

Validating Selected Candidate Mechanisms by High-throughput Proteomics – First results

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THE HUMAN PROTEIN ATLAS

Explore the Pathology Atlas

Welcome to the Pathology Atlas in which the patient overall survival as a consequence of the transcript levels of all individual human genes can be explored across all major cancer types. Here, individual genes and/or various cancer types can be investigated using an interactive and open access database. The atlas is described in more detail by Uhlen et al "A pathology atlas of the human cancer transcriptome" in Science (August 18, 2017). [Read more](#)

Explore the Cell Atlas

Spatial partitioning of biological processes is a phenomenon fundamental to life. The Cell Atlas resolves the spatial distribution of the human proteome at a subcellular level. A multitude of high-resolution confocal images are presented in this interactive database, describing organelle proteomes, multilocalizing proteins and single cell variations - altogether detailing the complex map of the human cell. [Read more](#)

Explore the Tissue Atlas

The tissue-restricted expression of the human proteome and transcriptome can be explored in all major tissues and organs in the human body. The list of genes with elevated expression in a particular tissue can be accessed with direct links to the primary data (images). [Read more](#)

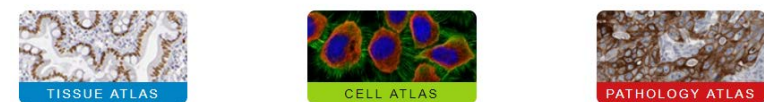


image of the day

Version: 17
Atlas updated: 2017-08-17
[release history](#)

Proteome analysis based on 25682 antibodies targeting 16998 unique proteins.

Find us at *Wallenberg* *LifeScience*

The Human Protein Atlas project is funded by the Knut & Alice Wallenberg foundation.

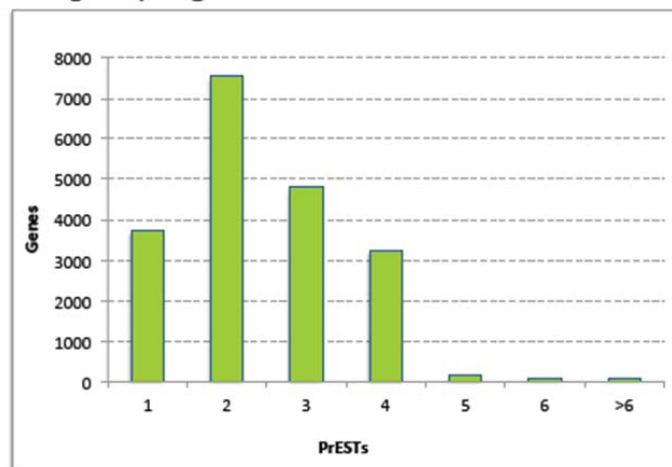


Current numbers in HPA

	Unique genes
57 697 sequence verified clones	19 171
42 970 MS verified antigens (~80aa)	19 021
50 027 array verified antibodies	18 858
25 511 antibodies on tissues with IHC	17 166
32 982 antibodies in cells with IF	17 232

Ensembl (83.38): **19628** genes
UniProt: **20197** genes

Antigens per gene



Human Protein Atlas in tissues

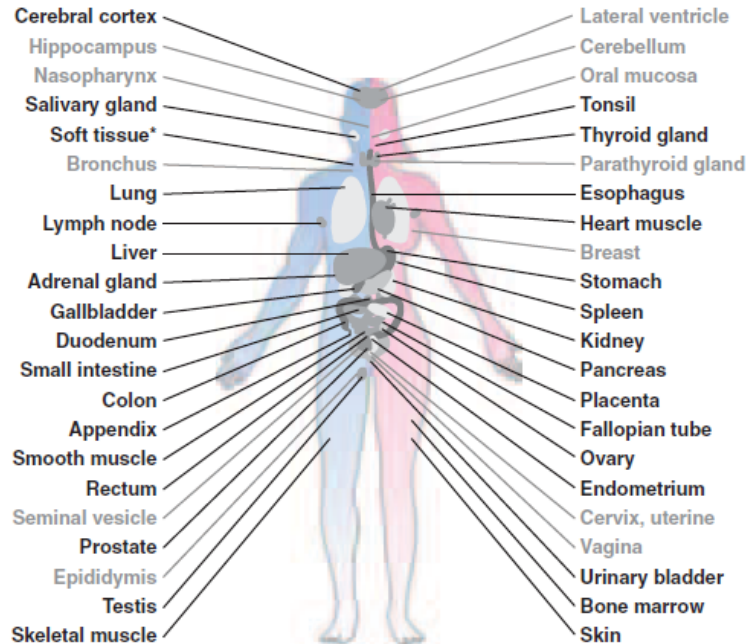
RESEARCH ARTICLE

Science
Jan 2015

PROTEOMICS

Tissue-based map of the human proteome

Mathias Uhlen,^{1,2,3*} Linn Fagerberg,¹ Björn M. Hallström,^{1,2} Cecilia Lindskog,⁴ Per Oksvold,¹ Adil Mardinoglu,⁵ Åsa Sivertsson,¹ Caroline Kampf,⁴ Evelina Sjöstedt,^{1,4} Anna Asplund,⁴ IngMarie Olsson,⁴ Karolina Edlund,⁶ Emma Lundberg,¹ Sanjay Navani,⁷ Cristina Al-Khalili Szgyarto,² Jacob Odeberg,¹ Dijana Djureinovic,⁴ Jenny Ottosson Takanen,² Sophia Hober,² Tove Alm,¹ Per-Henrik Edqvist,⁴ Holger Berling,² Hanna Tegel,² Jan Mulder,⁸ Johan Rockberg,² Peter Nilsson,¹ Jochen M. Schwenk,¹ Marica Hamsten,² Kalle von Feilitzen,¹ Mattias Forsberg,¹ Lukas Persson,¹ Fredric Johansson,¹ Martin Zwahlen,¹ Gunnar von Heijne,⁹ Jens Nielsen,^{3,5} Fredrik Pontén⁴



■ RNA and protein data
■ Only protein data

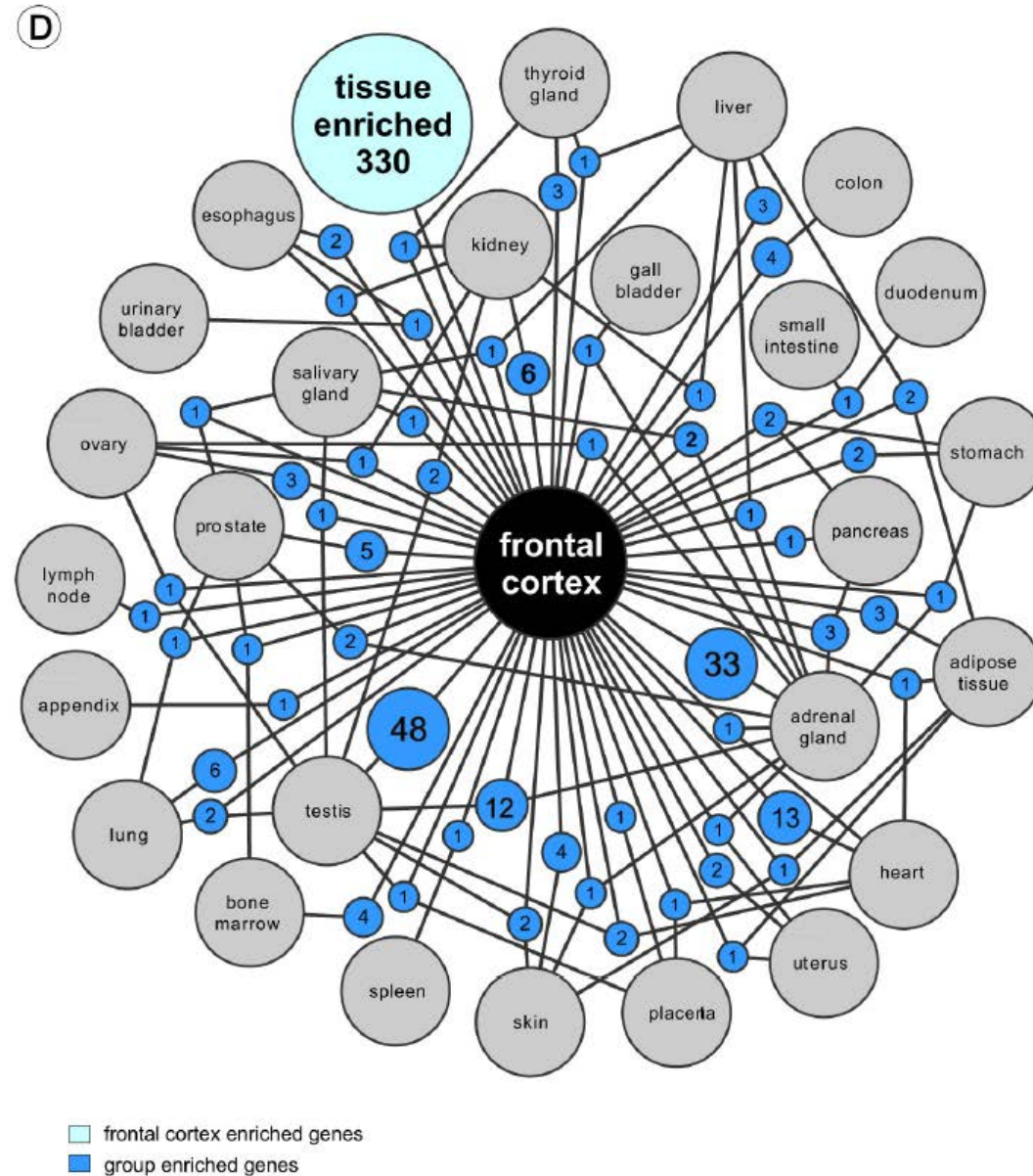
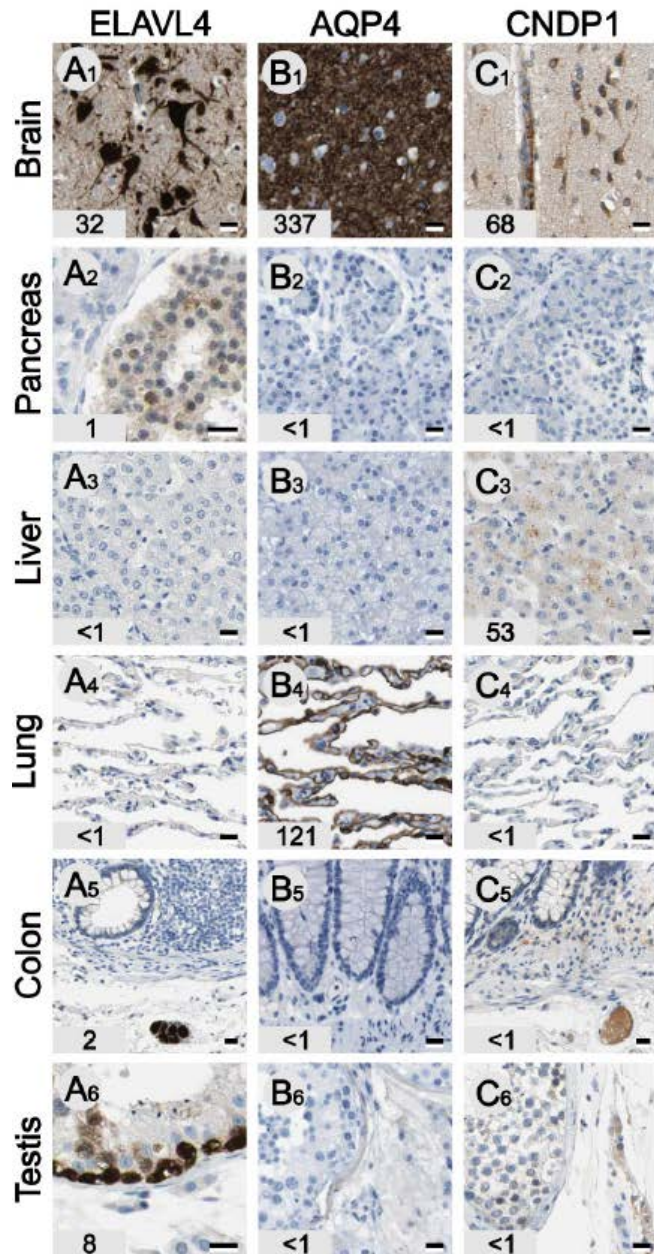
13 million images



The brain proteome

Defining the Human Brain Proteome Using Transcriptomics and Antibody-Based Profiling with a Focus on the Cerebral Cortex

Evelina Sjöstedt^{1,2}, Linn Fagerberg¹, Björn M. Hallström¹, Anna Häggmark¹, Nicholas Mitsios³, Peter Nilsson¹, Fredrik Pontén², Tomas Hökfelt³, Mathias Uhlén¹, Jan Mulder^{3*}



Human Protein Atlas in cells

Science

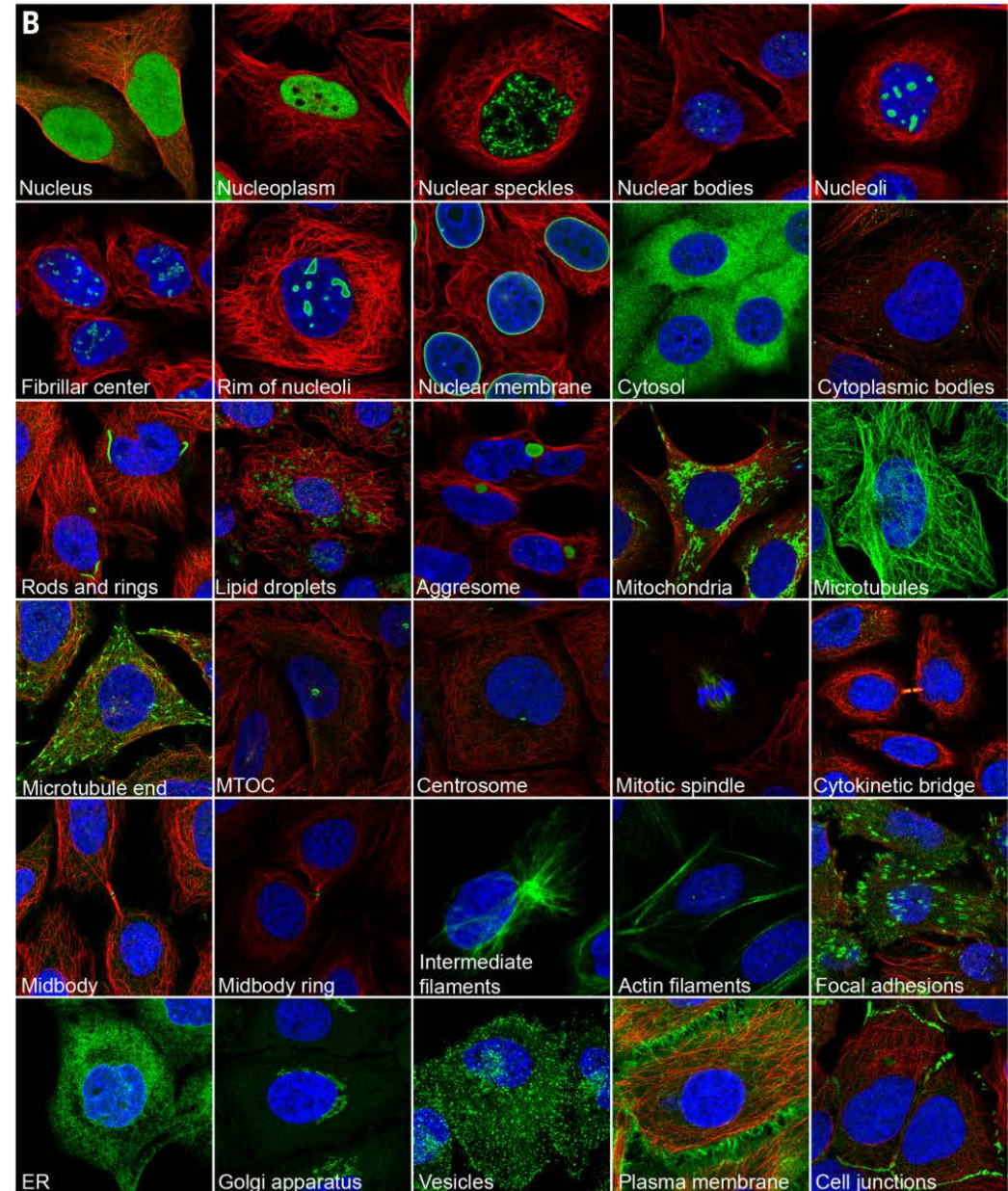
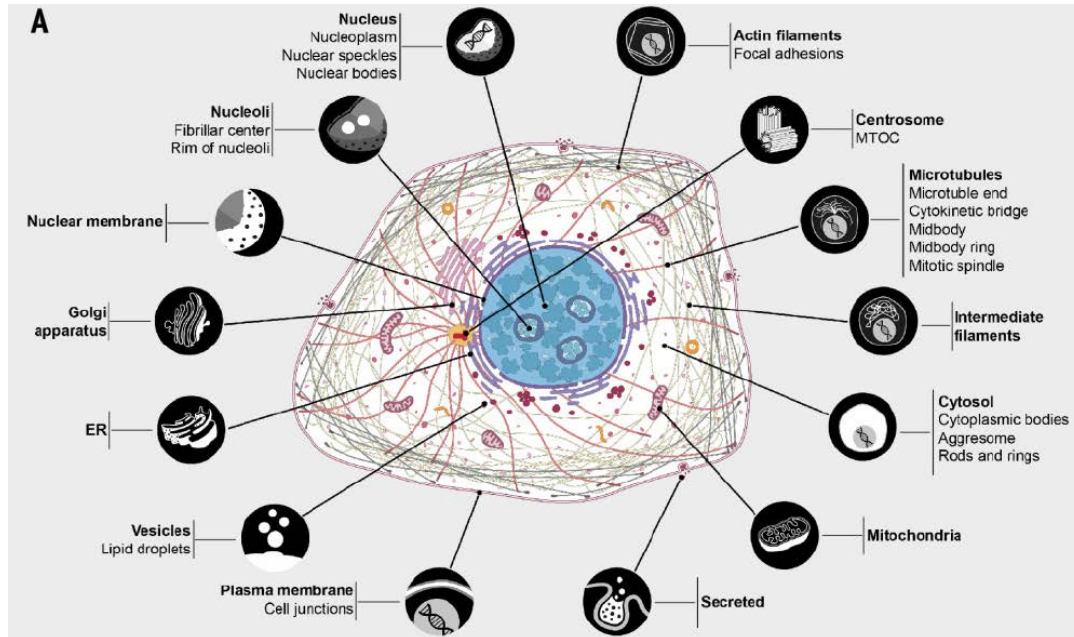
Science
May 2017

RESEARCH ARTICLES

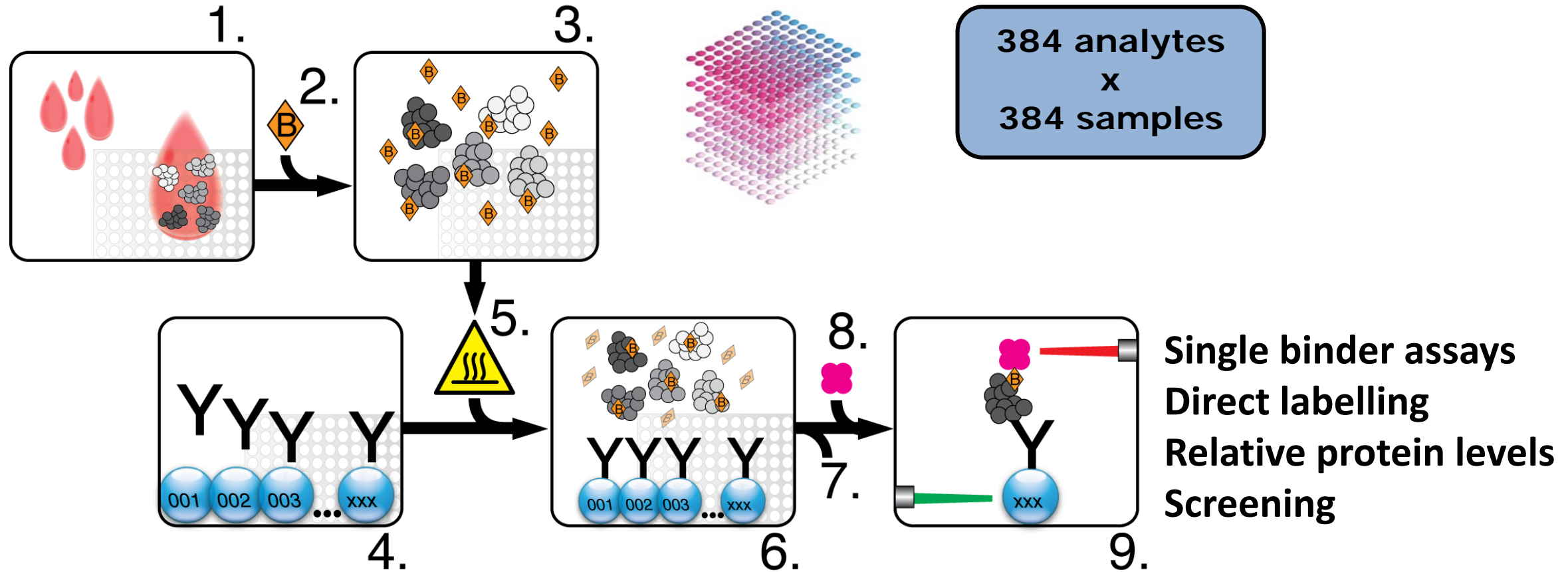
Cite as: P. J. Thul *et al.*, *Science*
10.1126/science.aal3321 (2017).

A subcellular map of the human proteome

Peter J. Thul,^{1*} Lovisa Åkesson,^{1*} Mikaela Wiking,¹ Diana Mahdessian,¹ Aikaterini Geladaki,^{2,3} Hammou Ait Blal,¹ Tove Alm,¹ Anna Asplund,⁴ Lars Björk,¹ Lisa M. Breckels,^{2,5} Anna Bäckström,¹ Frida Danielsson,¹ Linn Fagerberg,¹ Jenny Fall,¹ Laurent Gatto,^{2,5} Christian Gnann,¹ Sophia Hober,⁶ Martin Hjelmare,¹ Fredric Johansson,¹ Sunjae Lee,¹ Cecilia Lindskog,⁴ Jan Mulder,⁷ Claire M. Mulvey,² Peter Nilsson,¹ Per Oksvold,¹ Johan Rockberg,⁶ Rutger Schutten,¹ Jochen M. Schwenk,¹ Åsa Sivertsson,¹ Evelina Sjöstedt,⁴ Marie Skogs,¹ Charlotte Stadler,¹ Devin P. Sullivan,¹ Hanna Tegel,⁶ Casper Winsnes,¹ Cheng Zhang,¹ Martin Zwahlen,¹ Adil Mardinoglu,¹ Fredrik Pontén,⁴ Kalle von Feilitzen,¹ Kathryn S. Lilley,² Mathias Uhlén,^{1†} Emma Lundberg^{1†}



Antibody suspension bead arrays



Dec 2016

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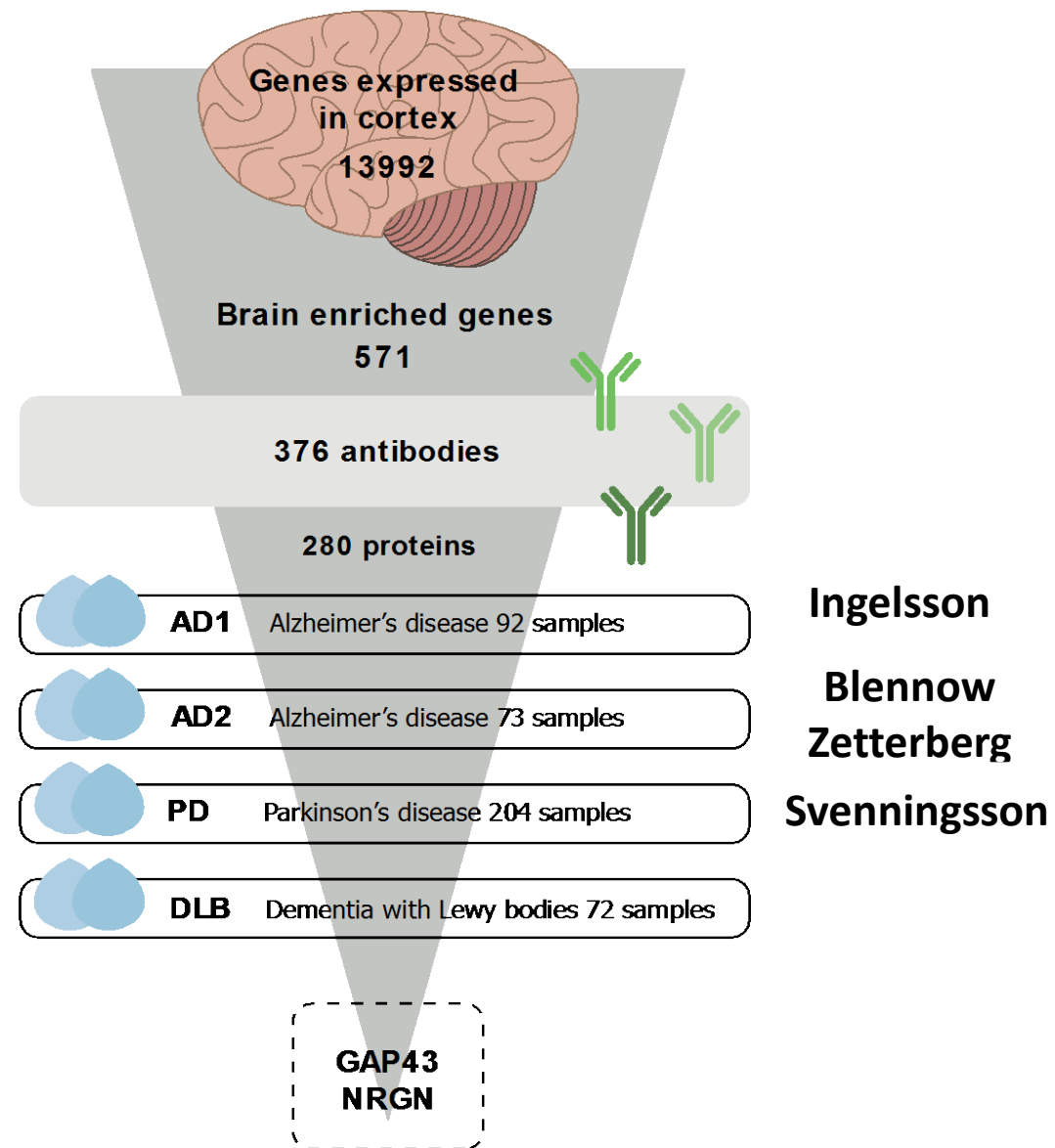
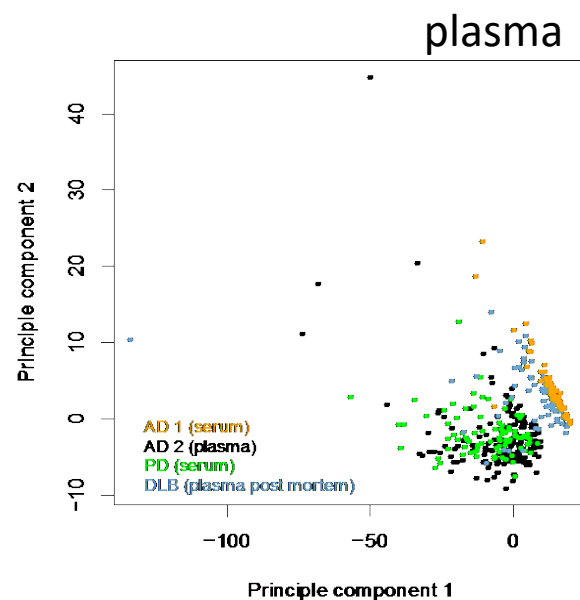
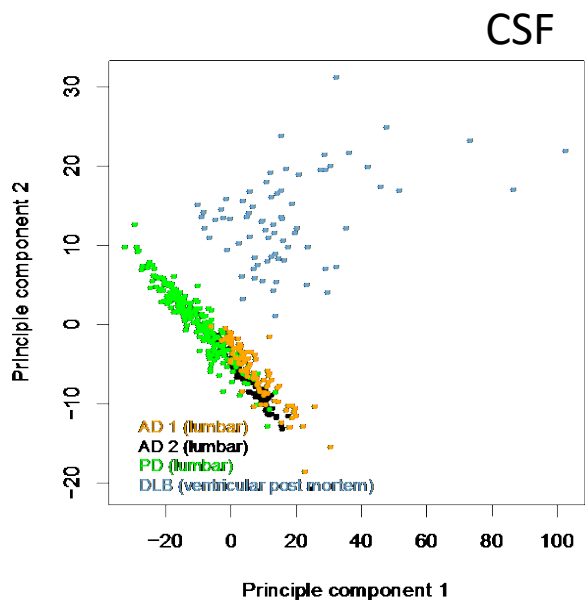
Research Article

CSF profiling of the human brain enriched proteome reveals associations of neuromodulin and neurogranin to Alzheimer's disease

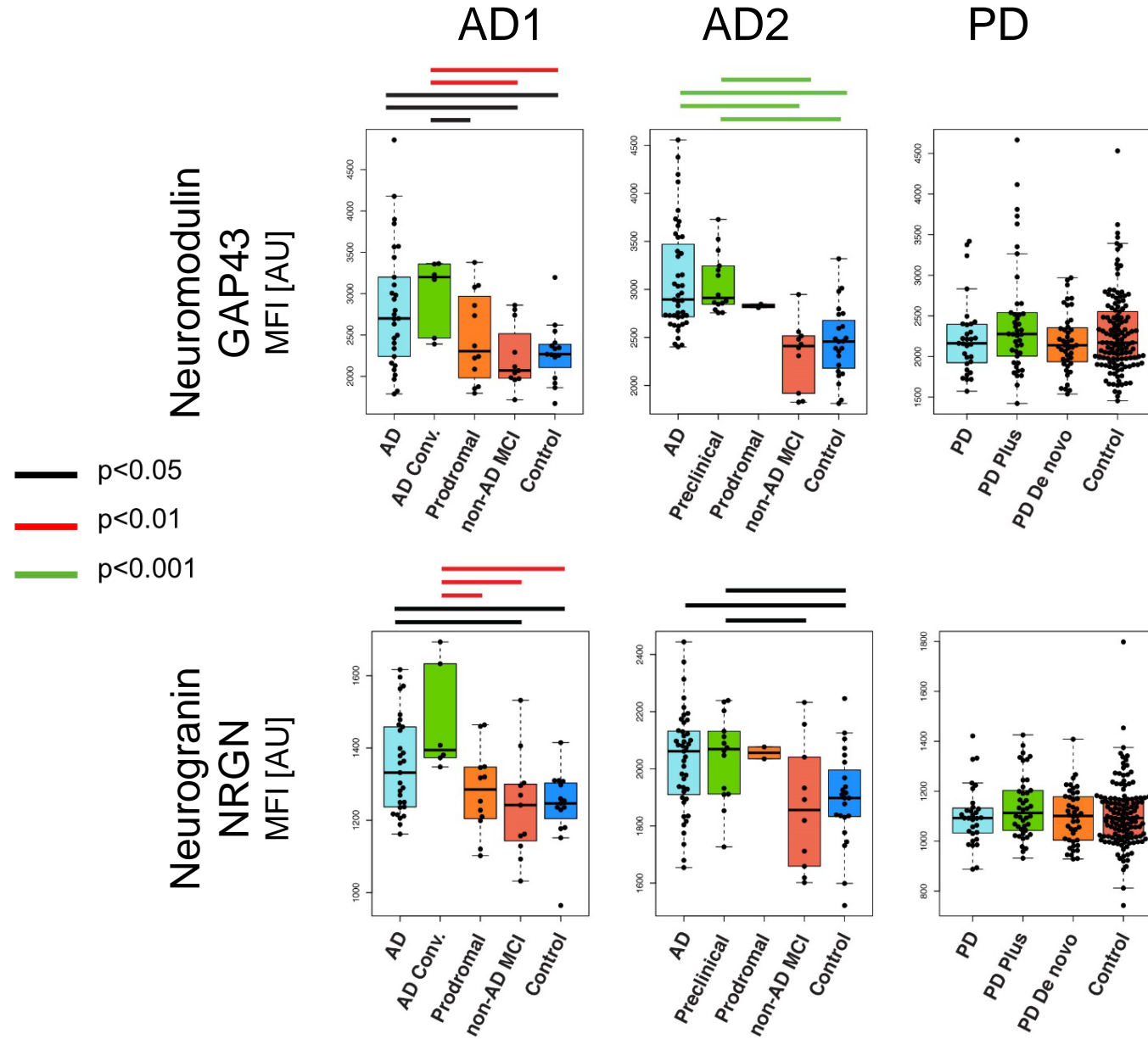
Julia Remnestål, David Just, Nicholas Mitsios, Claudia Fredolini, Jan Mulder, Jochen M Schwenk, Mathias Uhlén, Kim Kultima, Martin Ingelsson, Lena Kilander, Lars Lannfelt, Per Svenningsson, Bengt Nellgård, Henrik Zetterberg, Kaj Blennow, Peter Nilsson , Anna Häggmark-Månberg

First published: 10 October 2016 [Full publication history](#)

DOI: 10.1002/prca.201500150 [View/save citation](#)



Protein profiles in CSF



GAP43 is associated to axonal regeneration

Neurogranin regulates synaptic plasticity by regulating calmodulin

Aetionomy - Samples

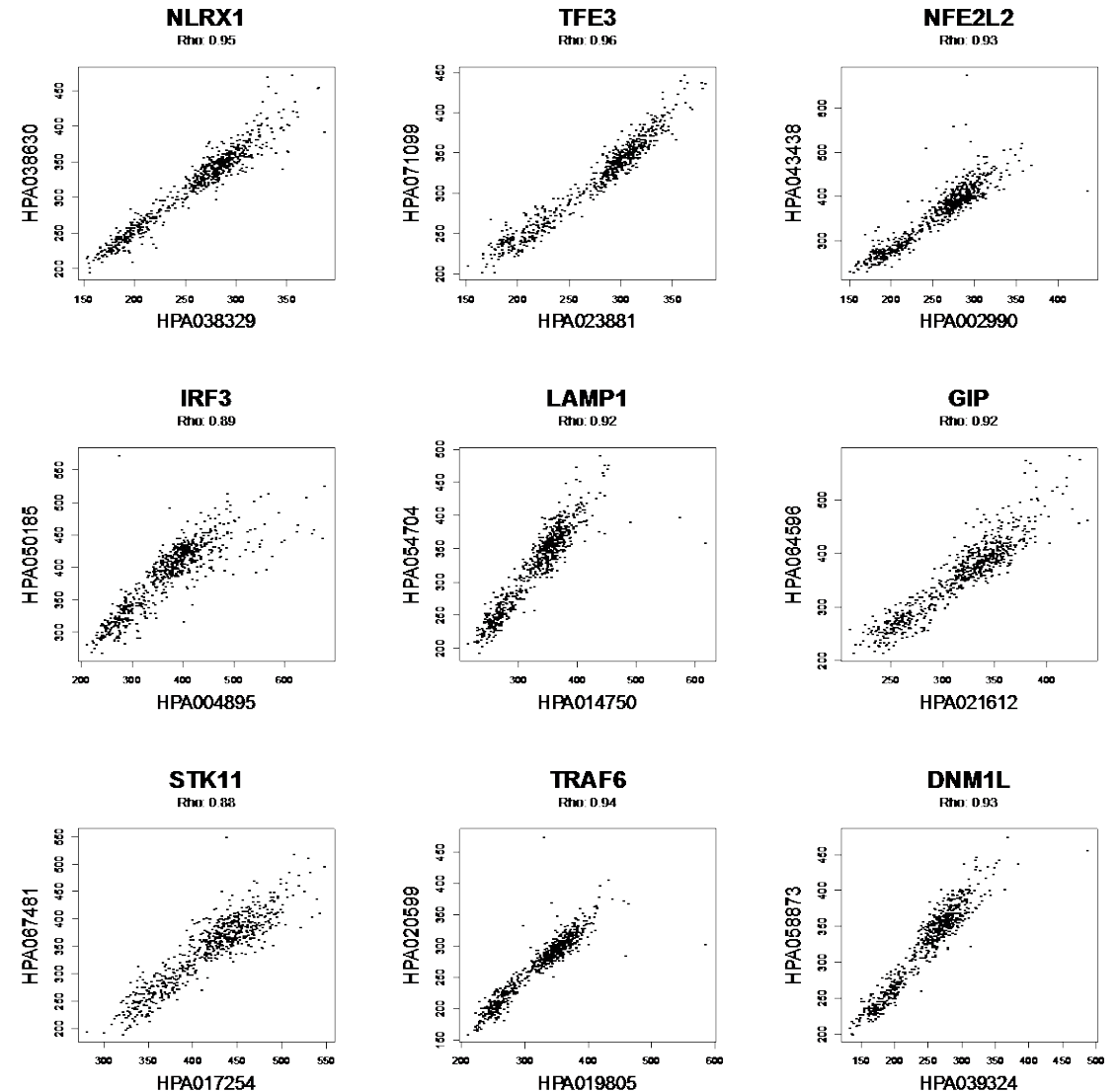
PD		Name	Sample material	total	IPD	HC-PD, HC-AD	PAD, AR- AD, AR- PD, FPD	EPD	LPD	Group comparison
Paris	Jean-Christophe Corvol	AET_01	CSF	66	39	12	1+4+7+3			iPD-Ctrl
Bonn	Ullrich Wüllner	AET_02	CSF	23	21	2				iPD-Ctrl
Stockholm	Per Svenningsson	AET_03	CSF	34	29	5				iPD-Ctrl
Tübingen		AET_04	CSF	75						-
				198	89	19	15			
Tübingen		AET_05	Plasma	249		88		95	50	LPD-EPD-Ctrl
AD				total	AD	MCI	PAD	ND	Controls	
Bonn	Michael Heneka	AET_06	CSF	220	103	77		40		AD-MCI-Ctrl
Barcelona	Raquel Sanchez-Valle	AET_07	CSF	136	67	44			25	AD-MCI-Ctrl
Paris	Bruno Dubois	AET_08	CSF	23			23			-
				379	170	121		40	25	

Antibody selection

824 CSF and plasma samples

Protein profiling of 216 proteins covered by 307 antibodies

39 novel proteins covered by 70 antibodies to enhance coverage of Aetionomy based mechanisms

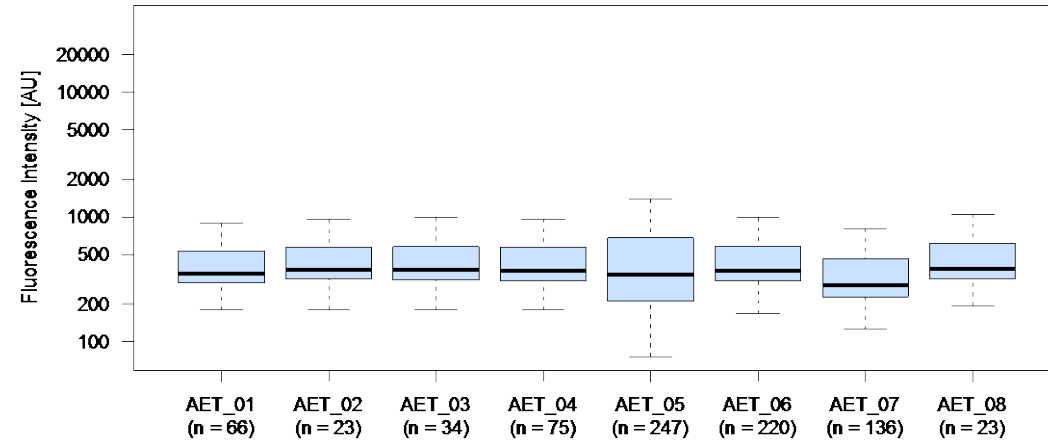


Overall characteristics of samples from cohorts

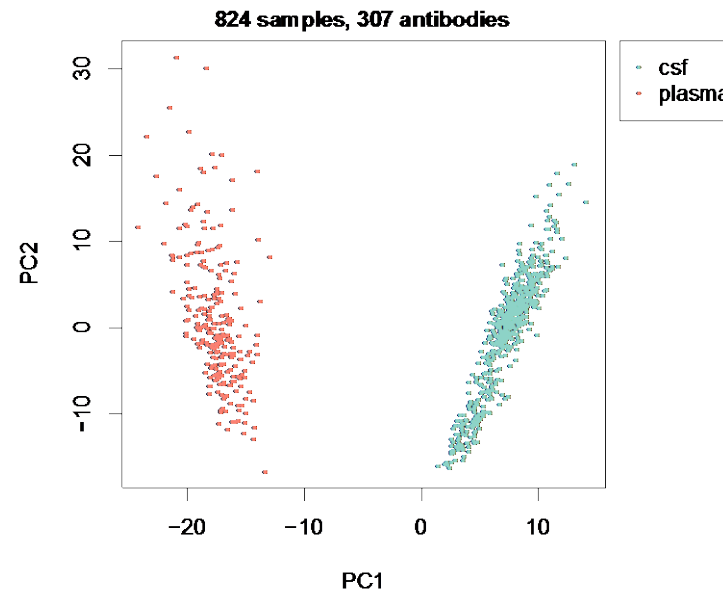
PD		Name
Paris	Jean-Christophe Corvol	AET_01
Bonn	Ullrich Wüllner	AET_02
Stockholm	Per Svenningsson	AET_03
Tübingen	CSF	AET_04
Tübingen	Plasma	AET_05

AD		
Bonn	Michael Heneka	AET_06
Barcelona	Raquel Sanchez-Valle	AET_07
Paris	Bruno Dubois	AET_08

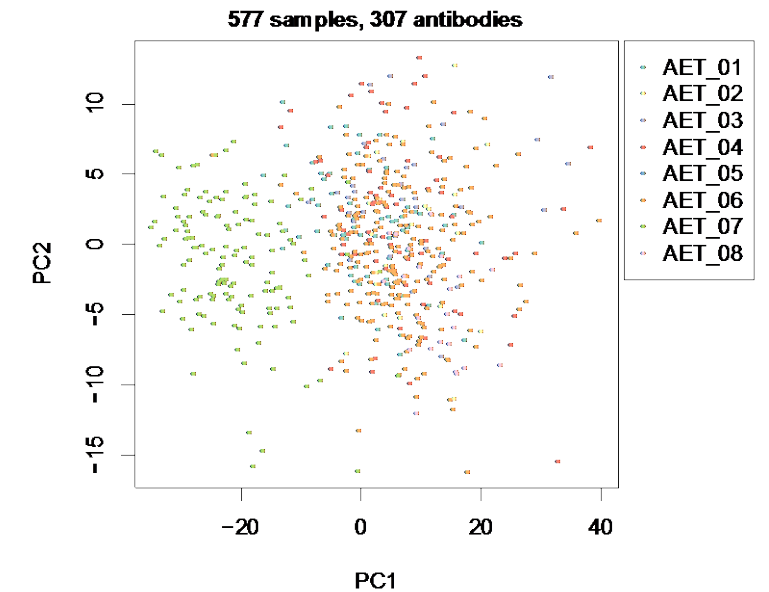
Signal per cohort



Plasma and CSF samples

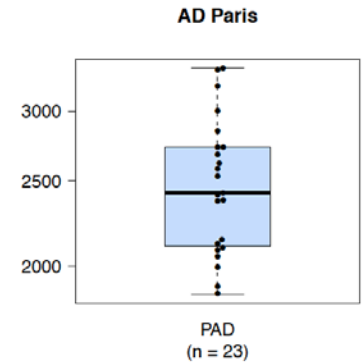
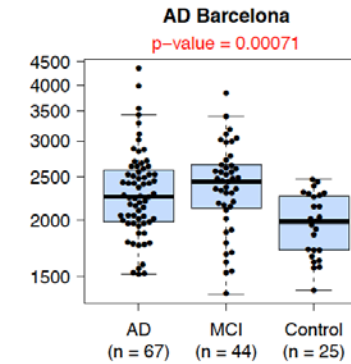
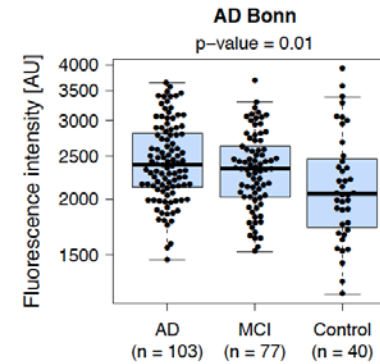
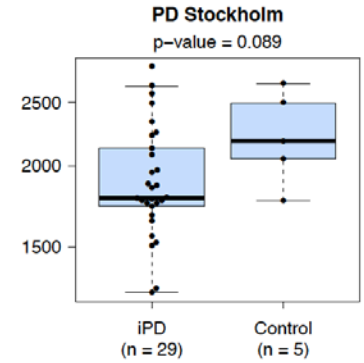
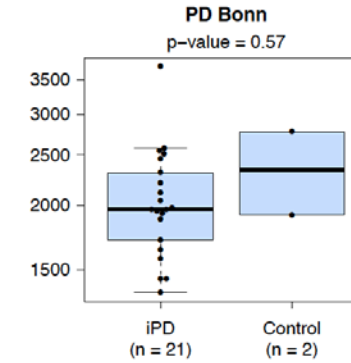
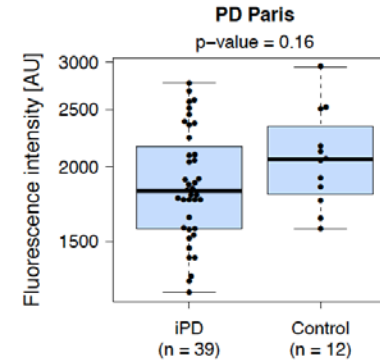
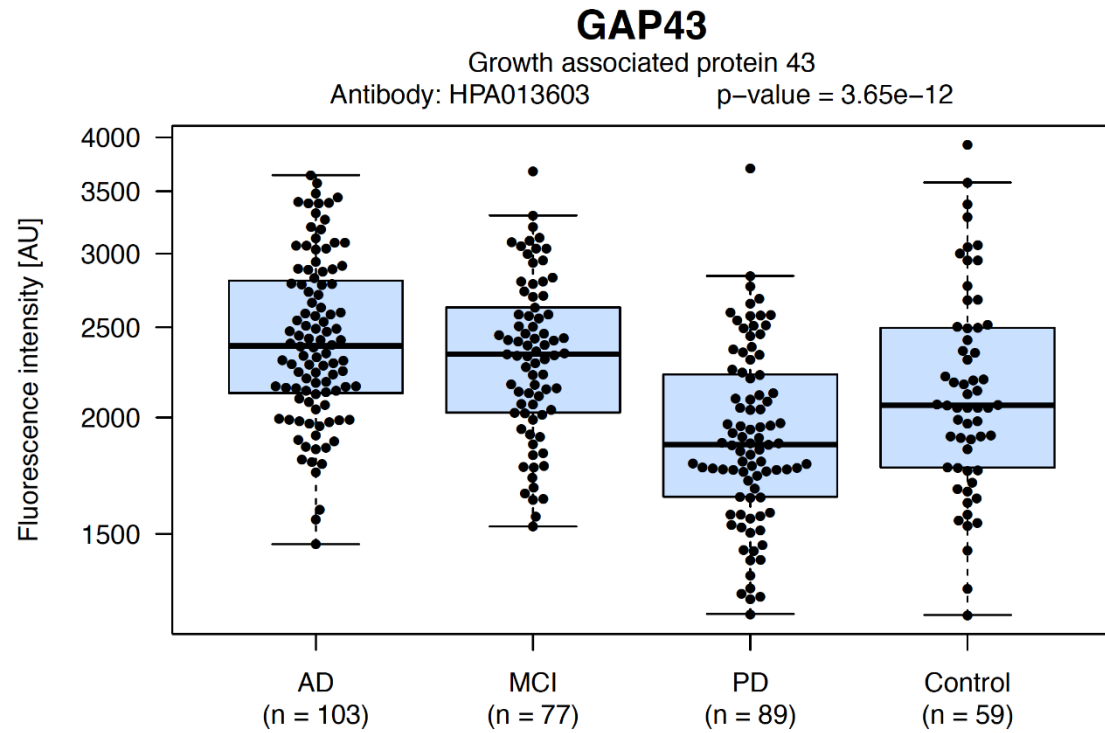


CSF samples



GAP43

Neuromodulin/ Growth associated protein 43



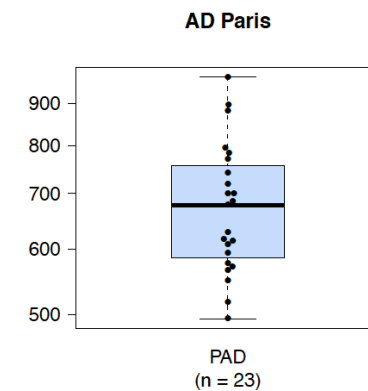
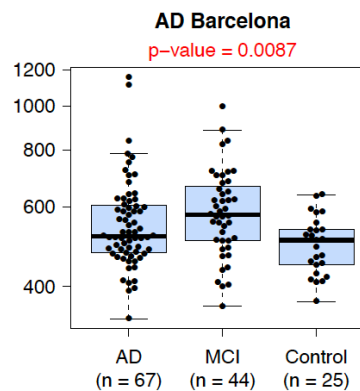
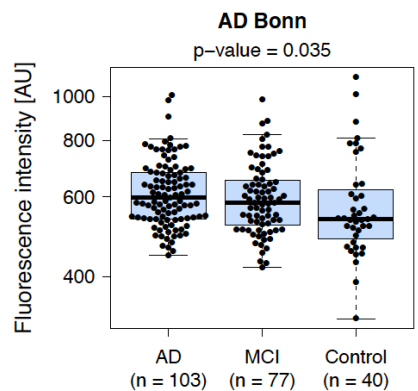
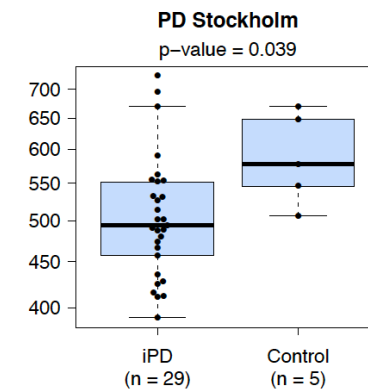
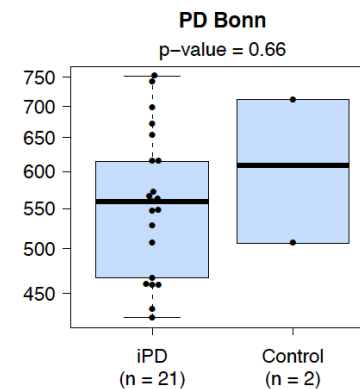
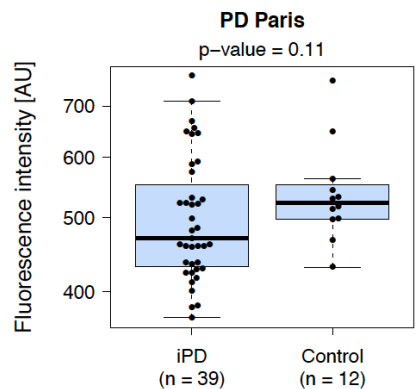
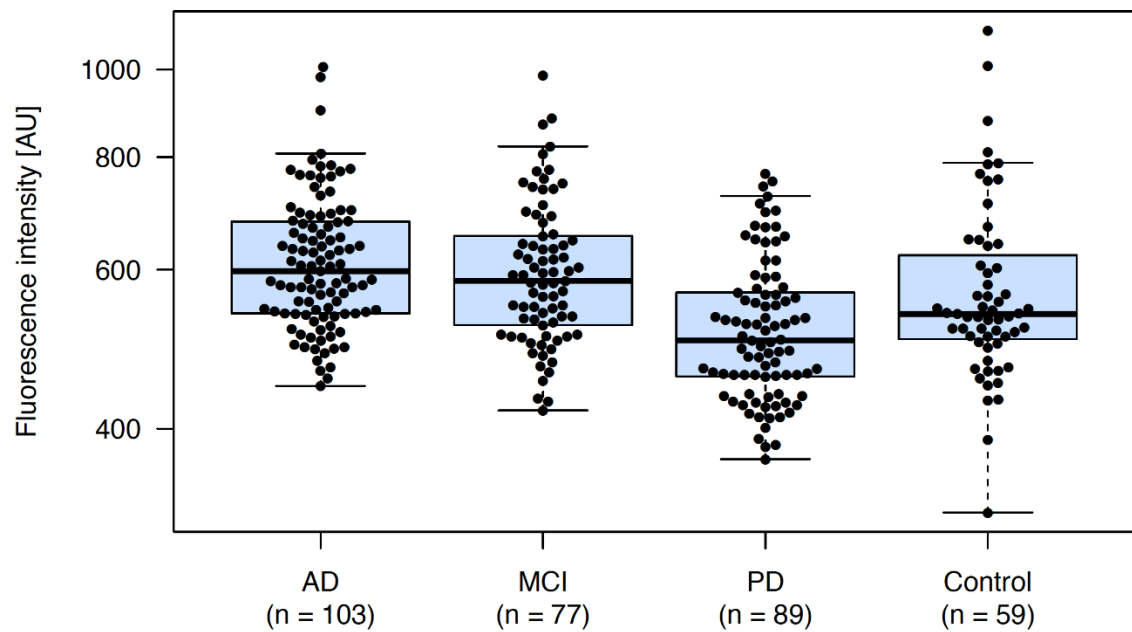
Neurogranin

NRGN

Neurogranin

Antibody: HPA038171

p-value = 7.84×10^{-10}

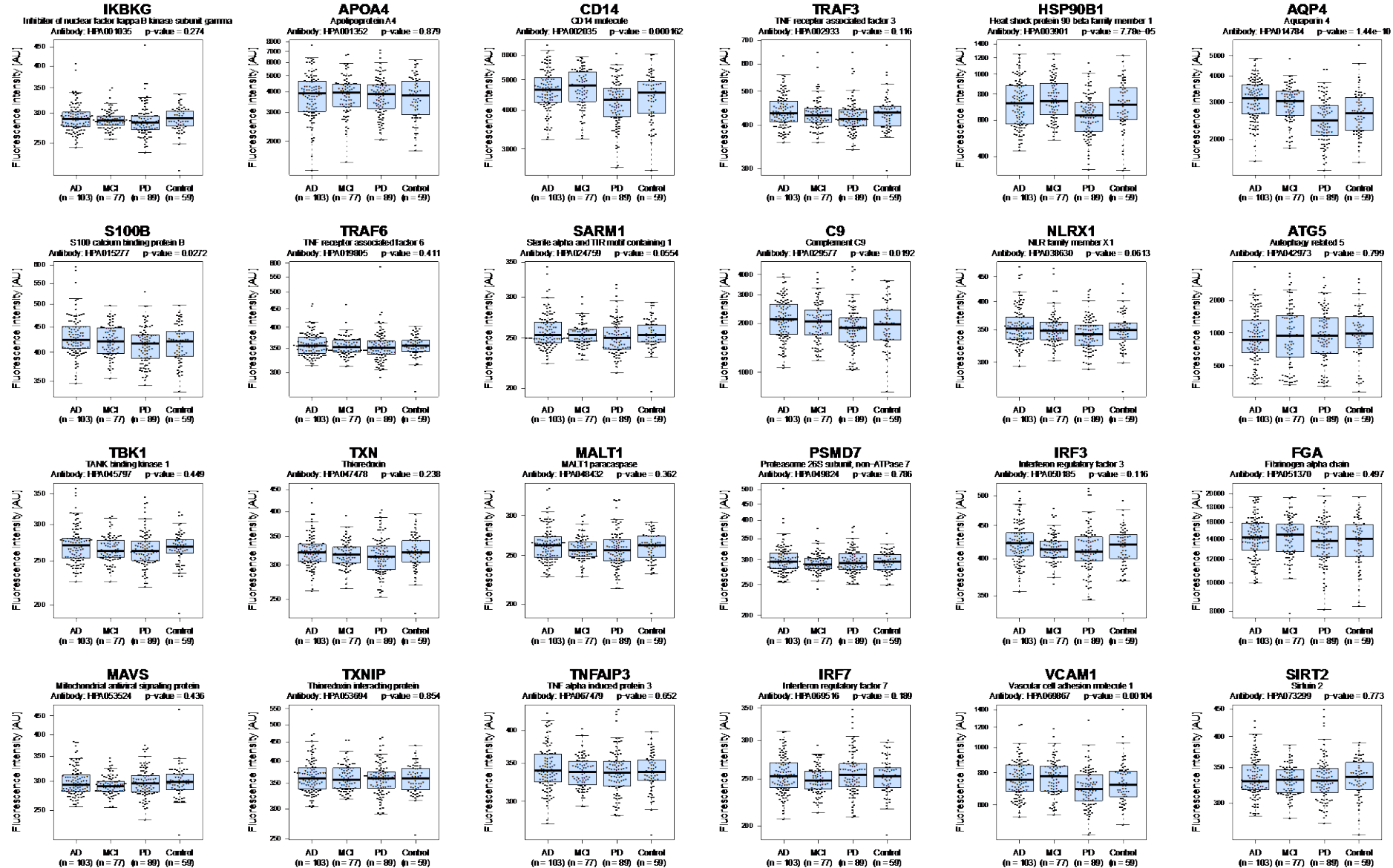


Protein targets selected from the Aetionomy candidate mechanisms:

- Innate Immunity
- Astroglial inflammation
- Diabetes related pathways

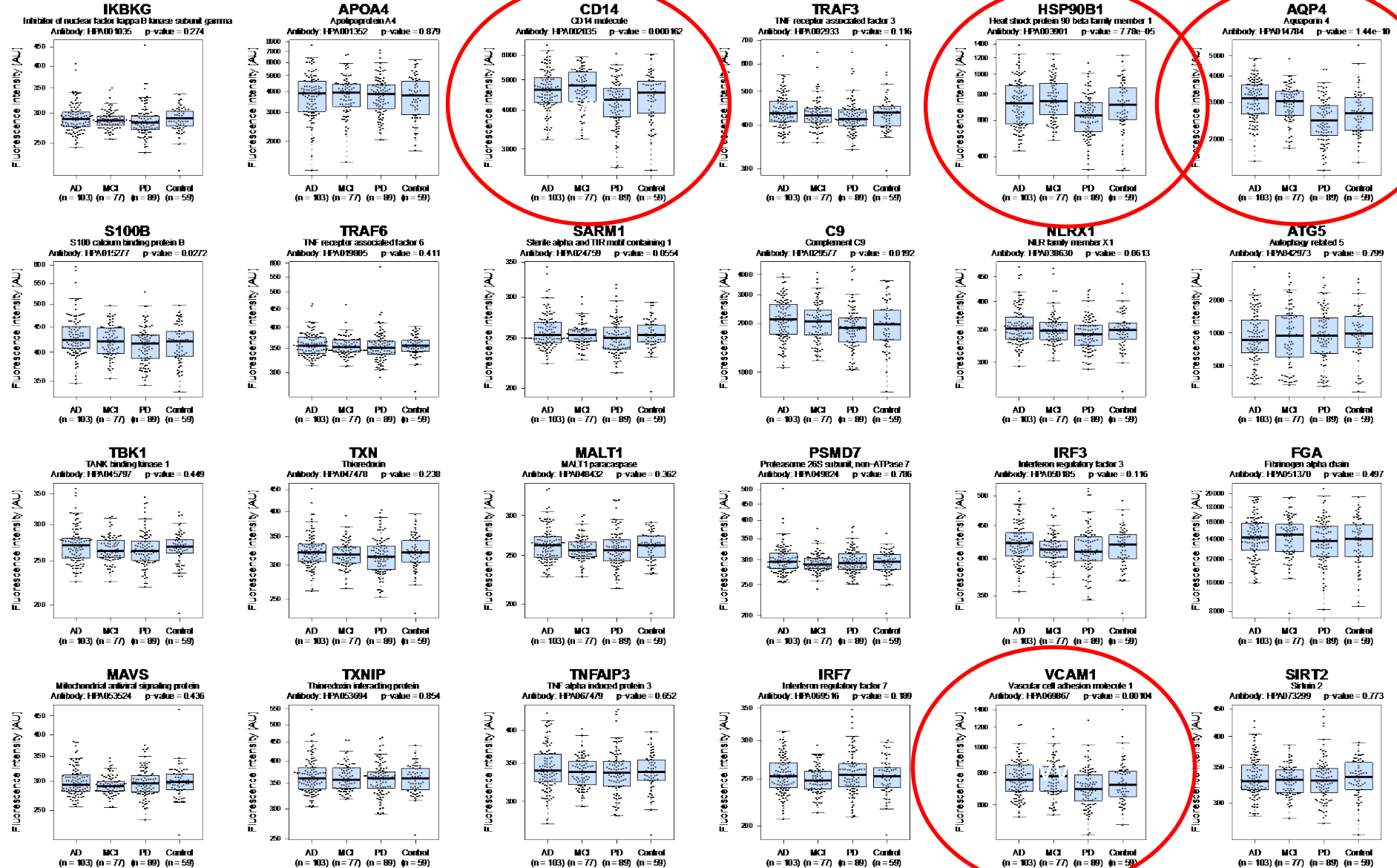
Neuroinflammation

Innate immune response and astroglial inflammation



Neuroinflammation

Innate immune response and astroglial inflammation

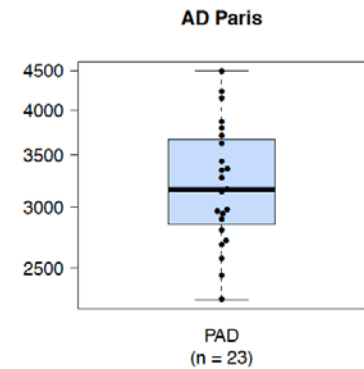
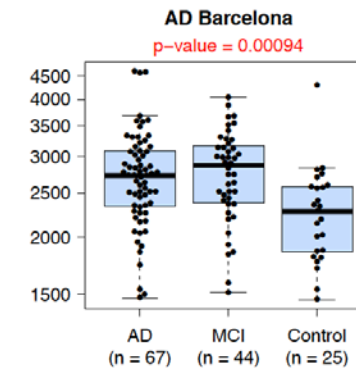
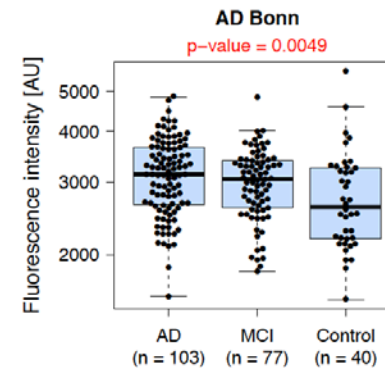
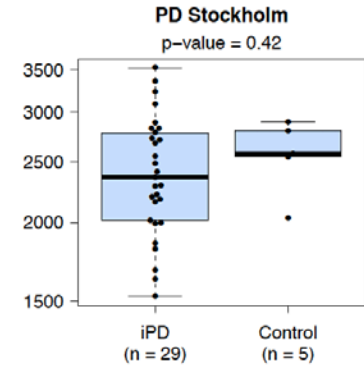
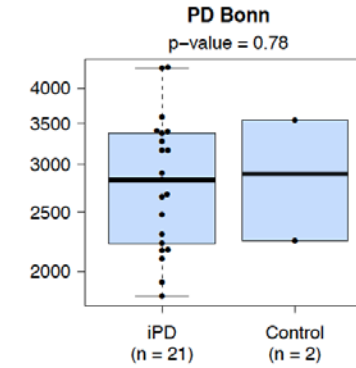
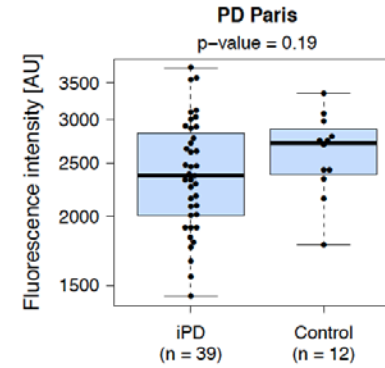
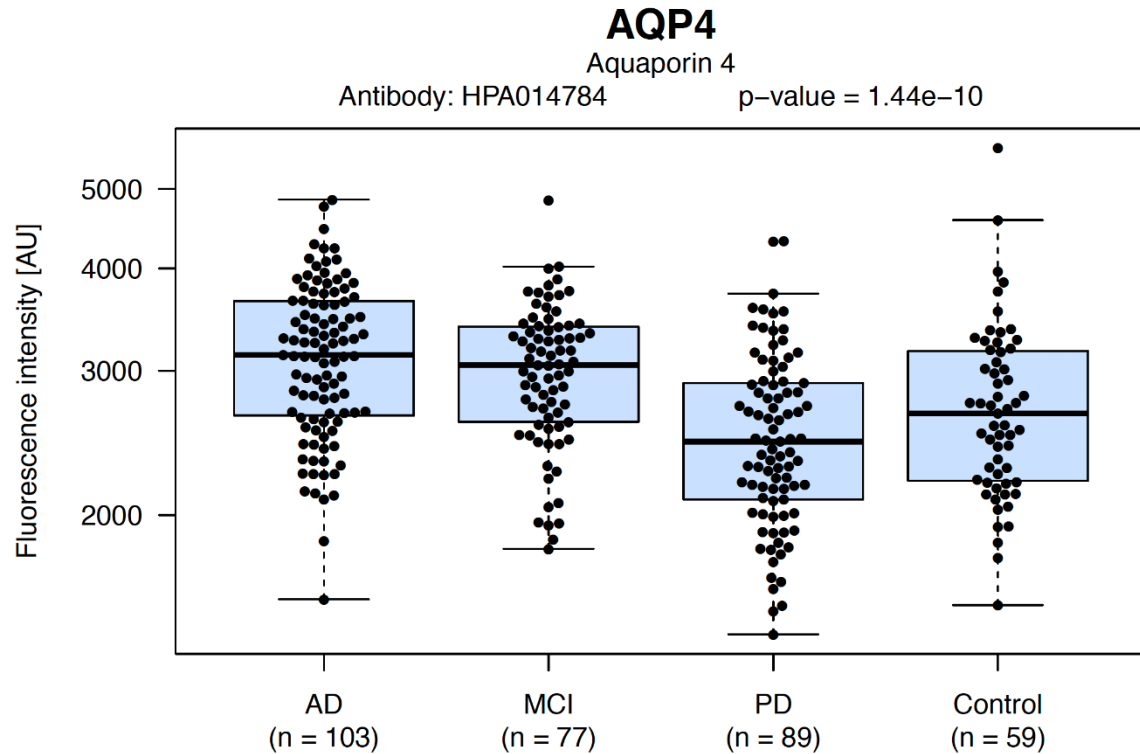


AQP4

Aquaporin 4

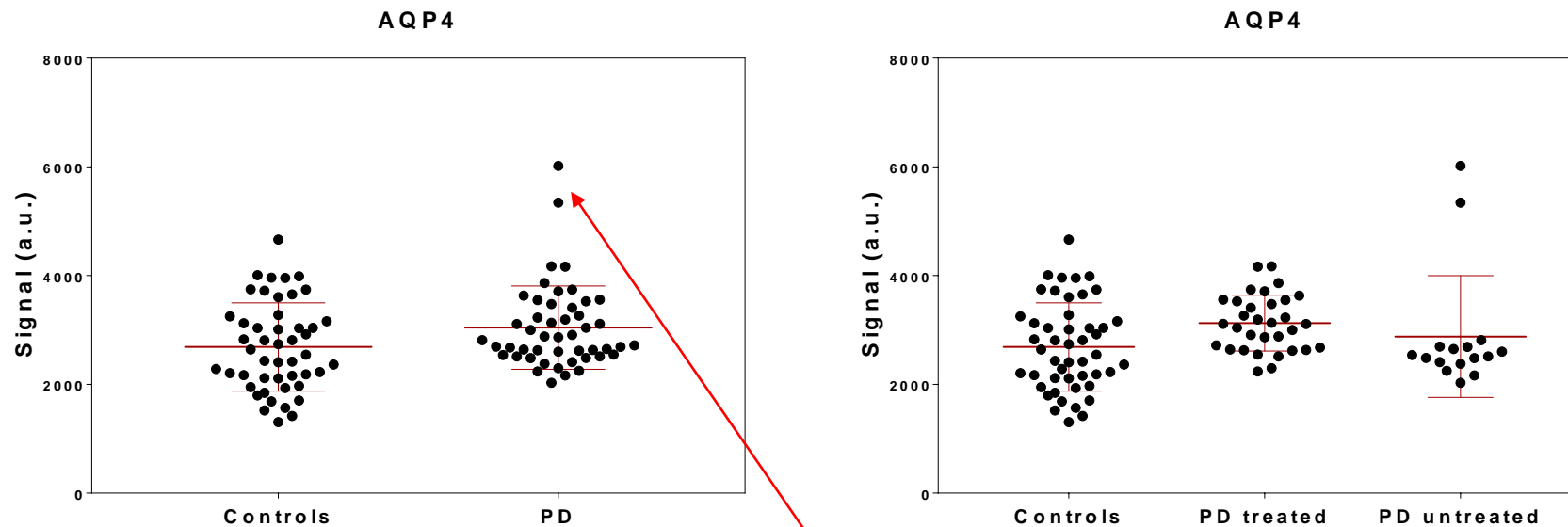
Astrocyte enriched protein

Regulates body water balance and mediates water flow within the central nervous system.



AQP4 in independent PD cohort

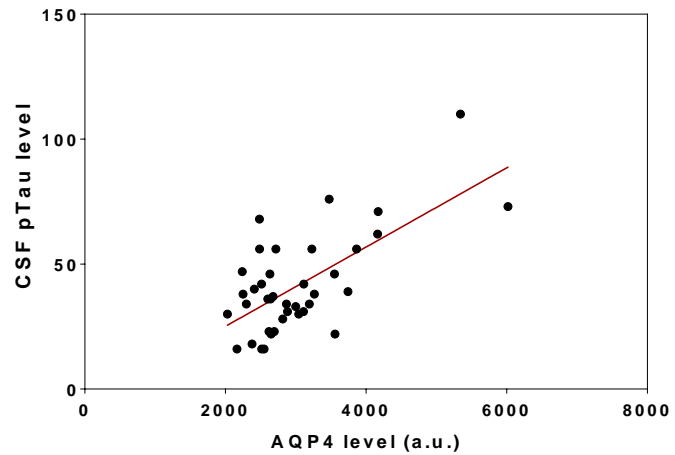
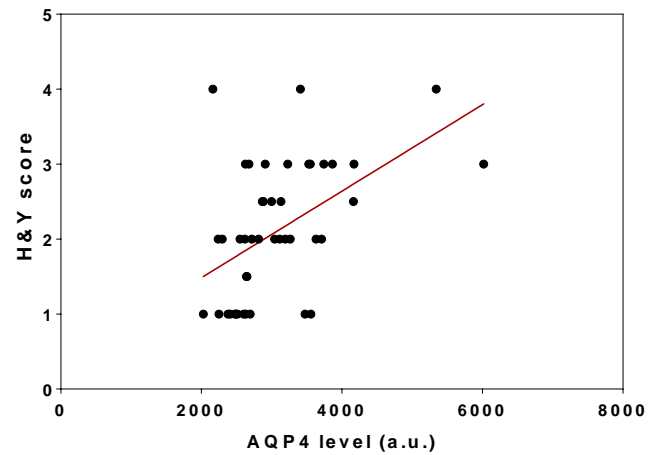
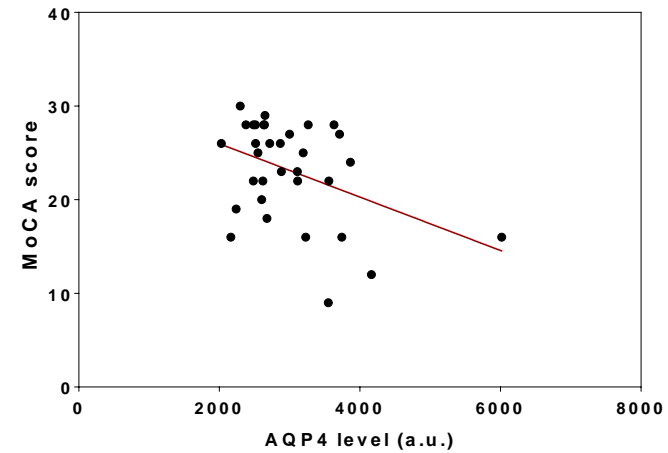
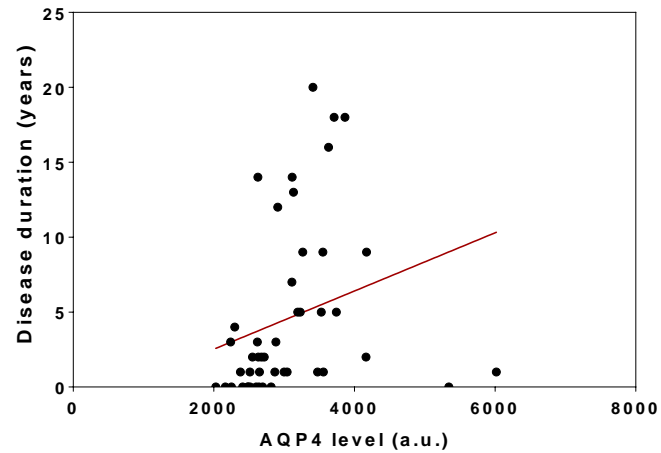
	Total	Male	Female	Age \pm SD
Controls	48	30	18	64.04 \pm 11.64
PD	48	29	19	64.27 \pm 10.23
PD treated	32	15	17	65.53 \pm 10.67
PD untreated	16	14	2	61.75 \pm 8.74



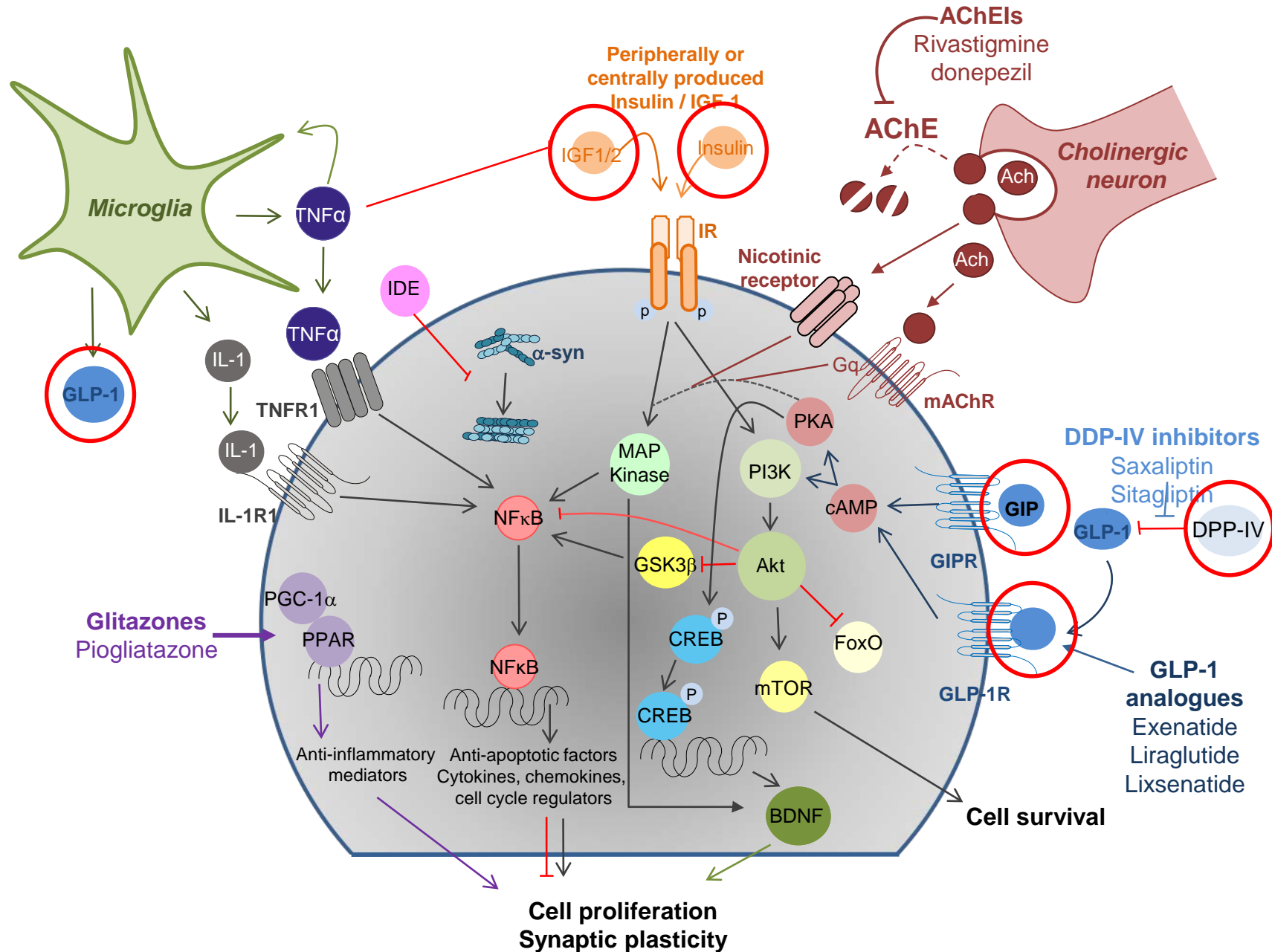
These patients have high
Tau and pTau levels

AQP4 correlation with symptoms

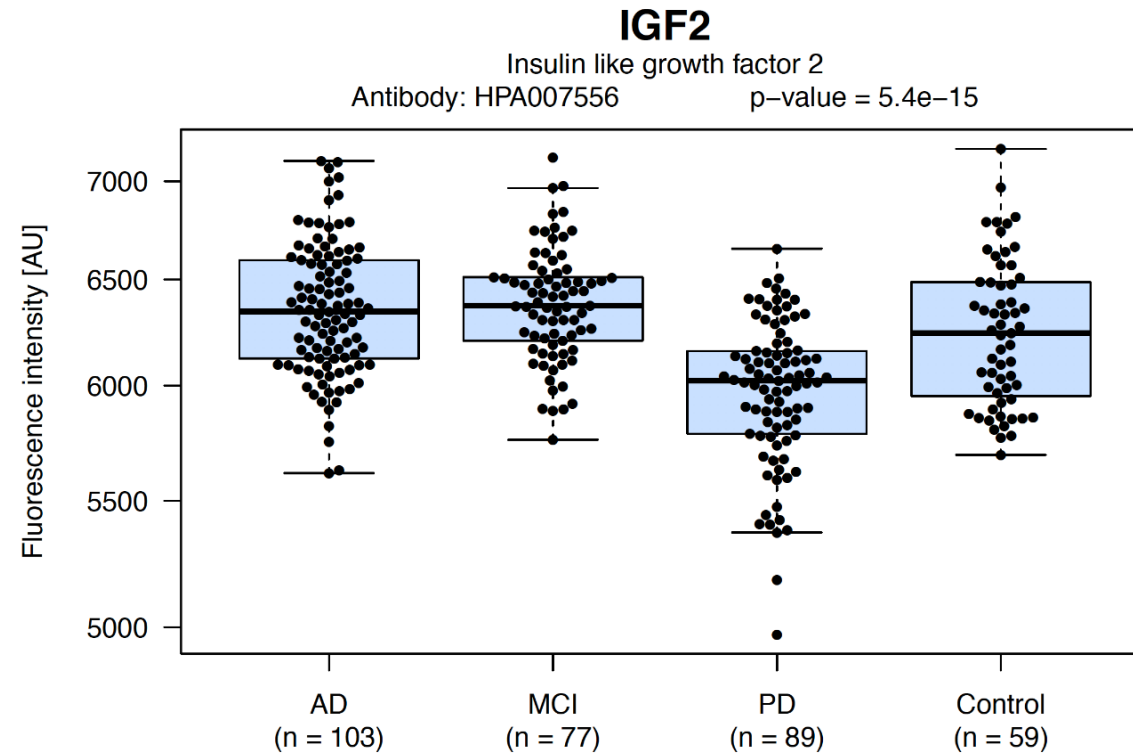
Correlation (green significant)													
	PD Duration	Hoehn& Yahr	LED (Therapy)	UPDRS-III	UPDRS total	NMS	HADS total	MoCA	CSF Ab42	CSF Tau	CSF P-Tau	Age (PD)	Age (controls)
p-value	0.0001	0.0001	0.0030	0.0516	0.0098	0.0620	0.1438	0.0394	0.2004	0.0008	0.0031	0.0880	0.4885
r-value	0.51916	0.53336	0.39907	0.29816	0.42384	0.28224	0.19722	-0.31025	-0.13839	0.49058	0.43020	0.19855	0.00429



Diabetes related pathways in dementia



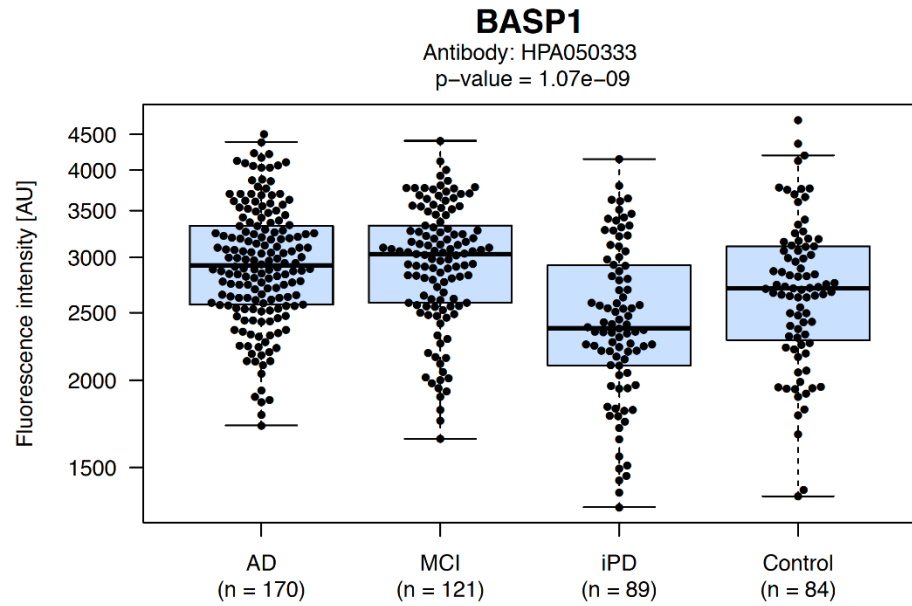
Diabetes related pathways



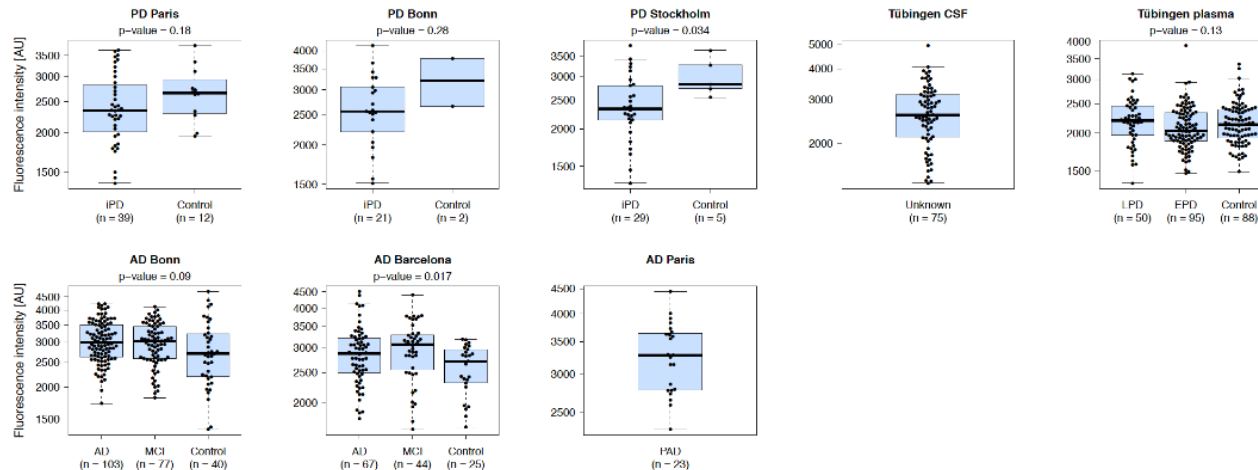
Protein targets selected from previous
neuroproteomics in-house efforts at
Prof Peter Nilsson/SciLifeLab.

BASP1

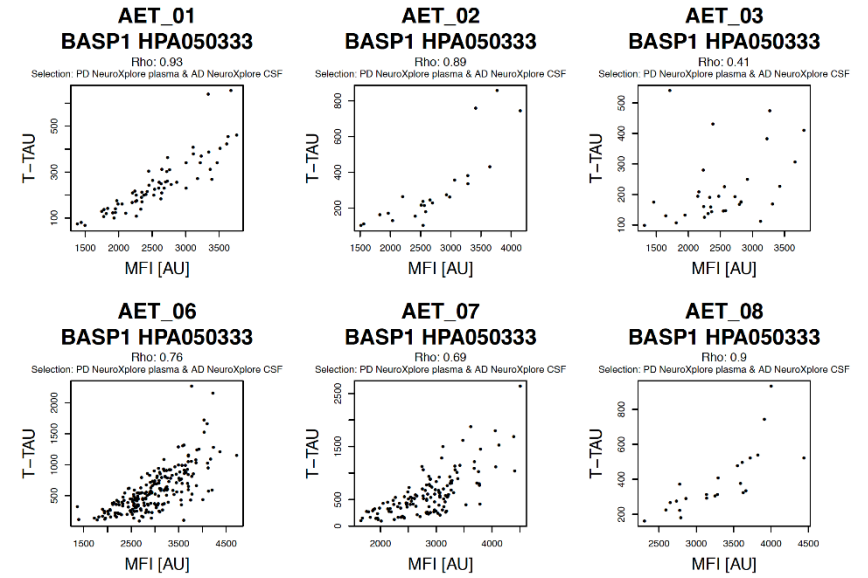
Brain abundant membrane attached signal protein 1



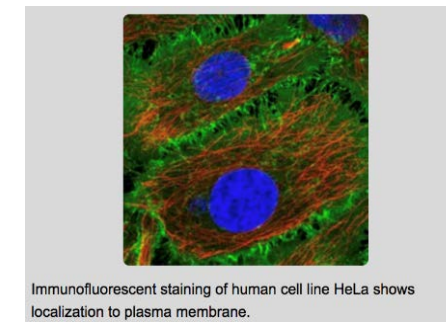
BASP1 Antibody: HPA050333



T-TAU

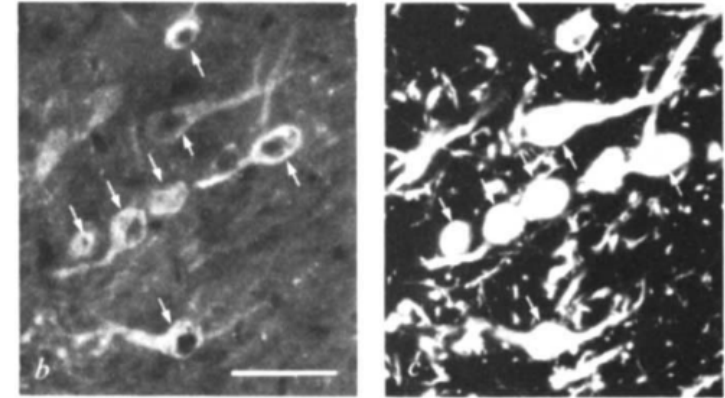


Immunocytochemistry



Evidence for coexistence of dopamine and CCK in meso-limbic neurones

T. Hökfelt*, J. F. Rehfeld†, L. Skirboll*, B. Ivemark‡, M. Goldstein§ & K. Markey§

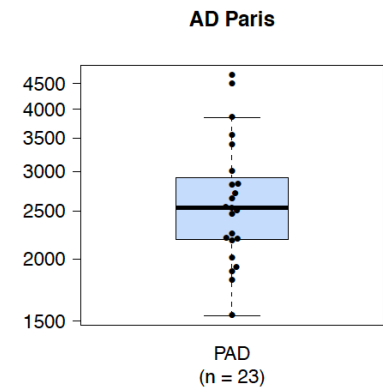
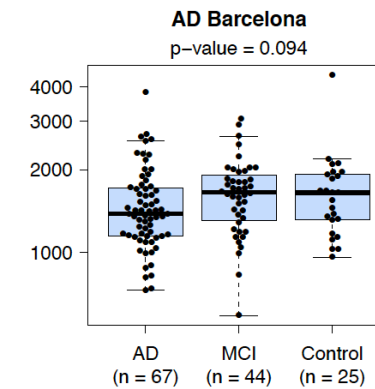
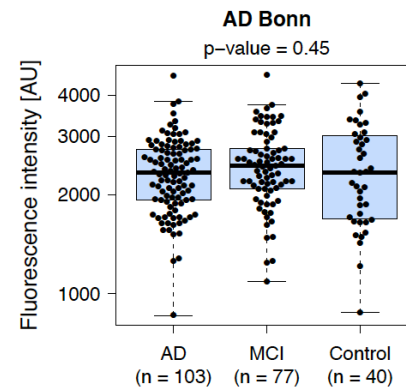
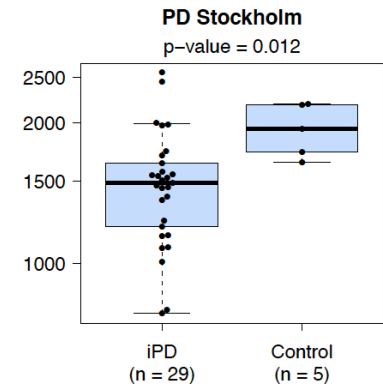
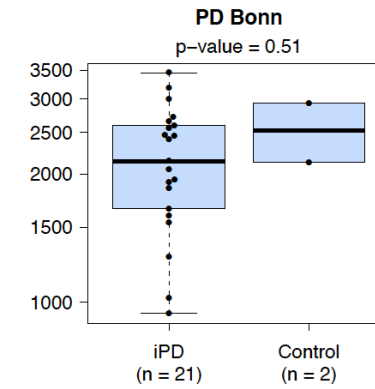
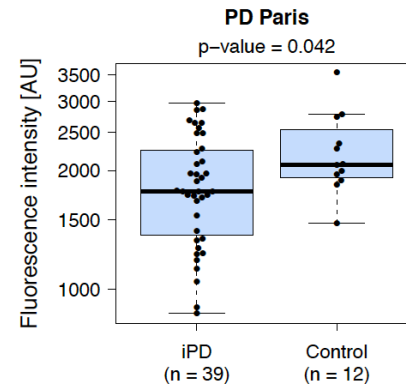
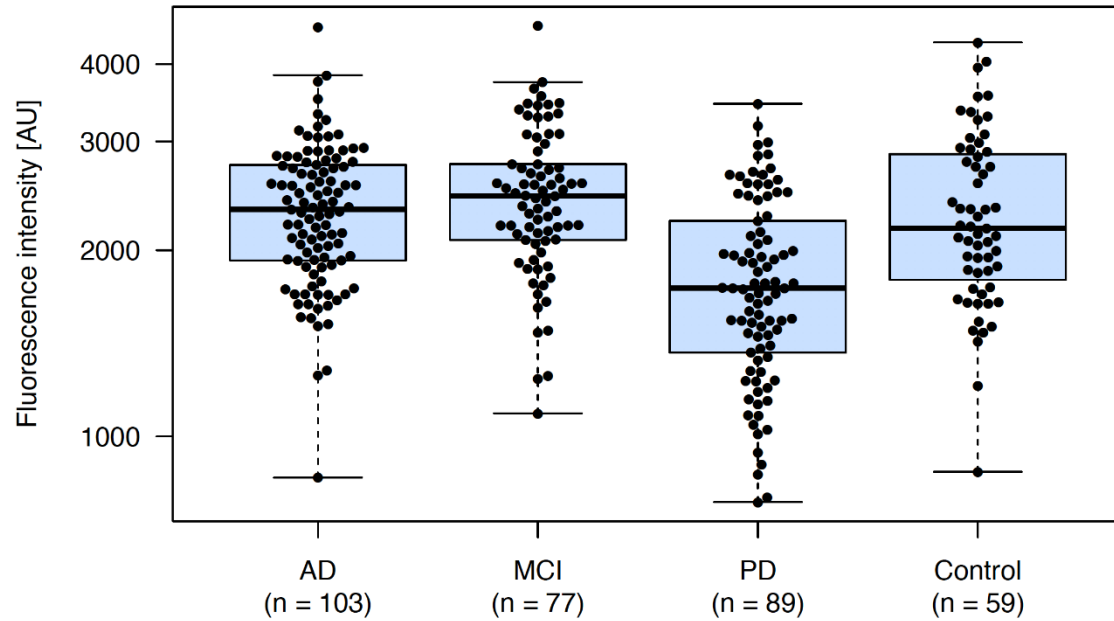


CCK

Cholecystokinin

Antibody: HPA069515

p-value = 2.74e-10



Conclusions

- Robust protein profiling from samples from different countries and cohorts
- Preliminary further evidence for increased neuroinflammation and altered diabetes-related signaling in neurodegeneration
- Many CSF changes in AD, but potential candidates also in PD

Future Directions

- Study PD samples with relation to the three genetic clusters described by Prof Corvol
- Multivariate analyses considering clinical signs and symptoms
- Verify findings with additional antibodies and alternative assays
- Correlate paired CSF and plasma for interesting candidates

Acknowledgments

Prof Jean Christophe
Corvol

Prof Ullrich Wuellner

Prof Michael Haneka

Prof Raquel

Sanchez-Vallecheal

Prof Bruno Dubois

UCB/Tubingen

Dr Sofia Bergström

Prof Peter Nilsson

Dr Anna Häggmark-Månberg

Dr Wojciech Paslawski

Dr Ioanna Markaki

Dr Panagiota Tsitsi

Ms Agneta Gunnar

