.13 0.11 0.10 CSF Fold charge 0.24 0.18 0.24 0.18 0.14 0.16 0.20	0.06 0.05 0.04 0.03 0.03 0.03 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.04 0.04 0.03 0.04 0.03 0.04 0.03 0.04 0.03 0.04 0.03 0.04 0.03 0.04 0.03 0.04 0.03 0.04 0.03 0.05	1.16x10* 1.16x10* 1.16x10* 0.042 0.028 0.034 0.002 0.004 0.002 0.004 0.0007 0.040 0.0007 0.040	-0.02 -0.17 -0.15 0.03 0.01 -0.04 -0.04 -0.04 0.36 0.05 -0.09 -0.09 -0.14 -0.08 -0.25 -0.14 -0.21 -0.21	0.08 0.05 0.07 0.04 0.07 0.05 7 <i>Plasma</i> 8.04 eror 0.13 0.05 0.05 0.05 0.05 0.05 0.05 0.05	1 1 0.35 1 1 1 1 1 1 1 1 1 1 1 1 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin ¹ Osteopontin GDNF family receptor alpha-1 <i>Als</i> - <i>BdC patients vs. Als</i> -controls Protein name Prasminogen activator inhibitor Osteoportegamin ¹ NT-3 growth factor receptor RGM domain family member B ¹ Contactin-5 Gilypican-5 Drawin Roundabout homolog 2	SMOG2'4 TINF-R2 EZR'1 OPN GFR-alpha-1 Protein abbreviation PAI OPG' NTRK3 RMB** CNTNS GCP6 DRAXIN ROB02 Protein	0.29 0.19 0.13 0.11 0.10 CSF Fold charge 0.24 0.18 0.24 0.18 0.14 0.16 0.20	0.06 0.05 0.04 0.04 0.03 0.03 0.03 0.05 0.05 0.04 0.05 0.05 0.05	1.16x10* 1.16x10* 1.16x10* 0.042 0.028 0.034 0.002 0.004 0.002 0.004 0.0007 0.040 0.0007 0.040	-0.02 -0.17 -0.15 0.03 0.01 -0.04 <i>Plasma</i> <i>Plasma</i> <i>Plasma</i> -0.04 0.036 0.05 0.05 -0.09 -0.25 -0.08 -0.14 -0.08	0.08 0.05 0.07 0.04 0.07 0.05 7 <i>Plasma</i> 8.04 eror 0.13 0.05 0.05 0.05 0.05 0.05 0.05 0.05	1 1 1 0.35 1 1 1 1 1 1 1 Plasma quadue 1 1 2.16x10 ⁴ 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin ¹ Osteopontin GDNF family receptor alpha-1 <i>Af: AfC f patients vs. Aβ-controls</i> Protein name Plasminogen activator inhibitor Osteoportogenri ¹ Ni ² gov/m factor receptor RGM domain family member B ¹ Contactin-5 Oracit Brown Boundabout homolog 2 <i>Af#: controls vs. Af#: controls</i> Protein name	SMOG2 ¹⁴ THF-R2 EZR ¹ OPN GFR-alpha-1 Protein abbreviation PAI OPG ¹ OPG ¹ OPG ¹ OPG ¹ OPG ¹ OPG ² CNTNS GOP5 DRAXIN ROB02 Protein abbreviation	0.29 0.19 0.13 0.11 0.10 CSF Fold change 0.24 0.18 0.24 0.18 0.24 0.18 0.24 0.14 0.14 0.14 0.17 0.20 0.20 0.20 CSF Fold change	0.06 0.05 0.04 0.04 0.03 0.03 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.04 0.03 0.04 0.03 0.03 0.04 0.03 0.03 0.05 0.04 0.03 0.03 0.05 0.04 0.03 0.03 0.05	1.16x10 ⁴ 3.03x10 ⁴ 0.042 0.028 0.034 0.04 0.034 0.04 0.02 0.04 0.04 0.02 0.04 0.04 0.0	-0.02 -0.17 -0.15 0.03 0.04 -0.04 <i>Plasma</i> Fold change -0.05 -0.09 -0.25 -0.09 -0.25 -0.14 -0.08 -0.21 -0.08 Plasma Fold change	0.08 0.05 0.07 0.04 0.07 0.05 Plasma 0.05	1 1 1 1 0.35 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin ¹ Osteopontin GDNF family receptor alpha-1 <i>Af-MCI patients vs. Aβ-controls</i> Protein name Plasmingen activator inhibitor Osteoportegorin ¹ NF-3 growth factor receptor RGM domain family member B ¹ Contractin-5 Diraxin Roundabout homolog 2 <i>Af+ controls</i> vs. <i>Af+controls</i>	SMOC2 ¹⁴ TINF-R2 EZR ¹ OPN dFR-alpha-1 Protein abbreviation PAI OPG ¹ ORKIP ⁴ CNTNS GCP5 DRAXIN ROB02 Protein abbreviation SMOC2 ²	0.29 0.19 0.13 0.11 CSF Fold change 0.24 0.24 0.18 0.18 0.18 0.18 0.18 0.14 0.16 0.17 0.20 0.20 0.23 CSF	0.06 0.05 0.04 0.04 0.03 0.03 0.05 0.05 0.05 0.05 0.05 0.05	1.16x10 ⁴ 3.03x10 ⁴ 3.03x10 ⁴ 0.042 0.028 CSF	-0.02 -0.17 -0.15 0.03 0.04 -0.04 Plasma Fold change 0.05 -0.09 -0.25 -0.09 -0.14 -0.08 -0.21 -0.18 Plasma	0.08 0.05 0.07 0.04 0.07 0.05 Plasma Std. error 0.05 0.07 0.06 0.07	1 1 1 1 0.35 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
binding protein 2 ¹⁴ Tumor necrosis factor receptor 2 Ezrin ¹ Gotseopontin GDNF family receptor alpha-1 <i>Ag-MCI patients vs. Ag-controls</i> Protein name Plasmingen activator inhibitor Osteoprotegerin ¹ NT-3 growth factor receptor GNM domain family member B ¹ Contactin-5 Draxin Roundabout homolog 2 <i>Age-controls vs. Age-controls</i> Protein name SPARC-related modular calcum-binding	SMOG2 ¹⁴ THF-R2 EZR ¹ OPN GFR-alpha-1 Protein abbreviation PAI OPG ¹ OPG ¹ OPG ¹ OPG ¹ OPG ¹ OPG ² CNTNS GOP5 DRAXIN ROB02 Protein abbreviation	0.29 0.19 0.13 0.11 0.10 CSF Fold change 0.24 0.18 0.24 0.18 0.24 0.18 0.24 0.14 0.14 0.14 0.17 0.20 0.20 0.20 CSF Fold change	0.06 0.05 0.04 0.04 0.03 0.03 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.04 0.03 0.04 0.03 0.03 0.04 0.03 0.03 0.05 0.04 0.03 0.03 0.05 0.04 0.03 0.03 0.05	1.16x10 ⁴ 3.03x10 ⁴ 0.042 0.028 0.034 0.04 0.034 0.04 0.02 0.04 0.04 0.02 0.04 0.04 0.0	-0.02 -0.17 -0.15 0.03 0.04 -0.04 <i>Plasma</i> Fold change -0.05 -0.09 -0.25 -0.09 -0.25 -0.14 -0.08 -0.21 -0.08 Plasma Fold change	0.08 0.05 0.07 0.04 0.07 0.05 Plasma 0.05	1 1 1 1 0.35 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1

Red text with asterisk^{*} = Protein is differentially regulated in both plasma and CSF

¹Protein is also differentially regulated in AD-dementia patients

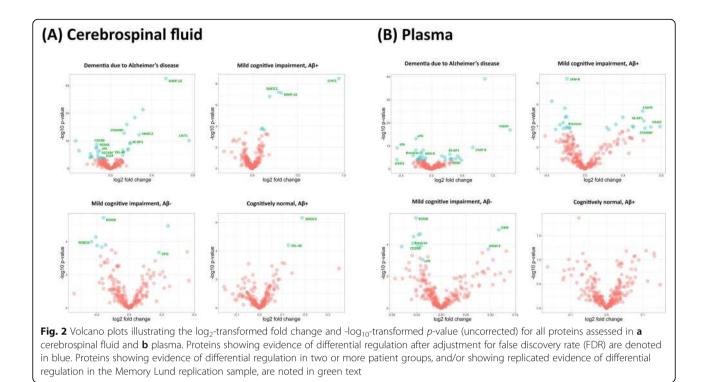
²Protein is also differentially regulated in AB+ MCI patients

³Protein is also differentially regulated in AB- MCI patients

⁴Protein is also differentially regulated in AB+ CN elderly individuals

CSF levels of OPG were increased, and RGMB were decreased, in AD and A β -negative MCI

Compared to A β - CN, CSF concentrations of osteoprotegerin (OPG) were significantly increased in both Aβ- MCI patients (d = 0.23; q = 0.004) and patients with AD (d = 0.2; $q = 3.75 \times 10^{-8}$; see Fig. 1a and Table 2). Aβ- MCI patients also showed significant decreases of repulsive guidance molecule B (RGMB;



d = -0.16; q = 0.0007), which was decreased in AD (d = -0.1; $q = 5.74 \times 10^{-5}$; see Fig. 1a and Table 2). An additional six proteins were differentially regulated in Aβ- MCI patients only (see Fig. 2a and Table 2).

Findings were replicated for eleven proteins in CSF

Altered levels of 11 CSF proteins, as observed in our primary analysis, were replicated in an independent cohort of 179 individuals. In the replication sample, CHIT1 CSF levels were significantly up-regulated in A β + MCI patients (d = 1.16, $p = 4.9 \times 10^{-6}$, unadjusted), Aβ- MCI patients (d = 0.8, p = 0.003, unadjusted), and A β + CN individuals $(d = 1.28, p = 2.63 \times 10^{-5}, \text{ unadjusted})$ compared to Aβ-CN. SMOC2 CSF levels were also increased in AB+ MCI patients (d = 0.4, $p = 2 \times 10^{-3}$, unadjusted) and $A\beta$ - + CN individuals (d = 0.45, $p = 5 \times 10^{-3}$, unadjusted) compared to Aβ- CN. CSF levels of LDL receptor were modestly decreased in A β + MCI patients (d = -0.09, p = 0.049, unadjusted) and A β + CN individuals (d = -0.14, p = 0.007, unadjusted). CSF levels of CD200 were also modestly decreased in A β + MCI patients d = -0.13, p = 0.043, unadjusted) and Aβ- MCI patients (d = -0.15, p = 0.03, unadjusted). Compared to A β - CN, A β + MCI patients showed increased CSF levels of MMP-10 (d = 0.32, p =0.008, unadjusted) and EIF4EBP1 (d = 0.13, p = 0.038, unadjusted), and decreased CSF levels of CD166 antigen (ALCAM; d = -0.12, p = 0.005, unadjusted). Compared to controls, ROBO2 (d = -0.27, p = 0.004, unadjusted) and RGMB protein (d = -0.11, p = 0.049, unadjusted) were decreased in the CSF of Aβ- MCI patients, whereas tissue plasminogen activator (tPA) was decreased (d = -0.2, p = 0.004, unadjusted) and STAM-binding protein (STAMBP) was increased (d = 0.09, p = 0.03, unadjusted) in A β + MCI patients (see Fig. 2a and Additional file 1: Table S7).

Plasma levels of HAGH, SIRT2, CASP8, EIF4EBP1, and IL-8 were increased in AD and A β -positive MCI

Compared to Aβ- CN, five plasma proteins were significantly increased in both AD and Aβ+ MCI patients, including HAGH (d = 0.79 in Aβ+ MCI; d = 1.28 in AD; q < 0.05), sirtuin-2 (SIRT2; d = 0.69 in Aβ+ MCI; d = 0.49 in AD; q < 0.05), caspase 8 (CASP8; d = 0.62 in Aβ+ MCI; d = 0.67 in AD; q < 0.01), EIF4EBP1 (d = 0.51 in Aβ+ MCI; d = 0.32 in Aβ+ MCI; d = 0.3 in AD; q < 0.05), and interleukin-8 (IL-8; d = 0.32 in Aβ+ MCI; d = 0.3 in AD; q < 0.05; see Fig. 1b and Table 3). AD-dementia and Aβ+ MCI patients showed additional increases in two distinct sets of six proteins, as detailed in Table 3.

Plasma levels of JAM-B, brevican, THY-1, RGMB, UNC5C and TRAIL were decreased in AD and A β -positive MCI

AD and A β + MCI patients showed decreases in six plasma proteins, including JAM-B (d = -0.23 in A β + MCI; d = -0.21 in AD; q < 0.001), brevican (d = -0.2 in A β + MCI; d = -0.23 in AD; q < 0.05), thy-1 membrane glycoprotein (THY1; d = --0.19 in A β + MCI; d = -0.13 in AD; $q < 1 \times 10^{-5}$), RGMB (d = -0.19 in A β + MCI; d = -0.12 in AD; q < 0.05), UNC5C (d = -0.16 in A β + MCI; d = -0.11 in AD; q < 0.05), and TRAIL (d = -0.16 in A β + MCI; d = -0.17 in AD; q < 0.05); see Fig. 1b and Table 3.

Table 3 Differentially regulated proteins in human plasma

Alzheimer's dementia vs. Aβ- controls							CSF
Protein name	Protein abbreviation	Plasma Fold change	Plasma Std. error	Plasma q-value	CSF Fold change	CSF Std. error	CSF q-value
Hydroxyacylglutathione hydrolase?	HAGH*2	1.28	0.15	2.86×10-11	N/A	N/A	N/A
Transferrin	TR	0.87	0.06	2.13x10 ⁻³⁷	N/A	N/A	N/A
Caspase 8 ²	CASP8*2	0.67	0.06	1.1x10 ²	0.16	0.02	2.21x10 ⁻¹⁴
Sintuin 2 ²							
C-X-C motif chemokine 6	SIRT22	0.49		0.038	0.05	0.04	1
C-X-C motil chemokine 6 Linker for activation of T cells	CXCL6	0.45		0.004	0.05	0.05	1
Eukaryotic translation initiation factor 4E-	LAT	0.43	0.09	5x10*i	N/A	N/A	N/A
Eukaryotic translation initiation factor 4E- binding protein 1 ²	EIF4EBP1*2	0.39	0.09	0.009	0.19	0.03	9.07×10 ⁻⁰
Oncostatin M ³	OSMP	0.33	0.08	0.006	-0.05	0.02	1
Sulfotransferase 1A1	ST1A1	0.32	0.08	0.016	N/A	N/A	N/A
C-X-C motif chemokine 5	CXCL5	0.32		0.012	-0.06	0.03	1
Interlukin 8²	IL8 ²	0.30	0.06	1x10 ⁻¹	0.11	0.04	0.34
Baar anna ha anna ha anna ha anna an							
Bone morphogenetic protein 4	BMP-4	0.22		0.032	-0.02	0.03	1
Metalloproteinase inhibitor 4 Latexin	TIMP4	0.22	0.05	0.002	-0.10	0.03	0.62
	LXN	0.17	0.04	6x10 ⁻⁴	N/A	N/A	N/A
Retinoic acid receptor responder protein 2	RARRES2	-0.09		0.034	-0.03	0.04	1
Netrin receptor UNC5C ²	UNC5C*2	-0.11	0.03	0.043	-0.09	0.02	0.026
RGM domain family member B ^{2.5}	RGMB*2,3	-0.12	0.03	0.045	-0.10	0.02	5.74x10 ⁻⁵
Thy-1 membrane glycoprotein	THY1	-0.13	0.02	1.49x10 ⁻⁶	0.00	0.01	1
Perlecan	PLC	-0.14		0.001	-0.02	0.03	1
Fms-related tyrosine kinase 3 ligand	Fit3L	-0.17	0.04	0.0029	0.04	0.02	1
lunction adhesion molecule B ^{2,3}	JAM-R*23	-0.17	0.04	4.11x10 ⁻⁶	-0.05	0.02	0.044
NF-related apoptosis-inducing ligand ^{2,3}	TRAIL*2.0						
NF-related apoptosis-inducing ligand** SPARC-related modular calcium-binding	(RAIL ^{-2,0}	-0.17	0.03	1.81x10 ⁻⁶	-0.13	0.02	3.64×10 ⁻⁷
rotein 2	SMOC2*	-0.18	0.04	0.002	0.28	0.04	1.09x10 ⁻¹⁰
Matrix extracellular phosphoglycoprotein	MEPE	-0.19	0.05	0.012	N/A	N/A	N/A
Brevican core protein ^a	BCAN ^{2,3}	-0.20		0.001	-0.02	0.01	1
Kynureninase	KYNU*	-0.20	0.04	0.034	-0.02	0.04	0.00076
.DL receptor	KYNU*			0.034		0.04	
	cocreeptor	-0.22	0.06		-0.09		0.025
Protein delta homolog 1	DLK1	-0.23		0.02	-0.04	0.02	1
Urokinase-type plasminogen activator	uPA ³	-0.25	0.03	1.43x10 ⁻¹¹	0.04	0.02	1
Kallikrein-6	KLK6	-0.25		2.24x10 ⁺⁶	-0.07	0.02	0.051
INF-related activation-induced cytokine3	TRANCE ³	-0.30	0.06	3x10-4	N/A	N/A	N/A
Tissue-type plasminogen activator	tPA*	-0.56	0.09	1.94x10-7	-0.12	0.02	0.0001
Axin-1	AXIN1	-0.57	0.14	0.02	N/A	N/A	N/A
Aβ+ MCI patients vs. Aβ- controls							
Protein name	Protein	Plasma	Plasma	Plasma	CSF	CSF	CSF
	abbreviation	Fold change	Std. error	q-value	Fold change	Std. error	q-value
Hydroxyacylglutathione hydrolase1	HAGH ¹	0.79	0.20	0.027	N/A	N/A	N/A
Sirtuin 21	SIRT21	0.69	0.18	0.029	0.03	0.05	1
STAM-binding protein	STAMBP	0.63	0.17	0.037	0.06	0.02	1
Caspase 81					0.00	0.02	1
,	CASP8 ¹	0.62	0.15	0.008	0.00	0.03	1
Platelet-derived growth factor alpha	CASP8 ¹ PDGFsubunitA	0.62	0.15	0.008	0.00	0.03	
Platelet-derived growth factor alpha Eukaryotic translation initiation factor 4E- binding protein 11	CASP8 ¹	0.62	0.15	0.008	0.00 0.04 -0.02	0.03 0.02 0.04	1
Platelet-derived growth factor alpha Lukaryosic translation initiation factor 4E- inding protein 11 Caspase 3	CASP8 ¹ PDGFsubunitA	0.62	0.15	0.008	0.00	0.03	1
Platelet-derived growth factor alpha Lukaryosic translation initiation factor 4E- inding protein 11 Caspase 3	CASP8 ¹ PDGFsubunitA EIF4EBP1 ¹	0.62 0.61 0.51	0.15 0.13 0.13	0.008 0.001 0.029	0.00 0.04 -0.02	0.03 0.02 0.04	1 1 1
Platelet-derived growth factor eipha Licanotic transition initiation factor 4E- kinding protein 1 ¹ Caspase 3 C-X-C motif chemokine 1	CASP8 ¹ PDGFsubunitA EIF4EBP1 ¹ CASP3	0.62 0.61 0.51 0.50	0.15 0.13 0.13 0.13	0.008 0.001 0.029 0.025	0.00 0.04 -0.02 N/A	0.03 0.02 0.04 N/A	1 1 1 N/A
Platviet-derived growth factor alpha Lawyofic translation initiation factor 4E- inding protein 11 Zaspase 3 2-X-C motif chemokine 1 Interfukin 81	CASP81 PDGFsubunitA EIF4EBP11 CASP3 CXCL1 IL81	0.62 0.61 0.51 0.50 0.40 0.32	0.15 0.13 0.13 0.13 0.09	0.008 0.001 0.029 0.025 0.004 0.017	0.00 0.04 -0.02 N/A 0.08 0.11	0.03 0.02 0.04 N/A 0.06 0.05	1 1 1 N/A 1 1
Nadeket-derived growth factor alpha Example: translation instation factor 4E- ixeding protein 11 Saspase 3 2-X-C motif chemokine 1 metrukin 8 ¹ Sicomych hydrolase Euror necrosis factor receptor	CASP8 ¹ PDGFsubunitA EIF4EBP1 ¹ CASP3 CXCL1 IL8 ¹ BLM-H	0.62 0.61 0.51 0.50 0.40 0.32 0.25	0.15 0.13 0.13 0.13 0.09 0.08	0.008 0.001 0.029 0.025 0.004 0.017 0.049	0.00 0.04 -0.02 N/A 0.08 0.11 N/A	0.03 0.02 0.04 N/A 0.06 0.05 N/A	1 1 1 1 1 1 1 1 1 1 1 1 1 N/A 1 1 N/A
Statest-clerived growth factor alpha Sharpeto transition initiation factor 45- olding predict 1: Sapase 3 2:X-C motif chemokine 1 merfukin 8 ¹ Socrinych hydrolase fumor mecrosile factor receptor updrafinity mercelie 14	CASP81 PDGFsubunitA EIF4EBP11 CASP3 CXCL1 IL81	0.62 0.61 0.51 0.50 0.40 0.32	0.15 0.13 0.13 0.13 0.09 0.08 0.06	0.008 0.001 0.029 0.025 0.004 0.017	0.00 0.04 -0.02 N/A 0.08 0.11 N/A -0.05	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03	1 1 1 N/A 1 1
standard-derived growth factor alpha Linarysic transition initiation factor eE- anarysic anarysis initiation factor eE- asspace 3 Scorp, ch hydrolase Unicor energies factor receptor updatrafy member 14 eterin receptor UNCSC1	CASP8 ¹ PDGFsubunitA EIF4EBP1 ¹ CASP3 CXCL1 IL8 ¹ BLM-H	0.62 0.61 0.51 0.50 0.40 0.32 0.25	0.15 0.13 0.13 0.13 0.09 0.08	0.008 0.001 0.029 0.025 0.004 0.017 0.049	0.00 0.04 -0.02 N/A 0.08 0.11 N/A	0.03 0.02 0.04 N/A 0.06 0.05 N/A	1 1 1 1 1 1 1 1 1 1 1 1 1 1 N/A 1 1 N/A
Natalek-derived growth factor spha Linknystic translation instation factor de- weigh protein 11 Satapase 3 2-2-4C- notif chemokine 1 metrikkin 81 Umore menosie factor recoptor uppetfamily member 14 Vetrin recoptor UNCSC ¹ TNF-estated appropriorihoutorg ligand ⁻³	CASP8 ¹ PDGFsubunitA EIF4EBP1 ¹ CASP3 CXCL1 IL8 ¹ BLM-H TNFRSF14	0.62 0.61 0.50 0.40 0.32 0.25 0.23	0.15 0.13 0.13 0.13 0.09 0.08 0.06	0.008 0.001 0.029 0.025 0.004 0.017 0.049 0.032	0.00 0.04 -0.02 N/A 0.08 0.11 N/A -0.05	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Natalek-derived growth factor spha Linknystic translation instation factor de- weigh protein 11 Satapase 3 2-2-4C- notif chemokine 1 metrikkin 81 Umore menosie factor recoptor uppetfamily member 14 Vetrin recoptor UNCSC ¹ TNF-estated appropriorihoutorg ligand ⁻³	CASP81 PDGFsubunitA EIF4E8P11 CASP3 CXCL1 IL81 BLM-H TNFRSF14 UNC5C1	0.62 0.61 0.51 0.50 0.40 0.32 0.25 0.23 -0.16	0.15 0.13 0.13 0.13 0.09 0.08 0.06 0.06	0.008 0.001 0.029 0.025 0.004 0.017 0.049 0.032 0.032	0.00 0.04 -0.02 N/A 0.08 0.11 N/A -0.05 -0.05	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Naterie-derived growth factor option catalogies transmiss instants factor ex- ercised growth 1 ⁻¹ Statistics 3 - Statistics 3 - Statistics 4	CASP81 PDGFsubunitA EIF4E8P11 CASP3 CXCL1 IL81 BLM-H TNFRSF14 UNC5C1 TRAIL ^{1,3}	0.62 0.61 0.51 0.50 0.40 0.32 0.25 0.23 -0.16 -0.16	0.15 0.13 0.13 0.13 0.09 0.08 0.06 0.06 0.04 0.04	0.008 0.001 0.029 0.025 0.004 0.017 0.049 0.032 0.034 0.034	0.00 0.04 -0.02 N/A 0.08 0.11 N/A -0.05 -0.05 -0.03	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Andrewski skriger og sovih filestor regener unangeste translation instanton faktor «K- regenerit» (K- Skorgenetit) filestore Korkongen filestore Korkongenetitisken (K- Korkongenetitisken) Korkongenetitisken Korkon	CASP81 PDGFsubunitA EIF4E8P11 CASP3 CXCL1 IL81 BLM-H TNFRSF14 UNCSC1 TRAIL13 CTSZ THY11	0.62 0.61 0.51 0.50 0.40 0.32 0.25 0.23 -0.16 -0.16 -0.19 -0.19	0.15 0.13 0.13 0.13 0.09 0.06 0.06 0.04 0.04 0.05 0.03	0.008 0.001 0.029 0.025 0.004 0.017 0.049 0.032 0.034 0.034 0.034 0.034 0.028	0.00 0.04 -0.02 N(A 0.08 0.11 N(A -0.05 -0.05 -0.05 -0.05 -0.06 0.01	0.03 0.02 0.04 N/A 0.06 0.05 0.05 0.03 0.03 0.03 0.03 0.03 0.03	1 1 1 1 N/A 1 1 N/A 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
alarske derived growth factor rights alarsyste: transition factor sights (e.g. centr) ¹ 24593858 3 24502 centr) factor f	CASP81 PDGFsubunitA EIF4E8P11 CASP3 CXCL1 IL81 BLM-H TNFRSF14 UNCSC1 TRAIL ¹³ CTS2 CTS2 THY11 RGM813	0.62 0.61 0.51 0.50 0.40 0.32 0.25 0.23 -0.16 -0.16 -0.19 -0.19 -0.19	0.15 0.13 0.13 0.13 0.09 0.08 0.06 0.04 0.04 0.05 0.03 0.04	0.008 0.001 0.029 0.025 0.004 0.017 0.049 0.032 0.034 0.034 0.034 0.028 9.63×10 ⁻⁷ 0.063	0.00 0.04 -0.02 N/A 0.08 0.11 N/A -0.05 -0.05 -0.05 -0.06 0.01 -0.06	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Nadaéé-derived growth factor alpha Linkrysis: transition initiation factor 4E- ostig portain 1 ⁻¹ Zaspase 3 2-X-C motil chemokine 1 Initiankan 8 ⁻¹ Stormych hydrolase Turror mecrosais factor receptor updartanity mombar 14 Lettrin receptor UNSCS ⁻¹ NFF-elabet approxis-inducing ligand ¹²	CASP81 PDGFsubuniA EIF4EBP11 CASP3 CXCL1 IL81 BLMH TNFRSF14 UNCSC1 TRAIL ¹³ CTSZ TRAIL ¹³ IL188P	0.62 0.61 0.51 0.50 0.40 0.32 0.25 0.25 0.23 -0.16 -0.19 -0.19 -0.19 -0.19 -0.19	0.15 0.13 0.13 0.13 0.09 0.06 0.06 0.04 0.05 0.03 0.04 0.05	0.008 0.001 0.029 0.025 0.004 0.017 0.049 0.032 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034	0.00 0.04 -0.02 NIA 0.08 0.11 NIA -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.02	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03 0.0	1 1 1 1 1 N/A 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Analysis of the second	CASP61 PDGFaubuniA EIF4E8P11 CASP3 CXCL1 IL81 BUMH TNFRSF14 UNCSC1 TRAIL ¹³ CTS2 THY11 RGM81 ³ IL188P CCS8	0.62 0.61 0.51 0.50 0.40 0.32 0.25 0.23 -0.16 -0.19 -0.19 -0.19 -0.19 -0.19 -0.20	0.15 0.13 0.13 0.13 0.09 0.06 0.06 0.04 0.04 0.05 0.04 0.05 0.05	0.006 0.001 0.029 0.025 0.004 0.017 0.017 0.049 0.034 0.034 0.034 0.034 0.028 9.63×10 ⁻⁷ 0.003 0.036 0.004	0.00 0.04 -0.02 NIA 0.08 0.11 NIA -0.05 -0.05 -0.05 -0.05 -0.05 -0.06 0.01 -0.08 0.01 -0.08	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03 0.0	1 1 1 1 N/A 1 1 N/A 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Analysis of the second	CASP61 PDCFsubuntA EIF4E8P11 CASP3 CXCL1 IL81 BLMAH TNFRSF14 UNCSC ¹ TRAIL ³ CTSZ TR41 ³ RCMB ¹³ LL188P COS8 JAM4B ¹³	0.62 0.61 0.51 0.50 0.40 0.32 0.25 0.23 -0.16 -0.19 -0.19 -0.19 -0.19 -0.20 -0.20 -0.20	0.15 0.13 0.13 0.13 0.09 0.08 0.06 0.04 0.04 0.04 0.04 0.04 0.05 0.05 0.05	0.006 0.001 0.029 0.025 0.004 0.017 0.032 0.034 0.034 0.034 0.034 0.034 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036	0.00 0.04 -0.02 NIA 0.08 0.11 -0.05 -0.05 -0.05 -0.06 0.01 -0.06 0.01 -0.01 -0.01 -0.02	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03 0.0	1 1 1 1 N/A 1 1 1 N/A 1 1 1 1 1 1 1 1 0.770 1 0.513 1
Nateried-Animed provih factor rights adaptation transferm instantin factor rights adaptation transferm instanting transferming and transferming and transferming Recompleting and transferming and transferming Recompleting and transferming and transferming Recompleting a	CASP61 PDCFsuburitA EIF4E8P11 CASP3 CXCL1 IL61 ELMAH TNFRSF14 UNCSC1 TRAIL13 CTSZ TRAIL13 CTSZ TRAIL13 RGMB13 IL168P CD39 JUANB13 BCAN19	0.62 0.61 0.61 0.51 0.40 0.40 0.32 0.25 0.23 0.23 0.23 0.21 0.19 0.19 0.19 0.19 0.20 0.22	0.15 0.13 0.13 0.13 0.09 0.06 0.04 0.04 0.05 0.04 0.05 0.05 0.05 0.05	0.008 0.001 0.029 0.025 0.001 0.004 0.017 0.049 0.032 0.034 0.034 0.034 0.035 9.63x10*7 0.003 0.036 0.036 0.003 0.036 0.004	0.00 0.04 -0.02 NIA 0.08 0.011 -0.05 -0.05 -0.05 -0.05 -0.05 -0.06 0.01 -0.08 0.01 -0.08 -0.01 -0.02 -0.03 -0.05 -	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03 0.0	1 1 1 1 N/A 1 1 1 1 1 1 1 1 1 1 1 1 1 0.770 1 0.513 1 1 1
Analosi de devined provéh factor rephra Lasargoto: transmon misitan factor de la conservation de la conservation de la conservation la conservation de la conservation de la conservation de la conservation la conservation de la conserv	CASP61 PDDFpbbmtA EIF4E8P11 CASP3 CXXL1 L8 ¹¹ BLM41 TNFR8F14 UNCSC ¹ UNCSC ¹ TXRL ¹³ CTSZ CTSZ CTSZ CTSZ CTSZ L158P ROM9 ¹³ L158P BCAN ¹³ L158P	0.62 0.61 0.51 0.50 0.40 0.32 0.25 0.23 0.25 0.10 0.10 0.10 0.19 0.19 0.20 0.20 0.21 0.22 0.22 0.22	0.15 0.13 0.13 0.13 0.09 0.08 0.04 0.04 0.04 0.04 0.04 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.06 0.06 0.06 0.06	0.008 0.001 0.029 0.025 0.027 0.049 0.032 0.034 0.035 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.037 0.038 0.039	0.00 0.04 -0.02 NA 0.08 0.01 NVA -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.03 -0.06 0.01 -0.06 0.01 -0.01 -0.01 -0.01 -0.02 -0.01 -0.02 -0.03 -0.03 -0.05 -0.0	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03 0.0	1 1 1 1 1 N/A 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 0.770 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
natural-darined growth flector sights alicitarystic transition factor galant (Con- stratuses) and alicitary of the second stratuses of the second second second second second second transmission (Constratus) and the second	CASP61 PDDFsbbmtA EIF4E8P11 CASP3 CXCL1 IL81 BLMH TNFRSF14 UNCSC ¹ TRALL ³ CTSZ THY11 RGM8 ⁻³ L188P CCS8 UAK9 ⁻³ BCAN ³ BCAN ³	0.62 0.61 0.61 0.50 0.40 0.32 0.25 0.23 -0.16 -0.16 -0.19 -0.20 -0.20 -0.22 -0.22 -0.28	0.15 0.13 0.13 0.13 0.09 0.06 0.04 0.04 0.05 0.04 0.05 0.05 0.05 0.05	0.008 0.001 0.029 0.025 0.026 0.017 0.049 0.032 0.034 0.034 0.034 0.034 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036	0.00 0.04 -0.02 NIA 0.08 0.011 -0.05 -0.05 -0.05 -0.05 -0.05 -0.06 0.01 -0.08 0.01 -0.08 -0.01 -0.02 -0.03 -0.05 -	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03 0.0	1 1 1 1 N/A 1 1 1 N/A 1 1 1 1 1 1 1 1 1 0.513 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Analysis Charles Parkin (Second Parkin) Analysis Charles Parkins (Second Parkin) Networks (Second Charles Parkin) Networks (Second Charles Parkin) Networks (Second Charles Parkin) Networks (Second Parkin) Networks (Secon	CASP61 PDDFpbbmtA EIF4E8P11 CASP3 CXXL1 L8 ¹¹ BLM41 TNFR8F14 UNCSC ¹ UNCSC ¹ TXRL ¹³ CTSZ CTSZ CTSZ CTSZ CTSZ L158P ROM9 ¹³ L158P BCAN ¹³ L158P	0.62 0.61 0.51 0.50 0.40 0.32 0.25 0.23 0.25 0.10 0.10 0.10 0.19 0.19 0.20 0.20 0.21 0.22 0.22 0.22	0.15 0.13 0.13 0.13 0.09 0.08 0.04 0.04 0.04 0.04 0.04 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.06 0.06 0.06 0.06	0.008 0.001 0.029 0.025 0.027 0.049 0.032 0.034 0.035 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.037 0.038 0.039	0.00 0.04 -0.02 NA 0.08 0.01 NVA -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.03 -0.06 0.01 -0.06 0.01 -0.01 -0.01 -0.01 -0.02 -0.01 -0.02 -0.03 -0.03 -0.05 -0.0	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03 0.0	1 1 1 1 1 N/A 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 0.770 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
And an experimentation of the provide analysis of transform mitation factor spin- electronic and the provide analysis of the provide and the provide and the provide and the provide analysis of the provide analysis	CASP61 PDDFsbbmtA EIF4E8P11 CASP3 CXCL1 IL81 BLMH TNFRSF14 UNCSC ¹ TRALL ³ CTSZ THY11 RGM8 ⁻³ L188P CCS8 UAK9 ⁻³ BCAN ³ BCAN ³	0.62 0.61 0.61 0.50 0.40 0.32 0.25 0.23 -0.16 -0.16 -0.19 -0.20 -0.20 -0.22 -0.22 -0.28	0.15 0.13 0.13 0.13 0.09 0.08 0.04 0.04 0.04 0.04 0.04 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.06 0.06 0.06 0.06	0.008 0.001 0.029 0.025 0.026 0.017 0.049 0.032 0.034 0.034 0.034 0.034 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036	0.00 0.04 -0.02 NA 0.08 0.01 NVA -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.03 -0.06 0.01 -0.06 0.01 -0.01 -0.01 -0.01 -0.02 -0.01 -0.02 -0.03 -0.03 -0.05 -0.0	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03 0.0	1 1 1 1 N/A 1 1 1 N/A 1 1 1 1 1 1 1 1 1 0.513 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
And a second sec	CASP6 ¹ PDDFpsbunkA EIF4E8P1 ¹ CASP3 CXCL1 TNFRSFH4 UNCSC ¹ UNCSC ¹ TRAIL ¹³ CTSZ TRAIL ¹³ CTSZ TRAIL ¹³ CTSZ TRAIL ¹³ CTSZ CD38 UNCSC ¹ UNCSC ¹ ROMB ¹³ UNCSC ¹ ROMB ¹³ ROMB ¹³ UNCSC ¹ ROMB ¹³ ROMB ¹³ ROMB ¹³ UNCSC ¹ ROMB ¹³ ROMB ¹³ R	0.62 0.61 0.61 0.50 0.40 0.32 0.25 0.25 0.23 0.23 0.23 0.21 0.21 0.23 0.23 0.23 0.23 0.23 0.23 0.23 0.23	0.15 0.13 0.13 0.13 0.09 0.06 0.04 0.04 0.05 0.03 0.04 0.05 0.05 0.04 0.06 0.05 0.04 0.06 0.06 0.06 0.06 0.09 0.04 0.09 0.05 0.09 0.04 0.05 0.05 0.05 0.05 0.05 0.04 0.05 0.07 0.05 0.05 0.07 0.05 0.05 0.07 0.05 0.05 0.07 0.05 0.05 0.07 0.05 0.07 0.05 0.07 0.05 0.05 0.07 0.07 0.07 0.05 0.07 0.07 0.07 0.05 0.07	0.008 0.001 0.001 0.029 0.028 0.004 0.017 0.049 0.034 0.034 0.034 0.034 0.038 9.88x109* 0.036 0.036 0.036 0.037 0.037 0.017	0.00 0.04 -0.02 NIA 0.08 0.11 NIA -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.01 -0.02 -0.01 -0.02 -0.01 NIA NIA NIA NIA NIA NIA NIA NIA NIA NIA	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03 0.0	1 1 1 1 N/A 1 1 N/A 1 1 1 1 1 1 1 1 1 0.770 1 0.513 1 1 1 1 1 1 N/A 0.87
Animal and animal provint fination factor approach analysis: contraction fination factor approach analysis: contraction fination analysis: contraction analysis: contref contrection contraction contraction contractio	CASP61 PDGFpsbunkA EIF4E8P11 CASP3 CXCL1 EIF4E911 CXCL1 EIF4 EIF4 CXCL1 TNFRSF14 UNCSC ¹ TNFRSF14 UNCSC ¹ TRAIL ⁹ CTS2 CTS2 CTS2 CTS2 THY11 RGM8 ³ EL68P8 EICAN ³ EL68PA EICAN ³ EI68PA EICAN ³ EI68PA EICAN ³ EI68PA	0.62 0.61 0.51 0.40 0.32 0.25 0.23 0.25 0.21 0.25 0.23 0.25 0.21 0.21 0.23 0.25 0.21 0.23 0.25 0.20 0.20 0.20 0.22 0.22 0.22 0.23 0.22 0.23 0.22 0.23 0.25 0.20 0.20 0.20 0.20 0.20 0.25 0.20 0.25 0.20 0.25 0.25	0.15 0.13 0.13 0.09 0.06 0.06 0.04 0.04 0.05 0.03 0.04 0.05 0.05 0.05 0.05 0.06 0.06 0.06 0.07 Plasma	0.000 0.000 0.001 0.025 0.004 0.017 0.032 0.034 0.032 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.003 0.008 0.006 0.006 0.006 0.006 0.007 0.011 0.018 0.01 0.01	0.00 0.04 -0.02 NA 0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.01 -0.01 -0.01 -0.01 -0.01 -0.01 -0.01 -0.01 -0.01 -0.01 -0.02 -0.05	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03 0.0	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
An and a second	CASP81 PDDFpibbrik EIF4E8P11 CASP3 CXCL1 BL/AH UNCSO ¹ TRAL ¹³ CTSZ TRAL ¹³ CTSZ CTSZ CTSZ CTSZ CTSZ CTSZ CTSZ CTSZ	0.62 0.61 0.61 0.40 0.40 0.42 -0.16 0.28 -0.16 -0.19 -0.19 -0.19 -0.19 -0.19 -0.20 -0.20 -0.20 -0.20 -0.20 -0.23 -0.23 -0.23 -0.23 -0.23 -0.23 -0.23 -0.23 -0.23 -0.23 -0.23 -0.23 -0.23 -0.25 -0.23 -0.25 -	0.15 0.13 0.13 0.13 0.09 0.06 0.06 0.04 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.05 0.04 0.05 0.05 0.04 0.05	0.008 0.009 0.009 0.029 0.025 0.004 0.017 0.04 0.032 0.034 0.034 0.034 0.038 0.038 0.038 0.038 0.038 0.038 0.038 0.038 0.038 0.038 0.038 0.038 0.031 0.018 0.01 0.01	0.00 0.04 -0.02 N/A 0.08 0.11 -0.08 -0.08 -0.08 -0.08 -0.06 -0.03 -0.06 -0.03 -0.06 -0.01 -0.02 -0.01 -0.07 N/A -0.07	0.03 0.02 0.04 N/A 0.06 0.05 N/A 0.03 0.03 0.03 0.03 0.03 0.03 0.03 0.0	1 1 1 1 N/A 1 1 1 1 1 1 1 1 1 1 1 1 1 1 0.513 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Verbein-derived growth fielder alphae autasyste: truncation fistation factor alphae autasyste: truncation fistation factor alphae autasyste: truncation fistation fistation truncation fistation fistation truncation fistation fistation automation fistation fistation automation fistation fistation fistation fistation fistation fistation automation fistation fistation automation fistation fistation fistation automation fistatio	CASP8 ¹ PPOGFactoreAnnot EIF4E8P11 CASP3 CASP3 CASP3 ELAP1 BLAP1 BLAP1 TNFR8F14 UNC50 ⁻¹ TTARL ¹⁻³ CT52 CT52 TTARL ¹⁻³ CT52 CT52 CT52 CT52 CT52 CT52 CT52 CT52	0.62 0.81 0.65 0.40 0.25 0.25 0.25 0.23 0.23 0.23 0.23 0.23 0.23 0.20 0.20	0.15 0.13 0.13 0.09 0.06 0.06 0.04 0.04 0.04 0.05 0.03 0.04 0.05 0.05 0.05 0.05 0.06 0.06 0.06 0.07 Phasma Sid. error	0.009 0.009 0.029 0.029 0.024 0.024 0.049 0.049 0.049 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.035 0.034 0.034 0.035 0.034 0.035 0.034 0.035 0.034 0.034 0.035 0.034 0.035 0.034 0.035 0.034 0.034 0.035 0.034 0.034 0.035 0.034 0.034 0.035 0.034 0.035 0.034 0.035 0.034 0.035 0.034 0.035 0.034 0.035 0.035 0.034 0.035 0.035 0.035 0.034 0.035 0.036 0.036 0.035 0.036 0.037 0.049 0.049 0.049 0.049 0.056 0.049 0.049 0.049 0.049 0.049 0.049 0.049 0.049 0.049 0.049 0.049 0.040 0.040 0.041 0.041 0.041 0.041 0.041 0.047 0.	0.00 0.04 -0.02 NiA 0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.06 0.01 -0.17 -0.08 -0.01 -0.01 -0.01 -0.01 -0.01 -0.01 -0.01 -0.02 -0.02 -0.02 -0.05 -0.02 -0.05 -0.02 -0.05	0.03 0.02 0.04 N/A 0.06 0.06 0.05 0.03 0.03 0.03 0.03 0.03 0.03 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Andrei-Animed provih factor aphra abargetic trustees instants factor aphra abargetic trustees instants factor aphra abargetic aphrane in the secondaria of productions of trustees in the secondaria of the secondaria of the secondaria of the secondaria of the secondaria of the se	CASP91 PDGFsbberkA EIF4EBP11 CASP3 CXCL1 L8 ¹ TNFRSF14 UNCSC ¹ TRALL ¹³ CTSZ CTSZ TRAL ¹³ CTSZ CTSZ CTSZ L188P CC00 BCAN ¹⁰ BCAN ¹⁰	0.62 0.61 0.51 0.60 0.32 0.32 0.55 0.33 0.55 0.51 0.51 0.51 0.51 0.51 0.51 0.51	0.15 0.13 0.13 0.09 0.00 0.06 0.04 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.06 0.05 0.04 0.06 0.05 0.04 0.06 0.05 0.07 0.05 0.07 0.07 0.07 0.07 0.07 0.05 0.07 0.05 0.07 0.07 0.07 0.05 0.07 0.05 0.07 0.07 0.07 0.05 0.07 0	0.006 0.001 0.029 0.029 0.004 0.077 0.049 0.032 0.049 0.032 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.035 0.004 0.003 0.006 0.004 0.005 0.006 0.005 0.005 0.005 0.004 0.029 0.029 0.040 0.040 0.029 0.040 0.040 0.040 0.040 0.040 0.029 0.040 0.040 0.040 0.040 0.040 0.040 0.040 0.040 0.040 0.040 0.040 0.040 0.040 0.040 0.040 0.040 0.040 0.050 0.040 0.050 0.040 0.050 0.040 0.050 0.040 0.050 0.040 0.050 0.040 0.050 0.050 0.050 0.040 0.050 0.050 0.050 0.050 0.040 0.0500 0.0500 0.0500 0.0500000000	0.00 0.04 -0.02 NiA 0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.01 -0.01 -0.01 -0.02 -0.02 -0.02 -0.02 -0.02 -0.02 -0.02 -0.02 -0.02 -0.02 -0.04 -0.05	0.03 0.02 0.04 0.04 0.06 0.05 0.03 0.04 CSF CSF Sci. error 0.04	1 1 1 1 NA 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Andreie-Jehrind growth factor aphra Langrote: truttation factor aphra langrote: trut	CASPS ¹ PPOFFactorial EIF4E8P ¹ CXSP3 CXSL1 EIF4E8P ¹ CXSL1 EIF4 EIF4 EIF4 UNCSC ¹ TTARL ¹³ CTSZ CTSZ CTSZ CTSZ CTSZ CTSZ CTSZ CTSZ	0.42 0.41 0.51 0.40 0.32 0.32 0.33 0.34 0.40 0.41 0.41 0.41 0.41 0.41 0.41 0.4	0.15 0.13 0.13 0.13 0.09 0.09 0.09 0.06 0.04 0.04 0.04 0.04 0.04 0.05 0.04 0.05 0.04 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.06 0.05 0.13 0.13	0.009 0.001 0.029 0.029 0.029 0.029 0.049 0.049 0.049 0.049 0.049 0.034 0.035 0.036 0.036 0.036 0.036 0.036 0.036 0.037 0.036 0.037 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.037 0.036 0.037 0.017 0.017 0.017 0.017 0.017 0.017 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.018 0.004 0.018 0.018 0.018 0.004 0.018 0.018 0.004 0.018 0.004 0.018 0.004 0.004 0.018 0.004 0.004 0.004 0.004 0.004 0.005 0.004 0.005 0.	0.00 0.04 0.02 0.04 0.05 0.05 0.05 0.05 0.05 0.00 0.01 0.06 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.000000	0.03 0.02 0.04 0.04 0.05 0.05 0.05 0.03 0.03 0.03 0.03 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Anterestantia growth field regions anterpret function factor affect approver 11 anterpret function factor affect approver 11 anterpret function factor affect approver 11 anterpret for anterpret for anterpret factor affect approver 11 anterpret for anterpret for anterpret factor affect approver 11 anterpret for anterpret for anterpret factor affect approver 11 anterpret factor affect approver 11 anterpret factor approver 11 anterpret for approver 11 anterpret factor approver	CASP9 ¹ PPOFINATIONEL EIF4E8P11 CSSP3 CSC31 EILAP1 EILAP1 EILAP1 EILAP1 EILAP1 EILAP1 EILAP1 EILAP1 EILAP1 CSSP3 CSSP1 EILAP3 E	0.62 0.81 0.81 0.60 0.40 0.32 0.32 0.25 0.23 0.23 0.23 0.23 0.23 0.23 0.23 0.23	0.15 0.13 0.13 0.03 0.06 0.06 0.06 0.06 0.05 0.05 0.05 0.05	0.009 0.009 0.029 0.029 0.029 0.04 0.049 0.049 0.049 0.032 0.034 0.035 0.034 0.034 0.034 0.035 0.034 0.034 0.035 0.034 0.035 0.034 0.035 0.034 0.035 0.034 0.035 0.036 0.036 0.036 0.036 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.037 0.036 0.037 0.037 0.037 0.031 0.037 0.031 0.037 0.031 0.037 0.017 0.017 0.017 0.036 0.036 0.036 0.037 0.017 0.017 0.017 0.017 0.017 0.017 0.018 0.017 0.018 0.019 0.019 0.018 0.019 0.019 0.019 0.018 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.003 0.019 0.019 0.003 0.019 0.003 0.019 0.019 0.003 0.019 0.003 0.019 0.003 0.019 0.005 0.005 0.019 0.005 0.005 0.005 0.011 0.005 0.0	0.00 0.04 0.02 0.02 0.03 0.01 0.05 0.05 0.05 0.05 0.01 0.05 0.01 0.01	0.03 0.02 0.04 N/A 0.05 0.05 0.05 0.03 0.03 0.03 0.03 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
viewei-derived provih fielder afpraa alaangste tunkteen instante faster 45- kaangste 2004 (1996) kaangste 30 kaangste	CASPS PDGFSuburiAC EPI4E8P11 CASP3 C	0 42 0 41 0 51 0 50 0 40 0 32 0 25 0 23 0 25 0 23 0 25 0 23 0 25 0 23 0 25 0 25	0.15 0.13 0.13 0.09 0.09 0.09 0.09 0.09 0.09 0.04 0.04	0.009 0.009 0.001 0.029 0.025 0.025 0.034 0.047 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.037 0.036 0.037 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.003 0.047 0.047 0.003 0.047 0.003 0.047 0.003 0.047 0.003 0.046 0.003 0.003 0.003 0.046 0.003 0.003 0.003 0.004 0.003 0.004 0.003 0.005 0.005 0.005 0.005 0.007 0.005 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.003 0.003 0.006 0.007 0.003 0.006 0.007 0.005 0.	0.00 0.04 -0.02 NUA 0.08 -0.02 -0.02 -0.02 -0.03 -0.05 -0.05 -0.05 -0.05 -0.07 -0.07 -0.07 -0.07 -0.05 -0.04 -0.04 -0.05 -0.04 -0.05 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.03 -0.05 -0.00	0.00 0.00 0.00 0.04 0.05 0.05 0.05 0.05	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Indeed-derived growth fielder alphoe anargede translation instantion factor alphoe anargede translation instantion factor anargede translation instantion anarged and anarged anarged anarged anarged and anarge	CASP9 ¹ PPOFINATIONEL EIF4E8P11 CSSP3 CSC31 EILAP1 EILAP1 EILAP1 EILAP1 EILAP1 EILAP1 EILAP1 EILAP1 EILAP1 CSSP3 CSSP1 EILAP3 E	0.62 0.81 0.81 0.60 0.40 0.32 0.32 0.25 0.23 0.23 0.23 0.23 0.23 0.23 0.23 0.23	0.15 0.13 0.13 0.03 0.06 0.06 0.06 0.06 0.05 0.05 0.05 0.05	0.009 0.009 0.029 0.029 0.029 0.04 0.049 0.049 0.049 0.032 0.034 0.035 0.034 0.034 0.034 0.035 0.034 0.034 0.035 0.034 0.035 0.034 0.035 0.034 0.035 0.034 0.035 0.036 0.036 0.036 0.036 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.036 0.037 0.037 0.036 0.037 0.037 0.037 0.031 0.037 0.031 0.037 0.031 0.037 0.017 0.017 0.017 0.036 0.036 0.036 0.037 0.017 0.017 0.017 0.017 0.017 0.017 0.018 0.017 0.018 0.019 0.019 0.018 0.019 0.019 0.019 0.018 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.019 0.003 0.019 0.019 0.003 0.019 0.003 0.019 0.019 0.003 0.019 0.003 0.019 0.003 0.019 0.005 0.005 0.019 0.005 0.005 0.005 0.011 0.005 0.0	0.00 0.04 0.02 0.04 0.02 0.05 0.01 0.05 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.02 0.07 Fold change 0.04 0.07 Fold change 0.04 0.00 0.04 0.07 Fold change 0.04 0.00 0.04 0.02 0.07 Fold change 0.04 0.00 0.00 0.07 0.07 Fold change 0.04 0.00 0.00 0.07 0.07 Fold change 0.04 0.00 0.07 0.07 0.07 Fold change 0.04 0.07 0.07 0.07 0.07 0.07 0.07 0.07	0.03 0.02 0.04 N/A 0.05 0.05 0.05 0.03 0.03 0.03 0.03 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
National-derived growth fields alphan Analysis (Charanteen Instanton Sature & Char Satapase 3 Satapase 3 Satap	CASP9 ¹ PPOFINATION EIF4E8P1 ¹ CASP3 CASP3 CASP3 CASP3 EIA4H TNFRSF14 UNCSC ¹ TFARL ¹³ CTSZ TFARL ¹³ CTSZ TFARL ¹³ CASP3	0.62 0.61 0.61 0.60 0.40 0.32 0.33 0.35 0.35 0.35 0.35 0.51 0.51 0.51 0.51 0.51 0.52 0.52 0.52 0.52 0.52 0.53 0.53 0.48 0.48 0.48 0.48 0.48 0.48 0.48 0.48	0.15 0.33 0.33 0.30 0.09 0.00 0.00 0.00 0.00	0.000 0.000 0.001 0.029 0.029 0.004 0.01 0.04 0.032 0.04 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.035 0.04 0.037 0.011 0.011 0.011 0.011 0.014 Plasma quasha 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.0	0.00 0.04 -0.02 NiA 0.08 -0.05 -0.05 -0.05 -0.06 -0.06 -0.06 -0.01 -0.06 -0.01 -0.07 -0.02 -0.07	00) 0.02 0.04 0.04 0.05 0.05 0.05 0.03 0.03 0.03 0.03 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Andrei-derived provih fielder alphal autarystic turkation fistaler alphal autarystic turkation fistaler alphal autarystic turkation fistaler alphal autarystic turkation fistaler autarystic turkatitettettettettettettettettettettettette	CASP9 ¹ PPOFeabourAL EIFEEP ¹ CXSP3 CXSL1 EILA ¹ BLM-H UNCSC ¹ TTARL ¹³ CTSZ CTSZ CTSZ TTARL ¹³ CTSZ CTSZ CTSZ CTSZ CTSZ CTSZ CTSZ CTSZ	0.42 0.41 0.51 0.40 0.32 0.32 0.32 0.34 0.34 0.34 0.34 0.34 0.34 0.34 0.35 0.35 0.35 0.35 0.35 0.35 0.35 0.35	0.15 0.13 0.13 0.13 0.09 0.06 0.04 0.04 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.05	0.009 0.001 0.029 0.029 0.029 0.029 0.049 0.049 0.049 0.049 0.049 0.049 0.049 0.034 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.036 0.049 0.048 0.049 0.048 0.048 0.044 0.046 0.	0.00 0.04 0.02 0.04 0.02 0.05 0.01 0.05 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.02 0.07 Fold change 0.04 0.07 Fold change 0.04 0.00 0.04 0.07 Fold change 0.04 0.00 0.04 0.02 0.07 Fold change 0.04 0.00 0.00 0.07 0.07 Fold change 0.04 0.00 0.00 0.07 0.07 Fold change 0.04 0.00 0.07 0.07 0.07 Fold change 0.04 0.07 0.07 0.07 0.07 0.07 0.07 0.07	00) 0.02 0.04 0.04 0.05 0.05 0.05 0.03 0.03 0.03 0.03 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Andrei-derived provih fielder alphal autarystic turkation fistaler alphal autarystic turkation fistaler alphal autarystic turkation fistaler alphal autarystic turkation fistaler autarystic turkation fistaler Bioconschell Micrometer alphal autarystic turkation fistaler autarystic turkation Bioconschell Micrometer alphal autarystic turkation Bioconschell Autor autarystic turkation autarystic turkatii autarystic turkation autarystic turkation	CASP9 ¹ PPOFINATION EIF4E8P1 ¹ CASP3 CASP3 CASP3 CASP3 EIA4H TNFRSF14 UNCSC ¹ TFARL ¹³ CTSZ TFARL ¹³ CTSZ TFARL ¹³ CASP3	0.62 0.61 0.61 0.60 0.40 0.32 0.33 0.35 0.35 0.35 0.35 0.51 0.51 0.51 0.51 0.51 0.52 0.52 0.52 0.52 0.52 0.53 0.53 0.48 0.48 0.48 0.48 0.48 0.48 0.48 0.48	0.15 0.33 0.33 0.30 0.09 0.00 0.00 0.00 0.00	0.000 0.000 0.001 0.029 0.029 0.004 0.01 0.04 0.032 0.04 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.035 0.04 0.037 0.011 0.011 0.011 0.011 0.014 Plasma quasha 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.0	0.00 0.04 -0.02 NiA 0.08 -0.05 -0.05 -0.05 -0.06 -0.06 -0.06 -0.01 -0.06 -0.01 -0.07 -0.02 -0.07	00) 0.02 0.04 0.04 0.05 0.05 0.05 0.03 0.03 0.03 0.03 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Haland-darined grooth fields alphan anargete transition instant factor alphan anargete transition instant factor anargete anarget Sector and transition in a sector transman B Horizon in Market Horizon monostra Market Horizon monostra Market Horizon anargete anarget Horizon anargete anarget Horizon anargete anarget Horizon anargete anarget Horizon anargete anarget Horizon anargete Horizon an	CASPS: CASPS: POGFactorial CASP3	0 42 0 41 0 41 0 51 0 40 0 40 0 43 0 43	0.15 0.13 0.13 0.13 0.09 0.06 0.06 0.04 0.04 0.04 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.05	0.009 0.001 0.029 0.029 0.029 0.029 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.035 0.003 1.10 ⁻¹ 1.10 ⁻¹ Plasma q-abu q-abu 0.04 0.001 0.005 0.04 0.04 0.05 0.05 0.005 0.005 0.04 0.005 0.0	0.00 0.04 0.02 0.04 0.02 0.05 0.05 0.05 0.05 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.02 0.02	0 00) 0.02 0.04 0.04 0.05 0.05 0.05 0.03 0.03 0.03 0.03 0.03	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Network-derived growth fields rights (K. 1999) Anages (K. 1999) Konnych hydrolas Konnych hydrolas	CASPS! PDGFSuburNA EIF4EBP1 CASP3 CA	0 42 0 41 0 40 0 51 0 40 0 32 0 32 0 32 0 32 0 33 0 43 0 43	0.15 0.13 0.13 0.13 0.06 0.06 0.06 0.04 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.05	0.009 0.001 0.029 0.029 0.025 0.04 0.04 0.04 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.036 0.036 0.036 0.036 0.036 0.037 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.058 0.057 0.047 0.057 0.0	0.00 0.04 -0.02 NUA 0.03 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.07 -0.07 -0.07 -0.05 -0.07 -0.05 -0.07 -0.04 -0.03 -0.04 -0.03 -0.03 -0.04 -0.03 -0.03 -0.04 -0.03 -0.03 -0.04 -0.03 -0.03 -0.03 -0.04 -0.03 -0.04 -0.05	0 00 0.02 0.02 0.04 0.05 0.05 0.05 0.05 0.03 0.00 0.00 0.00	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Andere-derived proof hector optical adaptics: functions instants factor optical adaptics: functions instants factor optical adaptics: functions in the sector of adaptical factor in adaptical adaptical factor in adaptical a	CASPS ¹ PPOFINATIONAL CASP3 C	0.42 0.41 0.51 0.50 0.32 0.32 0.32 0.32 0.33 0.40 0.40 0.40 0.40 0.40 0.40 0.40	0.15 0.13 0.13 0.13 0.06 0.06 0.06 0.04 0.04 0.05 0.04 0.05 0.05 0.05 0.05	0.009 0.001 0.029 0.029 0.029 0.029 0.034 0.047 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.035 0.005 0.046 0.046 0.046 0.046 0.046 0.046 0.046 0.046 0.046 0.046 0.046 0.046 0.046 0.046 0.046 0.046 0.056 0.046 0.057 0.056 0.057 0.056 0.057 0.056 0.057 0.056 0.057 0.056 0.	0.00 0.04 0.02 0.04 0.02 0.05 0.05 0.05 0.05 0.05 0.00 0.01 0.06 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.000 0.000000	00) 0.02 0.04 0.05 0.05 0.05 0.00 0.00 0.00 0.00	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Andread-derived growth factor sphra Ladacycle, trunsition i factor sphra Ladacycle, trunsition i factor sphra Ladacycle, trunsition i factor sphra Ladacycle, trunsition i factor mercekan 81 Biotomych hydrotaka (umor mercekan 10 George Composition factor mercekan 10 George Composition (Umor mercekan 10 George Composition) Factor and approximation (Umor March Read Acontain truny mercekan 81 Subject AC) (Umor Marchael Marchael 10 George Composition) Factor and explores indicates 1 Landons and readon (Umor Marchael 10 Landons and readons (Umor Marchael 10 Landons (Umo	CASPS! PDGFSuburNA EIF4EBP1 CASP3 CA	0 42 0 41 0 40 0 51 0 40 0 32 0 32 0 32 0 32 0 33 0 43 0 43	0.15 0.13 0.13 0.13 0.06 0.06 0.06 0.04 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.04 0.05 0.05	0.009 0.001 0.029 0.029 0.025 0.047 0.047 0.032 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.036 0.036 0.036 0.036 0.036 0.037 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.047 0.058 0.057 0.047 0.0570	0.00 0.04 -0.02 NUA 0.03 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.07 -0.07 -0.07 -0.05 -0.07 -0.05 -0.07 -0.04 -0.03 -0.04 -0.03 -0.03 -0.04 -0.03 -0.03 -0.04 -0.03 -0.03 -0.04 -0.03 -0.03 -0.03 -0.04 -0.03 -0.04 -0.05	0 00 0.02 0.02 0.04 0.05 0.05 0.05 0.05 0.03 0.00 0.00 0.00	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Heater-derived proof factor approach interpreter function factor approach approach interpreter function factor approach app	CASPS ¹ PPOFINATIONAL CASP3 C	0.42 0.41 0.51 0.50 0.32 0.32 0.32 0.33 0.34 0.16 0.16 0.19 0.51 0.51 0.51 0.51 0.51 0.52 0.52 0.52 0.53 0.53 0.54 0.55 0.55 0.55 0.55 0.55 0.55 0.55	0.15 0.13 0.13 0.13 0.06 0.06 0.06 0.04 0.04 0.05 0.04 0.05 0.05 0.05 0.05	0.009 0.001 0.029 0.029 0.029 0.029 0.034 0.047 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.034 0.035 0.005 0.046 0.028 0.007 0.046 0.048 0.048 0.048 0.054 0.054 0.055 0.048 0.055 0.057 0.057 0.057 0.057 0.058 0.057 0.058 0.	0.00 0.04 0.02 0.04 0.02 0.05 0.05 0.05 0.05 0.05 0.00 0.01 0.06 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.00 0.01 0.000 0.000000	00) 0.02 0.04 0.05 0.05 0.05 0.00 0.00 0.00 0.00	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1

Red text with asterisk* = Protein is differentially regulated in both plasma and CSF

¹Protein is also differentially regulated in AD-dementia patients

²Protein is also differentially regulated in AB+ MCI patients

³Protein is also differentially regulated in AB- MCI patients

An additional 13 proteins were decreased in AD patients only, and seven proteins were decreased in $A\beta$ + MCI patients only, when compared to $A\beta$ - controls (see Table 3).

The A β + CN group did not show any significant differential regulation of proteins in plasma when compared to A β - CN (q > 0.05).

Plasma levels of OSM were increased, and RGMB, JAM-B, TRAIL, TRANCE and brevican were decreased, in AD and Aβ-negative MCI

Compared to Aβ- CN, Aβ- MCI patients showed increased levels of oncostatin M (OSM; d = 0.58; q = 0.003) in plasma, which were also significantly increased in AD (d = 0.33; q = 0.006; see Table 3).

AD, A β + MCI, and A β - MCI patients all showed decreases of three proteins in plasma, including RGMB (d = -0.25 in A β - MCI; d = -0.19 in A β + MCI; d = -0.12 in AD; q < 0.05), JAM-B (d = -0.23 in A β - MCI; d = -0.21 in A β + MCI; d = -0.17 in AD; q < 0.001), TRAIL (d = -0.2 in A β - MCI; d = -0.16 in A β + MCI; d = -0.17 in AD; q < 0.05).

Two proteins were decreased in both Aβ- MCI and AD compared to Aβ- controls, including TNF-related activation-induced cytokine (TRANCE; d = -0.4 in Aβ-MCI; d = -0.3 in AD; q < 0.05) and brevican (d = -0.29 in Aβ- MCI; d = -0.2 in AD; q < 0.05); see Fig. 2b and Table 3.

Findings were replicated for six proteins in plasma

In an independent sample of 179 individuals, we observed differential regulation of seven proteins that were also differentially regulated in our primary analysis. Plasma levels of OSM were increased in AB+ MCI patients (d = 0.37, p = 0.035, unadjusted) and Aβ- MCI patients (d = 0.56, p = 0.002, unadjusted) compared to A β -CN. Plasma MMP-9 levels were increased in Aβ+ MCI patients (d = 0.41, p = 0.01, unadjusted) and A β - MCI patients (d = 0.55, p = 0.003, unadjusted) compared to A β -CN. Increased levels of HAGH (d = 0.6, p = 0.0061, unadjusted) and CD200 (d = 0.15, p = 0.02, unadjusted) were also observed in $A\beta$ + CN compared to $A\beta$ - CN. Pronounced decreases of AXIN1 were observed in the plasma of A β + MCI patients (*d* = 0.51, *p* = 0.02, unadjusted), Aβ- MCI patients (d = -0.77, p = 0.002, unadjusted), and A β + CN individuals (d = -0.77, p = 0.005, unadjusted) compared to $A\beta$ - CN. Finally, plasma levels of urokinase-type plasminogen activator (uPA) were decreased in A β + MCI patients (d = -0.14, p = 0.02, unadjusted), Aβ- MCI patients (d = -0.16, p = 0.043, unadjusted), and A β + CN individuals (d = -0.14, p =0.044, unadjusted) compared to A β - CN (see Fig. 2b and Additional file 1: Table S8).

CSF levels of MMP-10 and YKL-40 negatively associated with baseline cortical thickness levels

Quality inspection identified four MCI patients and one control with segmentation errors; thus, 410 participants were included in the final MRI analysis.

AD-signature cortical thickness [17] was negatively associated with four proteins in CSF, including MMP-10 and YKL-40 (q < 0.05), both of which were differentially

regulated in the cross-sectional analyses, and two proteins in plasma, including elafin and lymphotoxin-beta receptor (q < 0.01; Additional file 1: Table S9). Baseline hippocampal volume was not significantly associated with protein levels in plasma or CSF (q > 0.05).

Multiple differentially regulated CSF and plasma proteins associated with cognitive performance

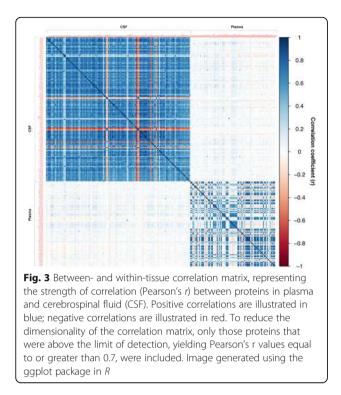
Baseline CDR-SB scores were significantly associated with levels of sixteen proteins in CSF, including SMOC2, IL8, MMP-10, CCL3, TNF-R2, ezrin, RGMB and OPN, all of which were differential regulated in our univariate analysis (q < 0.05; Additional file 1: Table S10). Baseline CDR-SB score was also associated with concentrations of eight proteins in plasma, including positive associations with IL-8 and TIMP4, and negative associations with JAM-B, THY1 and latexin, all of which were differentially regulated in our univariate analysis (q < 0.05; Additional file 1: Table S11). Baseline MMSE scores negatively associated with levels of four proteins in plasma, including IL8 and PDF subunit alpha (- 0.1 <b < -0.05; q < 0.05), and positively associated with levels of fifteen proteins in plasma, including THY1, RGMB, brevican, brorin, kallikrein-6, bone morphogenetic protein 4, TRANCE, and delta homolog 1 (q < 0.05; Additional file 1: Tables S12-S13). In CSF, MMP-10, OPN and TNF-R2 were nominally associated with baseline MMSE score, but did not survive FDR adjustment (q >0.05).

Approximately half of CSF proteins correlated modestly with their analogs in plasma

Overall, the strongest protein-protein correlations were observed within fluids, as illustrated in Fig. 3 and Additional file 1: Table S14. Between fluids, moderate-to-strong, positive correlations were observed for 14 proteins in CSF and their corresponding analogs in plasma, including CHIT1, which was significantly up-regulated in our primary univariate analysis of patients with AD-dementia and A β + MCI versus A β - controls (0.5 < r < 0.73; $q < 1 \times 10^{-61}$). Weak-to-modest positive correlations were observed across an additional 123 proteins in CSF and their analogs in plasma, including 35 proteins showing evidence of differential regulation in our univariate cross-sectional analyses (0.08 < r < 0.49; q < 0.05; Additional file 1: Table S14).

Multivariate modeling predicted early AD with high accuracy in CSF

A series of multivariate LASSO regression models produced high predictive accuracy estimates in CSF for AD dementia, in a model that included 36 biomarkers (AUC = 0.95, 95%; CI = 0.9–0.99), and for A β + MCI, in a model that included 43 biomarkers and gender (AUC =



0.92; 95% CI = 0.80–0.98). AUCs for CSF models were non-significant for A β - MCI (AUC = 0.78, 95% CI = 0.46–0.98), and low for A β + CN, in a model that included 14 biomarkers and gender (AUC = 0.64, 95% CI = 0.57–0.7; Additional file 1: Table S2).

Multivariate modeling predicted AD with high accuracy, and MCI with moderate accuracy, in plasma

In plasma, multivariate regression produced high AUCs for AD dementia, in a model that included 74 biomarkers and age (AUC = 0.94, 95% CI = 0.87–0.98). Predictive accuracy was moderate for A β + MCI, in a model that included 53 biomarkers and age (AUC = 0.78, 95% CI = 0.68–0.87; see Additional file 1: Table S3). The plasma models were not significant for A β - MCI (AUC = 0.76, 95% CI = 0.47–0.92) or A β + CN (AUC = 0.58, 95% CI = 0.47–0.72).

Discussion

In one of the broadest multiplex proteomics studies of dementia conducted to date, we identified a series of significant alterations across plasma and CSF, implicating multiple proteins involved in regulation of the inflammatory response, apoptosis, endocytosis, leukocyte proliferation, and other biological processes believed to be downstream of, and potentially orthogonal to, $A\beta$ and tau deposition. A subset of proteins collectively discriminated individuals with AD dementia from healthy controls with 95% predictive accuracy in CSF, and 94% accuracy in plasma, representing an improvement over

prior multiplex panels [13, 16, 36, 42, 43]. With the exceptions of YKL-40 [1, 11, 18] and CHIT1 [27] in CSF, and MMP-9 [7] in blood, our findings highlight a set of relatively unexplored candidate biomarkers of neurode-generation, warranting further validation in independent disease cohorts using targeted proteomic assays.

Our findings highlight the roles of several functionally pleiotropic proteins in AD, such as CASP8, which was increased in the plasma and CSF of AD-dementia patients, and in the plasma of A β + MCI patients. CASP8 is involved in synaptic plasticity, amyloid processing, memory, and regulation of microglial pro-inflammatory activation [60]. The *CASP8* gene has shown a significant rare variant burden association with AD susceptibility [46], and prior immunohistochemical analyses have revealed activation of CASP8 in AD hippocampal tissue [47]. Caspase inhibition has been proposed as a mechanism to promote neuronal survival [49], and may be a beneficial therapeutic strategy for AD.

Similarly, JAM-B, a protein involved in synaptic adhesion, lymphocyte transendothelial migration [21], and vascular inflammation [59], was down-regulated in the plasma and CSF of AD patients and the plasma of MCI patients compared with cognitively normal A β - controls. In plasma, JAM-B levels negatively associated with baseline CDR-SB scores. Polymorphisms in or near the *JAM2* gene have shown suggestive associations with cognitive performance [34], postmortem A β load [51], and longitudinal changes in amyloid plaque burden on PET [44].

CSF concentrations of MMP-10 were elevated in $A\beta$ + MCI and AD patients, positively correlated with cognitive performance, and negatively associated with AD-signature cortical thickness. Other matrix metalloproteinase-related proteins, including MMP-9, TIMP-4, and ADAM22, were also up-regulated in AD. These findings highlight the complex pathophysiological role of endopeptidases in AD, potentially via direct degradation of A β deposits [32] or indirect mediation of Aβ-induced blood-CSF barrier dysfunction [6]. Transferrin receptor, which facilitates brain iron uptake, was also significantly increased in the plasma of AD patients, implicating elevated brain iron levels, potentially via blood-brain barrier (BBB) breakdown, in disease pathophysiology [54]. Further investigation of the role of metalloproteinases, endothelial proteins and adhesion molecules, particularly as they relate to meningeal lymphatics, BBB function and iron levels in AD [54], may facilitate novel therapeutic target discovery.

In the CSF and plasma of AD patients, we found decreased concentrations of tPA, a blood clotting enzyme which co-localizes with amyloid-rich regions and phosphorylated tau in post-mortem AD brains [30], and has been linked to accelerated A β degradation in-vivo [37]. In AD plasma, we found decreased levels of another plasminogen activator, uPA, which has been associated with inhibition of A β neurotoxicity and fibrillogenesis [56] and recovery after axonal injury [31].

Other notable proteins that showed evidence of differential regulation in AD compared to healthy elderly individuals included CD200, a glycoprotein previously associated with enhanced in-vivo and in-vitro amyloid phagocytosis [57], UNC5, an axonal guidance protein receptor which has previously shown genetic links to familial, late-onset AD via increased susceptibility to neuronal cell death [61], and SMOC2, a member of the SPARC protein family, which is involved in microgliosis and functional recovery after cortical ischemia [24], and was significantly associated with cognitive performance in our study. We also observed profound increases of HAGH, also known as glyoxalase II, in plasma, reemphasizing the potential role of advanced glycation end products in neurodegeneration [23, 63].

Our study highlights the changes and potential contributions of several chemokines (CXCL1, CCL3, CXCL5, CXCL6, CCL3, CCL19), interleukins (IL8, IL6-RA, IL18-BP), and other immune markers (OSM, ALCAM, OPG, CHIT1, YKL-40, STAMBP, MMP-9, MMP-10) in the prodromal and dementia phases of AD. YKL-40, a chitinase expressed by astrocytes and microglia in the CNS [8], was increased in the CSF of A β + CN individuals and patients with AD, and negatively associated with thickness measures in AD-vulnerable brain regions, replicating prior findings [2] and reemphasizing similar findings from the same cohort, using a standard ELISA assay [19]. However, elevations of YKL-40 in CSF were modest compared with prior investigations [1, 11, 18] and were negligible in plasma, indicating limited diagnostic utility of this biomarker in isolation [27]. CHIT1, another putative marker of microglial activation, showed more pronounced elevations in the CSF of AB+MCI and AD patients, supporting prior observations of up-regulated CHIT1 in progressive brain illnesses [53, 58], and warranting further investigation of the role of chitinases in immune response and neurodegeneration.

Compared with A β - CNs, MCI patients without evidence of pathological CSF A β showed significant differential regulation of OPG, RGMB and ROBO2 protein in CSF, and differential regulation of multiple proteins in plasma, including brevican. OPG, RGMB, and ROBO2 have been implicated in CNS development, axonal growth, and recovery after nerve injury [15, 25, 50], whereas upregulation of brevican has been observed in the CNS during the consolidation of long-term memories [35]. Thus, dysregulation of these proteins in A β -MCI may reflect broader mechanisms involved in neuro-degeneration, potentially unrelated to A β pathology.

Conversely, certain proteins, dysregulated when $A\beta$ + patients were compared to $A\beta$ - controls, may reflect the presence of $A\beta$ deposits rather than a specific diagnosis of AD or MCI. To address this possibility, we conducted a series of supplementary analyses, as detailed in Additional file 1: Note 1. These analyses revealed that, with the exceptions of CHIT1, YKL-40 and SMOC2 in CSF, most differentially regulated proteins identified in $A\beta$ + patients may represent markers of disease diagnosis, rather than $A\beta$ deposition alone, as they showed similar patterns of differential regulation when $A\beta$ + groups were compared with one another directly (see Additional file 1: Tables S23-S32).

Some differentially regulated proteins may reflect the influences of coexisting pathologies in AD, such as Lewy body inclusions or TDP-43 aggregates. To test this hypothesis, we conducted supplementary analyses in a small, independent cohort of Aβ- healthy elderly individuals compared with Aβ- patients with Parkinson's disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP; see Additional file 1: Note 1). This analysis indicated that MMP-10, STAMBP, LDL receptor, and EIF4EBP1 likely represent diseasespecific biomarkers of AD, whereas CHIT1, ALCAM, CD200, OPG, ROBO2, and RGMB may serve as broader neurodegeneration biomarkers, potentially influenced by coexisting pathologies beyond Aβ- and tau (Additional file 1: Tables S33-S38). Further studies of patients with Lewy body dementia, frontotemporal dementia, and other neurodegenerative illnesses are strongly recommended to help validate these findings.

Despite its scale, our study has limitations. Many differentially regulated proteins yielded small-to-modest effect sizes (0.05 < d < 0.4), and the functions of some proteins demonstrating AD-related changes are not fully understood. Also, given the study's cross-sectional design, we could not investigate the precise temporal dynamics of important biological processes such as innate immunity in AD. Future investigations will combine longitudinal plasma and CSF measurements with genomewide genotyping to disentangle causal from consequential biomarkers, and to map the development of protein biomarkers throughout the progression of disease. Additionally, the Olink[™] PEA technology takes advantage of unique tags and polymerase chain reaction to measure up to 92 proteins in parallel, including many lowexpressing analytes typically undetected using traditional multiplex assays. The technology therefore represents a relatively focused screen, whereby protein levels are reported as normalized protein concentration (NPX). Prospective experiments should combine more unbiased proteomics approaches (such as mass spectrometry) with targeted assays (such as enzyme-linked immunoabsorbance assays, single molecule arrays, or customized Olink $^{\text{\tiny M}}$ panels), reporting results as absolute concentrations.

Finally, while we identified subsets of proteins that accurately discriminated MCI and AD patients from elderly controls, further work is required to identify a suitable selection of biomarkers for very early detection of cognitive impairment, prior to the presentation of overt clinical symptoms. Replication studies in independent cohorts, complemented by larger multiplex proteomics panels, genetic risk scores, advanced neuroimaging, neuropsychological assessments, and post-mortem expression studies will help characterize early contributors towards longitudinal cognitive decline in AD [33].

Conclusion

In conclusion, we have implicated multiple markers of neuroinflammation, cerebrovascular dysfunction, apoptosis, and other CNS processes in the preclinical, prodromal, and dementia phases of AD. Approximately one third of proteins successfully assayed in CSF significantly correlated with their analogs in plasma, and several differentially regulated proteins were associated with cortical atrophy and cognitive performance. These findings inform our understanding of AD biology, and indicate that blood-based biomarker panels may facilitate AD diagnosis, pending further refinement and validation.

Additional file

Additional file 1: Supplementary Materials, Part 1: Notes S1-S2, Figures S1-S8, and Tables S1-S6. Supplementary Materials, Part 2: Tables S7-S39. (ZIP 789 kb)

Authors' contributions

Conception and design: OH, AM, CDW. Acquisition of data: OH, SJ, ES, NM. Data analysis: CDW, NM, MN, SV, CLH. Interpretation of data: CDW, NM, MN, SV, CLH, SJ, ES, JL, LF, TS, GR, RM, AM, OH. Writing of manuscript: CDW, AM, OH. Review and/or revision of manuscript: CDW, NM, MN, SV, CLH, SJ, ES, JL, LF, TS, GR, RM, AM, OH. PI for the BioFINDER study: OH. All authors read and approved the final manuscript.

Funding

The study was supported by the European Research Council, the Swedish Research Council, the Knut and Alice Wallenberg foundation, the Marianne and Marcus Wallenberg foundation, the Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's disease) at Lund University, the Swedish Alzheimer Foundation, the Swedish Brain Foundation, The Parkinson foundation of Sweden, The Parkinson Research Foundation, the Skåne University Hospital Foundation, and the Swedish federal government under the ALF agreement. The study was partially supported by a Digital Data Innovation Fund grant, awarded by Pfizer Worldwide Research & Development.

Availability of data and materials

Anonymized data will be shared by request from a qualified academic investigator for the sole purpose of replicating procedures and results presented in the article and as long as data transfer is in agreement with EU legislation on the general data protection regulation and decisions by the Ethical Review Board of Sweden and Region Skåne.

Competing interests

CDW and GR are employees of Biogen Inc. MN, CH, JL, LF, and AM are employees of Pfizer Worldwide Research & Development. TS is an employee of Sanofi. CDW, GR, TS, and RM were employed at Pfizer Worldwide Research & Development during the conduct of this study. OH has acquired research support (for the institution) from Roche, GE Healthcare, Biogen, AVID Radiopharmaceuticals, Fujirebio, and Euroimmun. In the past 2 years, he has received consultancy/speaker fees (paid to the institution) from Biogen, Roche, and Fujirebio.

Author details

¹Research and Early Development (RED), Biogen Inc., Cambridge, MA 02139, USA. ²Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Lund, Sweden. ³Wallenberg Center for Molecular Medicine, Lund University, Lund, Sweden. ⁴Pfizer Worldwide Research & Development, Cambridge, MA 02139, USA. ⁵Department of Medicine, Karolinska Institutet, Vetenskapsvagen 10, 171 76 Stockholm, Sweden. ⁶Rare and Neurologic Disease Research, Sanofi Research and Development, Framingham, MA 01701, USA. ⁷CNS Research Solutions LLC, Cambridge, MA 02139, USA. ⁸Memory Clinic, Skåne University Hospital, SE-20502 Malmö, Sweden.

Received: 15 July 2019 Accepted: 24 August 2019 Published online: 06 November 2019

References

- Alcolea D, Martínez-Lage P, Sánchez-Juan P, Olazarán J, Antúnez C, Izagirre A et al (2015) Amyloid precursor protein metabolism and inflammation markers in preclinical Alzheimer disease. Neurology 85:626–633
- Alcolea D, Vilaplana E, Pegueroles J, Montal V, Sánchez-Juan P, González-Suárez A et al (2015) Relationship between cortical thickness and cerebrospinal fluid YKL-40 in predementia stages of Alzheimer's disease. Neurobiol Aging 36:2018–2023
- Alzheimer's Association, 2017. 2017 Alzheimer's disease facts and figures. Alzheimer's & Dementia. Elsevier; 2017; 13(4): 325-373
- Assarsson E, Lundberg M, Holmquist G, Björkesten J, Thorsen SB, Ekman D et al (2014) Homogenous 96-Plex PEA Immunoassay Exhibiting High Sensitivity, Specificity, and Excellent Scalability. PLOS ONE 9:e95192
- Blennow K (2017) A review of fluid biomarkers for Alzheimer's disease: Moving from CSF to blood. Neurol Ther 6:15–24
- 6. Brkic M, Balusu S, Van Wonterghem E, Gorlé N, Benilova I, Kremer A et al (2015) Amyloid β oligomers disrupt blood–CSF barrier integrity by activating matrix metalloproteinases. J Neurosci Soc Neurosci 35:12766–12778
- Cai Z-Y, Yan Y, Yan L, Wang F-Y, Huang H, Wang Y-L et al (2007) Serum level of MMP-2, MMP-9 and ox-LDL in Alzheimer's disease with hyperlipoidemia. J Med Coll PLA 22:352–356
- Cantó E, Tintoré M, Villar LM, Costa C, Nurtdinov R, Álvarez-Cermeño JC et al (2015) Chitinase 3-like 1: prognostic biomarker in clinically isolated syndromes. Brain 138:918–931
- Cho S-H, Sun B, Zhou Y, Kauppinen TM, Halabisky B, Wes P et al (2011) CX3CR1 protein signaling modulates microglial activation and protects against plaque-independent cognitive deficits in a mouse model of Alzheimer disease. J Biol Chem 286:32713–32722
- Cook D, Brown D, Alexander R, March R, Morgan P, Satterthwaite G et al (2014) Lessons learned from the fate of AstraZeneca's drug pipeline: a fivedimensional framework. Nat Rev Drug Discov 13(6):419–431
- Craig-Schapiro R, Perrin RJ, Roe CM, Xiong C, Carter D, Cairns NJ et al (2010) YKL-40: a novel prognostic fluid biomarker for preclinical Alzheimer's disease. Biol Psychiatry 68:903–912
- Cummings J, Lee G, Mortsdorf T, Ritter A, Zhong K (2017) Alzheimer's disease drug development pipeline: 2017. Alzheimers Dement 3:367–384
- Doecke JD (2012) Blood-based protein biomarkers for diagnosis of Alzheimer disease. Archives of Neurology American Medical Association 69: 1318–1325
- 14. Fan Z, Brooks DJ, Okello A, Edison P (2017) An early and late peak in microglial activation in Alzheimer's disease trajectory. Brain 140:792–803
- Hivert B (2002) Robo1 and Robo2 are Homophilic binding molecules that promote axonal growth. Mol Cell Neurosci 21:534–545
- Hye A, Riddoch-Contreras J, Baird AL, Ashton NJ, Bazenet C, Leung R et al (2014) Plasma proteins predict conversion to dementia from prodromal disease. Alzheimers Dementia 10:799–807.e2

- Jack CR, Wiste HJ, Weigand SD, Knopman DS, Mielke MM, Vemuri P et al (2015) Different definitions of neurodegeneration produce similar amyloid/ neurodegeneration biomarker group findings. Brain 138:3747–3759
- Janelidze S, Hertze J, Zetterberg H, Waldö ML, Santillo A, Blennow K et al (2015) Cerebrospinal fluid neurogranin and YKL-40 as biomarkers of Alzheimer's disease. Ann Clin Transl Neurol 3:12–20
- Janelidze S, Mattsson N, Stomrud E, Lindberg O, Palmqvist S, Zetterberg H et al (2018) CSF biomarkers of neuroinflammation and cerebrovascular dysfunction in early Alzheimer disease. Neurology 91:e867–e877
- Janelidze S, Zetterberg H, Mattsson N, Palmqvist S, Vanderstichele H, Lindberg O et al (2016) CSF a β42/a β40 and a β42/a β38 ratios: better diagnostic markers of Alzheimer disease. Ann Clin Transl Neurol 3:154–165
- Johnson-Léger CA, Aurrand-Lions M, Beltraminelli N, Fasel N, Imhof BA (2002) Junctional adhesion molecule-2 (JAM-2) promotes lymphocyte transendothelial migration. Blood 100:2479–2486
- Knopman DS, Siemers ER, Bain LJ, Hendrix JA, Carrillo MC (2018) National Institute on Aging – Alzheimer"s association research framework lays the groundwork for deeper understanding of Alzheimer"s disease. Alzheimers Dementia 14:261–262
- Kuhla A, Ludwig SC, Kuhla B, Münch G, Vollmar B. Advanced glycation end products are mitogenic signals and trigger cell cycle reentry of neurons in Alzheimer's disease brain. Neurobiology of Aging. Elsevier 2015; 36(2); 753-761
- Lloyd-Burton SM, York EM, Anwar MA, Vincent AJ, Roskams AJ (2013) SPARC regulates microgliosis and functional recovery following cortical ischemia. J. Neurosci 33:4468–4481
- Ma CHE, Brenner GJ, Omura T, Samad OA, Costigan M, Inquimbert P et al (2011) The BMP Coreceptor RGMb promotes while the endogenous BMP antagonist noggin reduces neurite outgrowth and peripheral nerve regeneration by modulating BMP signaling. J. Neurosci 31:18391–18400
- Mattsson N, Insel PS, Palmqvist S, Stomrud E, van Westen D, Minthon L et al (2016) Increased amyloidogenic APP processing in APOE ε4-negative individuals with cerebral β-amyloidosis. Nat Commun 7:10918
- Mattsson N, Tabatabaei S, Johansson P, Hansson O, Andreasson U, Månsson J-E et al (2011) Cerebrospinal fluid microglial markers in Alzheimer's disease: elevated Chitotriosidase activity but lack of diagnostic utility. Neuromol Med 13:151–159
- Mattsson N, Zetterberg H, Janelidze S, Insel PS, Andreasson U, Stomrud E et al (2016) Plasma tau in Alzheimer disease. Neurology 87:1827–1835
- McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr et al (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers & Dement 7:263–269
- Medina MG, Ledesma MD, Domínguez JE, Medina M, Zafra D, Alameda F et al (2005) Tissue plasminogen activator mediates amyloid-induced neurotoxicity via Erk1/2 activation. EMBO J 24:1706–1716
- Merino P, Diaz A, Jeanneret V, Wu F, Torre E, Cheng L et al (2017) Urokinase-type plasminogen activator (uPA) binding to the uPA receptor (uPAR) promotes axonal regeneration in the central nervous system. J. Biol. Chem 292:2741–2753
- Miners JS, Baig S, Palmer J, Palmer LE, Kehoe PG, Love S (2008) SYMPOSIUM: Clearance of Aβ from the Brain in Alzheimer"s Disease: Aβ-Degrading Enzymes in Alzheimer"s Disease. Brain Pathol 18:240–252
- 33. Mormino EC, Papp KV, Rentz DM, Donohue MC, Amariglio R, Quiroz YT et al (2017) Early and late change on the preclinical Alzheimer's cognitive composite in clinically normal older individuals with elevated amyloid β . Alzheimers Dement 13:1004–1012
- Need AC, Attix DK, McEvoy JM, Cirulli ET, Linney KL, Hunt P et al (2009) A genome-wide study of common SNPs and CNVs in cognitive performance in the CANTAB. Hum Mol Genet 18:4650–4661
- Niekisch H, Steinhardt J, Berghäuser J, Bertazzoni S, Kaschinski E, Kasper J et al (2019) Learning induces transient upregulation of brevican in the auditory cortex during consolidation of long-term memories. J. Neurosci:39(36)2499–2418
- O'Bryant SE, Xiao G, Barber R, Huebinger R, Wilhelmsen K, Edwards M et al (2011) A Blood-Based Screening Tool for Alzheimer's Disease That Spans Serum and Plasma: Findings from TARC and ADNI. PLOS ONE 6:e28092
- Oh SB, Byun CJ, Yun J-H, Jo D-G, Carmeliet P, Koh J-Y et al (2014) Tissue plasminogen activator arrests Alzheimer's disease pathogenesis. Neurobiol Aging 35:511–519
- Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M et al (2016) CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 15:673–684

- Palmqvist S, Janelidze S, Stomrud E, Zetterberg H, Karl J, Zink K et al (2019) Performance of Fully Automated Plasma Assays as Screening Tests for Alzheimer Disease–Related β-Amyloid Status. JAMA Neurol https://doi.org/1 0.1001/jamaneurol.2019.1632
- 40. Palmqvist S, Schöll M, Strandberg O, Mattsson N, Stomrud E, Zetterberg H et al (2017) Earliest accumulation of β -amyloid occurs within the default-mode network and concurrently affects brain connectivity. Nat Commun 8:1214
- Palmqvist S, Zetterberg H, Blennow K, Vestberg S, Andreasson U, Brooks DJ, Owenius R, Hägerström D, Wollmer P, Minthon L, Hansson O (2014) Accuracy of brain amyloid detection in clinical practice using cerebrospinal fluid β-amyloid 42: a cross-validation study against amyloid positron emission tomography. JAMA Neurol 71(10):1282–1289
- 42. Paterson RW, Heywood WE, Heslegrave AJ, Magdalinou NK, Andreasson U, Sirka E et al (2016) A targeted proteomic multiplex CSF assay identifies increased malate dehydrogenase and other neurodegenerative biomarkers in individuals with Alzheimer's disease pathology. Transl Psychiatry 6(11):e952–e952
- Pedrini S, Gupta VB, Hone E, Doecke J, O'Bryant S, James I et al (2017) A blood-based biomarker panel indicates IL-10 and IL-12/23p40 are jointly associated as predictors of β-amyloid load in an AD cohort. Sci Rep 7:14057
- Ramanan VK, Risacher SL, Nho K, Kim S, Shen L, McDonald BC et al (2015) GWAS of longitudinal amyloid accumulation on 18F-florbetapir PET in Alzheimer's disease implicates microglial activation gene IL1RAP. Brain 138:3076–3088
- 45. Ramanan VK, Saykin AJ (2013) Pathways to neurodegeneration: mechanistic insights from GWAS in Alzheimer"s disease, Parkinson"s disease, and related disorders. American Journal of Neurodegenerative Disease. e-Century Publishing Corporation 2:145–175
- Rehker J, Rodhe J, Nesbitt RR, Boyle EA, Martin BK, Lord J et al (2017) Caspase-8, association with Alzheimer's Disease and functional analysis of rare variants. PLOS ONE 12:e0185777
- 47. Rohn TT, Head E, Nesse WH, Cotman CW, Cribbs DH (2001) Activation of Caspase-8 in the Alzheimer's disease brain. Neurobiol Dis 8:1006–1016
- Seppälä TT, Nerg O, Koivisto AM, Rummukainen J, Puli L, Zetterberg H et al (2012) CSF biomarkers for Alzheimer disease correlate with cortical brain biopsy findings. Neurology 78:1568–1575
- Shabanzadeh AP, D'Onofrio PM, Monnier PP, Koeberle PD (2015) Targeting caspase-6 and caspase-8 to promote neuronal survival following ischemic stroke. Cell Death Dis 6:e1967–e1967
- Shimamura M, Nakagami H, Osako MK, Kurinami H, Koriyama H, Zhengda P et al (2014) OPG/RANKL/RANK axis is a critical inflammatory signaling system in ischemic brain in mice. Proc Natl Acad Sci USA 111:8191–8196
- Shulman JM, Chen K, Keenan BT, Chibnik LB, Fleisher A, Thiyyagura P et al (2013) Genetic susceptibility for Alzheimer disease Neuritic plaque pathology. JAMA Neurol 70:1150–1157
- Sims R, van der Lee SJ, Naj AC, Bellenguez C, Badarinarayan N, Jakobsdottir J et al (2017) Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglialmediated innate immunity in Alzheimer's disease. Nat Genet 49:1373–1384
- 53. Steinacker P, Verde F, Fang L, Feneberg E, Oeckl P, Roeber S et al (2017) Chitotriosidase (CHIT1) is increased in microglia and macrophages in spinal cord of amyotrophic lateral sclerosis and cerebrospinal fluid levels correlate with disease severity and progression. J Neurol Neurosurg Psychiatry 41: jnnp-2017–jnn317138
- Sweeney MD, Sagare AP, Zlokovic BV (2018) Blood–brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol 14:133–150
- 55. Tibshirani R (1996) Regression shrinkage and selection via the lasso. Journal of the Royal Statistical Society. Series B (Methodological) 58(1):267–288
- Tucker HM, Ehmann MK, Estus S (2002) Urokinase-type plasminogen activator inhibits amyloid-β neurotoxicity and fibrillogenesis via plasminogen. J. Neurosci. Res 70:249–255
- 57. Varnum MM, Kiyota T, Ingraham KL, Ikezu S, Ikezu T (2015) The antiinflammatory glycoprotein, CD200, restores neurogenesis and enhances amyloid phagocytosis in a mouse model of Alzheimer's disease. Neurobiol Aging 36:2995–3007
- Watabe-Rudolph M, Song Z, Lausser L, Schnack C, Begus-Nahrmann Y, Scheithauer MO et al (2012) Chitinase enzyme activity in CSF is a powerful biomarker of Alzheimer disease. Neurology 78:569–577
- 59. Weber C, Fraemohs L, Dejana E (2007) The role of junctional adhesion molecules in vascular inflammation. Nat Rev Immunol 7:467–477
- Wei W, Norton DD, Wang X, Kusiak JW (2002) Aβ 17–42 in Alzheimer's disease activates JNK and caspase-8 leading to neuronal apoptosis. Brain 125:2036–2043

- Wetzel-Smith MK, Hunkapiller J, Bhangale TR, Srinivasan K, Maloney JA, Atwal JK et al (2014) A rare mutation in <i>UNC5C</i> predisposes to lateonset Alzheimer's disease and increases neuronal cell death. Nat Med 20: 1452–1457
- Wong MW, Braidy N, Poljak A, Pickford R, Thambisetty M, Sachdev PS (2017) Dysregulation of lipids in Alzheimer's disease and their role as potential biomarkers. Alzheimers Dement 13:810–827
- Yaffe K, Lindquist K, Schwartz AV, Vitartas C, Vittinghoff E, Satterfield S et al (2011) Advanced glycation end product level, diabetes, and accelerated cognitive aging. Neurology 77:1351–1356

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

