

Identifying Blood Proteomic Markers of Parkinson's Disease Dementia Using High-Throughput Approaches

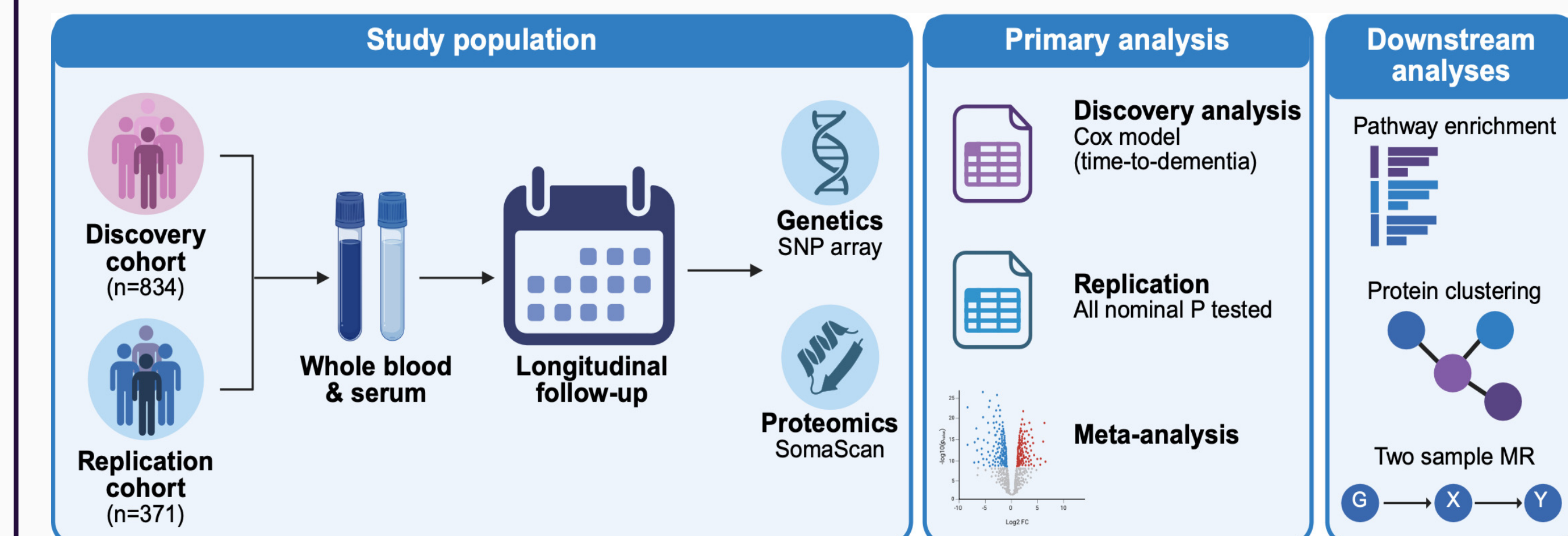
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Background

Parkinson's disease (PD) presents with a constellation of motor and non-motor symptoms, including cognitive impairment and dementia. Recognising which individuals with PD are at increased risk of developing dementia remains a significant challenge, particularly early in the disease course. Here, we aim to identify proteomic profiles associated with development of dementia in recently diagnosed PD patients by using high throughput proteomic assays. This may in turn lead to the identification of protein markers that could potentially be developed into clinical assays, as well as highlighting disease mechanisms underlying the development of dementia in PD.

Study Design



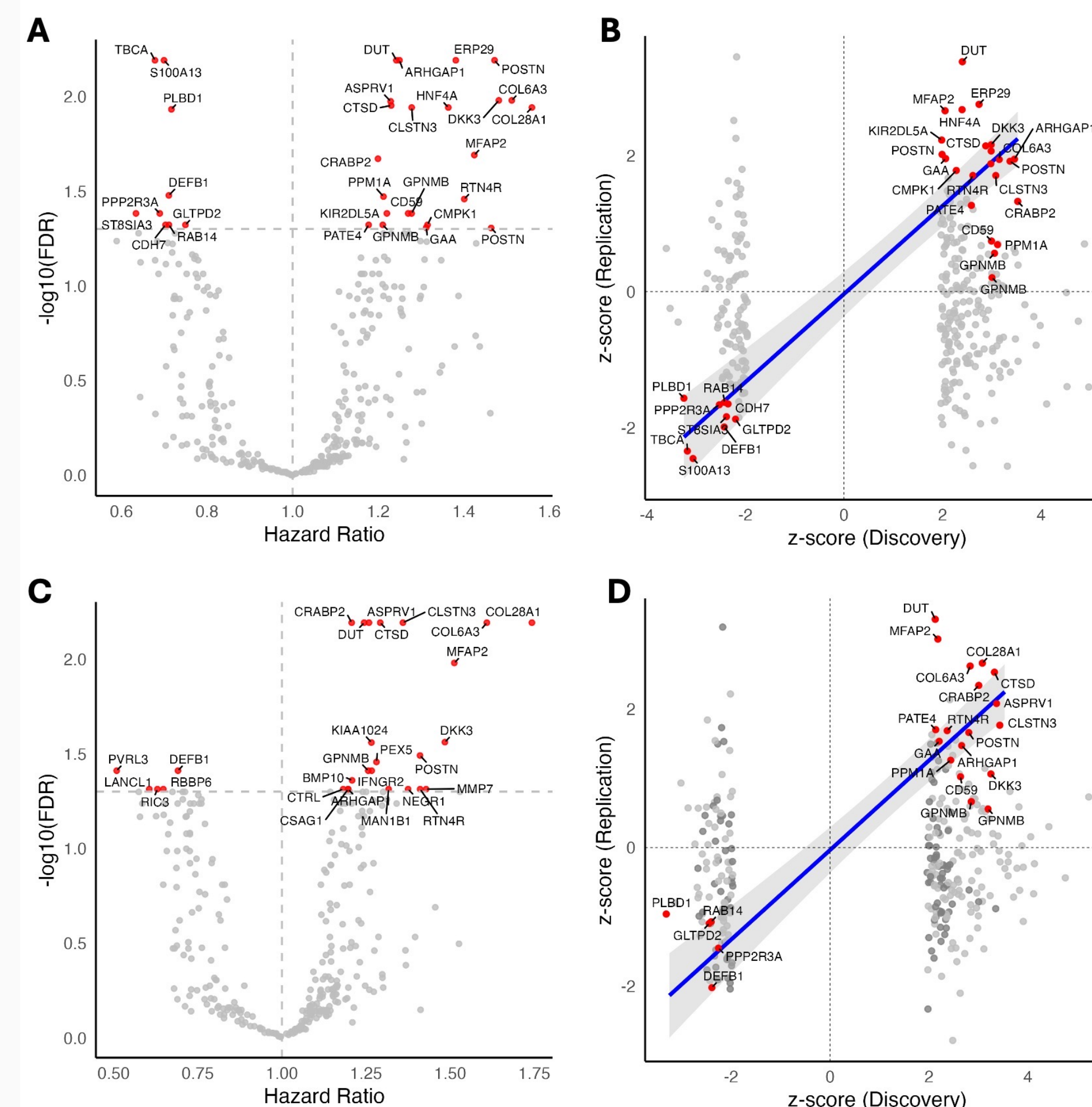
We used the SomaScan® v4.1 assay to quantify baseline serum proteins from individuals with PD: 834 participants from the Tracking Parkinson's (TPD) cohort (discovery dataset) and 371 participants from the Oxford Parkinson's Disease Centre (OPDC) cohort (replication dataset). All participants underwent serial cognitive assessments using the Montreal Cognitive Assessment (MoCA). Dementia was defined based on MoCA scores ≤ 21 . ≥ 2 affected cognitive domains and impaired activities of daily living, as defined by the MDS-UPDRS part 11. We used Cox proportional hazards models adjusted for sex, age and disease duration at serum sampling and APOE $\epsilon 4$ status to identify proteins associated with time-to-dementia. Proteins nominally significant in the discovery stage were used in the replication stage, and results were meta-analysed. We then performed pathway enrichment analysis and two-sample Mendelian Randomisation to explore causality between proteins identified in the survival analysis and dementia outcomes, using publicly available pQTL and GWAS summary data, and testing for directionality, pleiotropy and heterogeneity. P-values were corrected using the Benjamini-Hochberg method (FDR).

Cohort description

		Discovery (TPD)				Replication (OPDC)			
		PD total N=834	PD N=678	PDD N=83	P-value	PD total N=371	PD N=303	PDD N=58	P-value
Sex, n (%)	Female	308 (36.9)	272 (40.1)	18 (21.7)	0.001	137 (36.9)	119 (39.3)	15 (25.9)	0.053
	Male	526 (63.1)	406 (59.9)	65 (78.3)		234 (63.1)	184 (60.7)	43 (74.1)	
Age onset, median (IQR)		65.2 (12.3)	64.4 (12.3)	68.6 (8.7)	3.7e-06	65.4 (12.9)	64.9 (14.1)	69.4 (11.6)	1.8e-04
Age baseline, median (IQR)		68.1 (11.9)	67.0 (11.9)	72.1 (7.8)	3.7e-08	68.1 (13.3)	67.5 (3.6)	72.3 (11.7)	1.6e-04
Disease duration baseline, median (IQR)		11 (1.6)	11 (1.6)	11 (1.5)	0.53	0.70 (0.9)	0.73 (1.0)	0.65 (0.9)	0.84
MoCA baseline, median (IQR)		26 (5)	26 (4)	22 (4)	2.8e-13	26 (5)	26 (4)	23 (4)	2.7e-08
APOE status, n (%)	$\epsilon 4$ carrier	217 (26.0)	167 (24.6)	35 (42.2)	1.9e-04	88 (23.7)	60 (19.8)	24 (41.4)	2.6e-04
	$\epsilon 4$ non-carrier	525 (62.9)	452 (66.7)	38 (45.8)		246 (66.3)	213 (70.3)	28 (48.3)	
	Missing	92 (11.0)	59 (8.7)	10 (12.0)		37 (10.0)	30 (9.9)	6 (10.3)	

In both discovery and replication cohorts, participants who developed dementia were older at disease onset and at the baseline assessment. The dementia groups had the highest proportion of male participants and of APOE $\epsilon 4$ allele carriers. The median ($\pm$ IQR) time between baseline serum sampling and the development of dementia was 3.11 ($\pm$ 2.97) and 3.79 ($\pm$ 3.80) years in the TPD and OPDC cohorts, respectively.

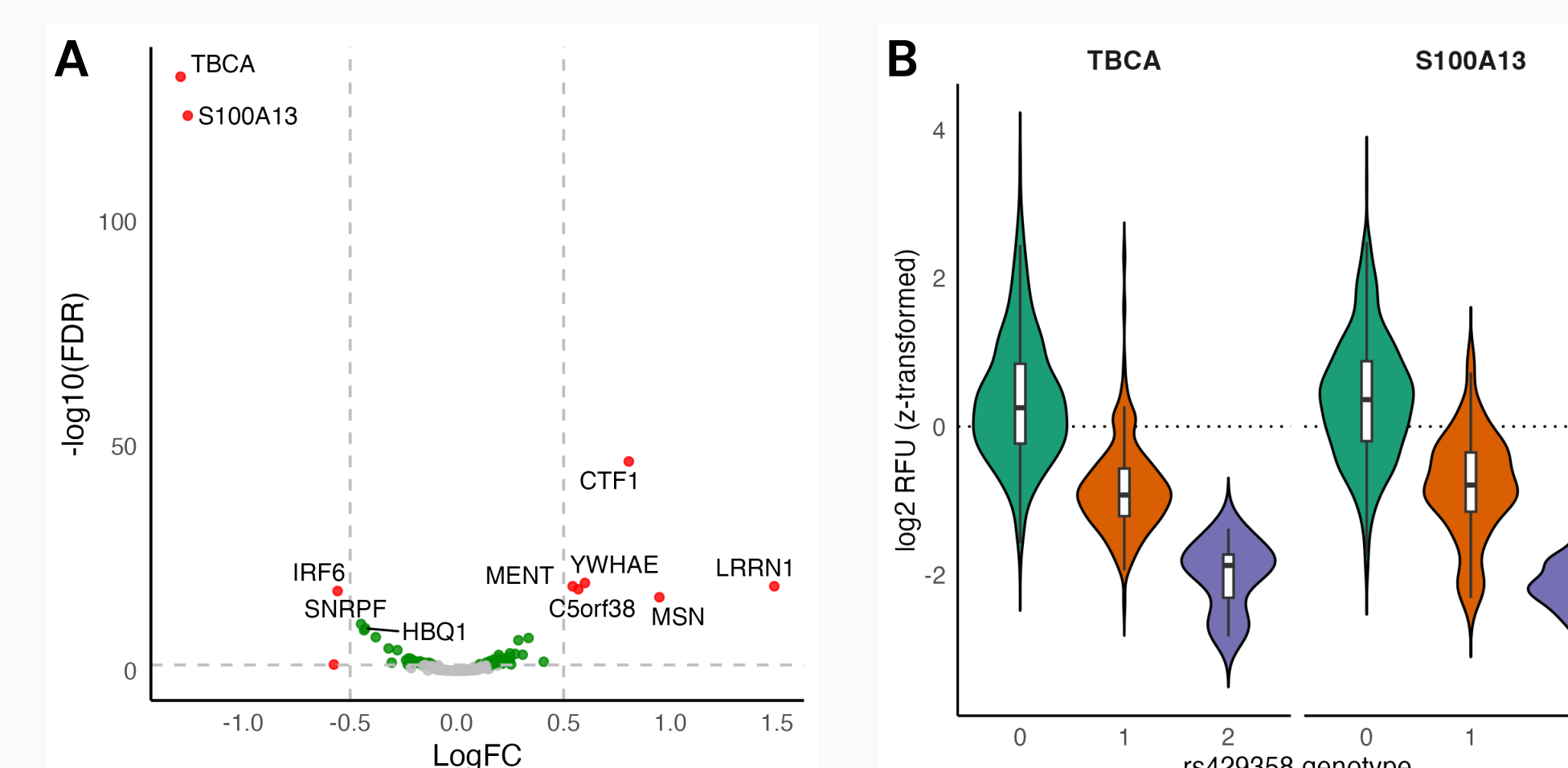
Survival meta-analysis identified proteins associated with progression to dementia



(A-C) Volcano plot of survival meta-analysis without (A) and with (C) APOE $\epsilon 4$ as a covariate. (B-D) Correspondence plot between the z-score of the estimate in the Discovery and Replication cohorts without (B) and with (D) APOE $\epsilon 4$ as a covariate. There was a strong correlation between the z-score of the effect sizes of significant proteins in both cohorts (Pearson's correlation: $r = 0.90$, $P = 3.69e-12$).

Colour scheme: red, FDR-adjusted $P < 0.05$; grey, FDR-adjusted $P > 0.05$.

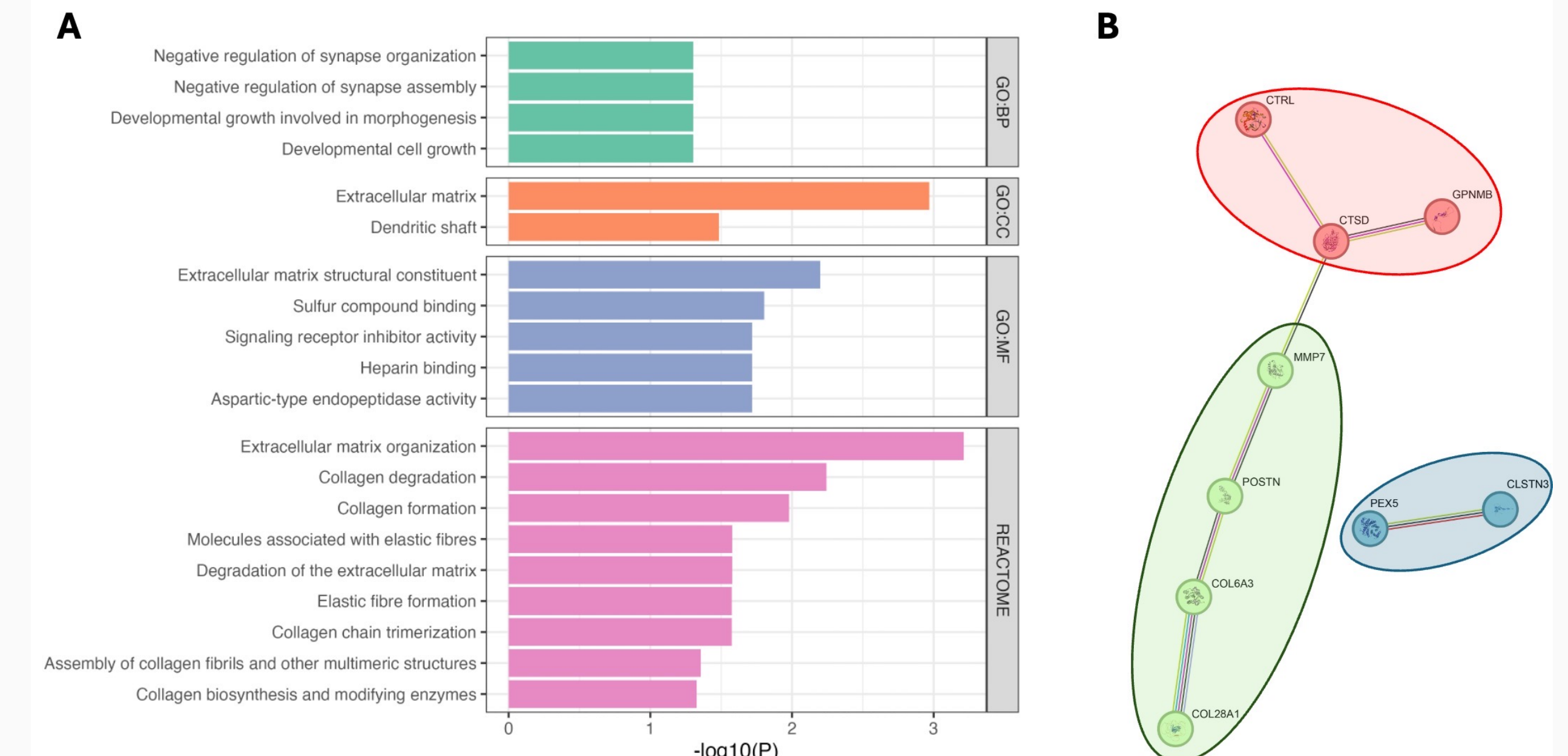
Some proteins associated with dementia in PD are regulated by the APOE genotype



(A) Volcano plot of differential protein abundance meta-analysis in PD cases with and without the APOE $\epsilon 4$ allele. TBCA and S100A13 were the only proteins in common with the survival meta-analysis. (B) Violin plots demonstrating a dose-dependent association of the APOE $\epsilon 4$ tagging SNP rs429358 with protein levels of TBCA and S100A13 in the discovery cohort. Mediation analysis did not find evidence that TBCA or S100A13 significantly mediate the effect of APOE $\epsilon 4$ on dementia risk.

Colour scheme: red, FDR-adjusted $P < 0.05$ and $|\log FC| > 0.5$; green, FDR-adjusted $P < 0.05$ and $|\log FC| < 0.5$; grey, FDR-adjusted $P > 0.05$.

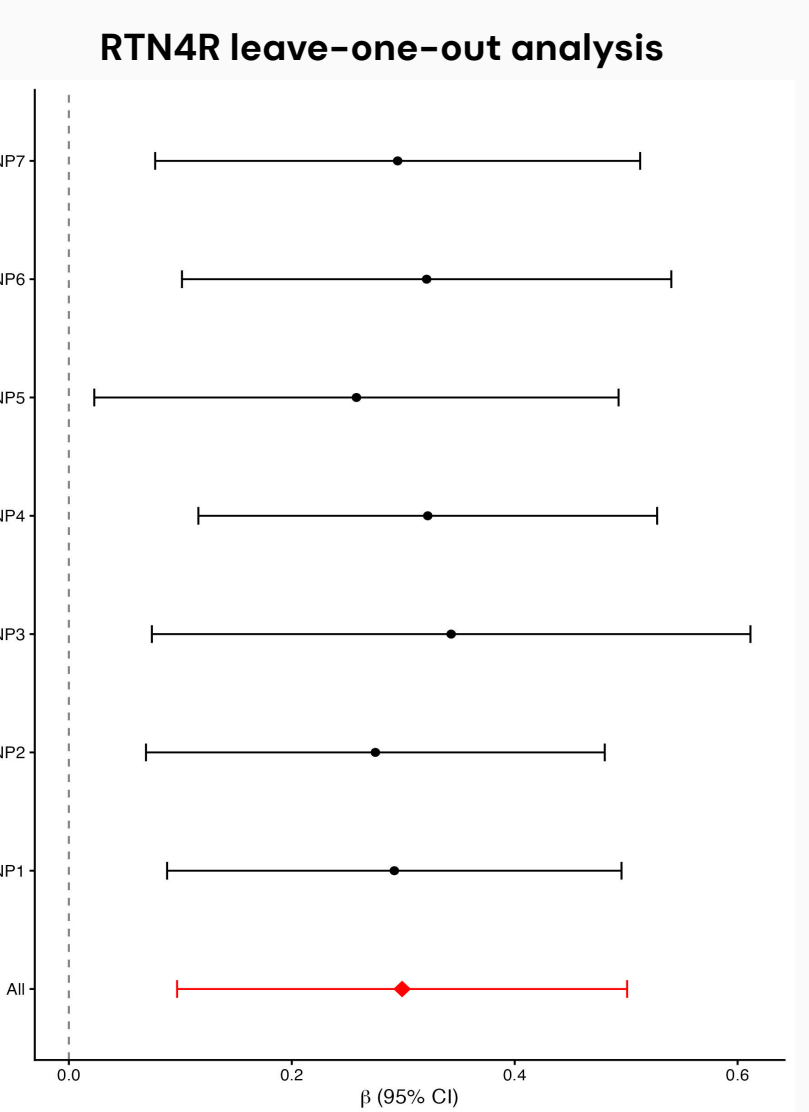
Proteins associated with dementia are predominantly involved in synaptic plasticity, protein degradation and extracellular matrix organisation



MR identified a causal association between genetically predicted levels of RTN4R and the hazard of developing Lewy body dementia

		AD (Bellenguez et al, 2022)				Outcome				PDD (Real et al, 2023)							
Exposure	Method	nSNP	BETA	SE	PVAL	P_FDR	nSNP	LBD	BETA	SE	PVAL	P_FDR	nSNP	Real	SE	PVAL	P_FDR
BMP10	IVW	5	-0.015	0.02	0.45	0.92	4	-0.064	0.12	0.59	0.89	—	—	—	—	—	—
CD59	IVW	2	0.018	0.04	0.66	0.92	3	-0.137	0.18	0.44	0.61	—	—	—	—	—	—
CLSTN3	IVW	12	-0.002	0.02	0.90	0.92	6	-0.008	0.09	0.93	0.94	—	—	—	—	—	—
COL28A1	IVW	22	-0.018	0.01	0.06	0.47	12	0.047	0.04	0.25	0.55	4	-0.043	0.18	0.80	0.91	0.91
COL6A3	IVW	2	-0.029	0.12	0.81	0.92	—	—	—	—	—	—	2	0.881	0.95	0.36	0.87
	Wald ratio	—	—	—	—	—	1	-0.478	0.74	0.52	0.70	—	—	—	—	—	—
CTRL	Wald ratio	1	0.16	0.12	0.20	0.20	1	-0.217	0.57	0.70	0.70	1	2.254	1.29	0.08	0.16	0.16
CTSD	IVW	7	-0.008	0.03	0.78	0.92	5	0.025	0.12	0.83	0.94	3	0.281	0.55	0.61	0.87	0.87
DKK3	IVW	10	0.006	0.04	0.88	0.92	3	-0.208	0.19	0.28	0.55	2	-0.08	0.69	0.91	0.91	0.91
GNPMB	IVW	8	-0.010	0.03	0.70	0.92	2	-0.14	0.15	0.35	0.55	4	-0.709	0.40	0.08	0.39	0.39
IFNGR2	IVW	31	0.006	0.01	0.51	0.92	6	-0.107	0.09	0.25	0.55	5	0.040	0.17	0.81	0.91	0.91
MMP7	IVW	4	0.048	0.03	0.09	0.47	—	—	—	—	—	—	2	0.164	0.32	0.61	0.87
	Wald ratio	—	—	—	—	—	1	-0.682	0.36	0.06	0.18	—	—	—	—	—	—
POSTN	IVW	7	0.049	0.03	0.10	0.47	4	0.146	0.15	0.33	0.55	3	0.669	0.35	0.06	0.39	0.39
RTN4R	IVW	7	0.018	0.03	0.49	0.92	7	0.299	0.10	0.00	0.04	5	-0.340	0.30	0.25	0.83	0.83
S100A13	IVW	5	0.030	0.05	0.57	0.92	4	0.014	0.19	0.94	0.94	3	-0.40	0.57	0.68	0.87	0.87
TBCA	IVW	2	-0.005	0.06	0.92	0.92	2	-0.406	0.30	0.17	0.55	—	—	—	—	—	—
	Wald ratio	—	—	—	—	—	—	—	—	—	—	—	1	0.341	0.72	0.43	0.67

Criteria for genetic instrument selection: ± 1 Mb cis window, P -value $< 5e-8$; F-statistic > 10 . LD clumping was performed using default settings ($r^2 < 0.001$; clump window ± 10 Mb) using the 1000 Genomes European reference panel. pQTL data used as genetic instruments obtained from Hawkes et al, 2025. IVW, Inverse variance weighted.



Discussion

- We identified several serum proteins associated with progression to dementia in PD
- Changes in blood proteome precede development of clinical symptoms by many years, providing a window of opportunity to identify at-risk individuals early on
- Dysregulated proteins are involved in synaptic function and protein clearance
- Some of these proteins could reflect upregulation of neuroprotective mechanisms (e.g., CTSD, GNMB)
- MR analysis suggested a causal association between the Nogo receptor RTN4R and Lewy body dementia