Clinical workpackage

Partners: ICM (JC Corvol)

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BBRC (JL Molinuevo)

KI (P Svenningsson)

AETIONOMY PD cohort

Towards mechanism-based classification

Neurodegenerative diseases

Susceptibility factors

Genetic factors

Environmental factors

Cellular dysfunction

Oxidative stress

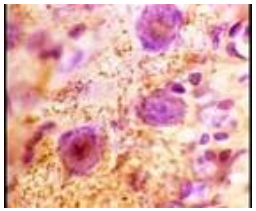
Mitochondria

Neuroinflammation

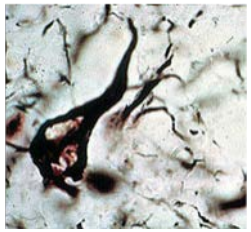
Excitotoxicity

Protein aggregation

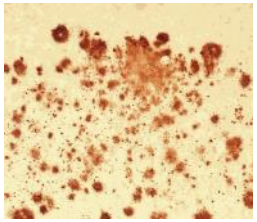
synuclein



tau



amyloid



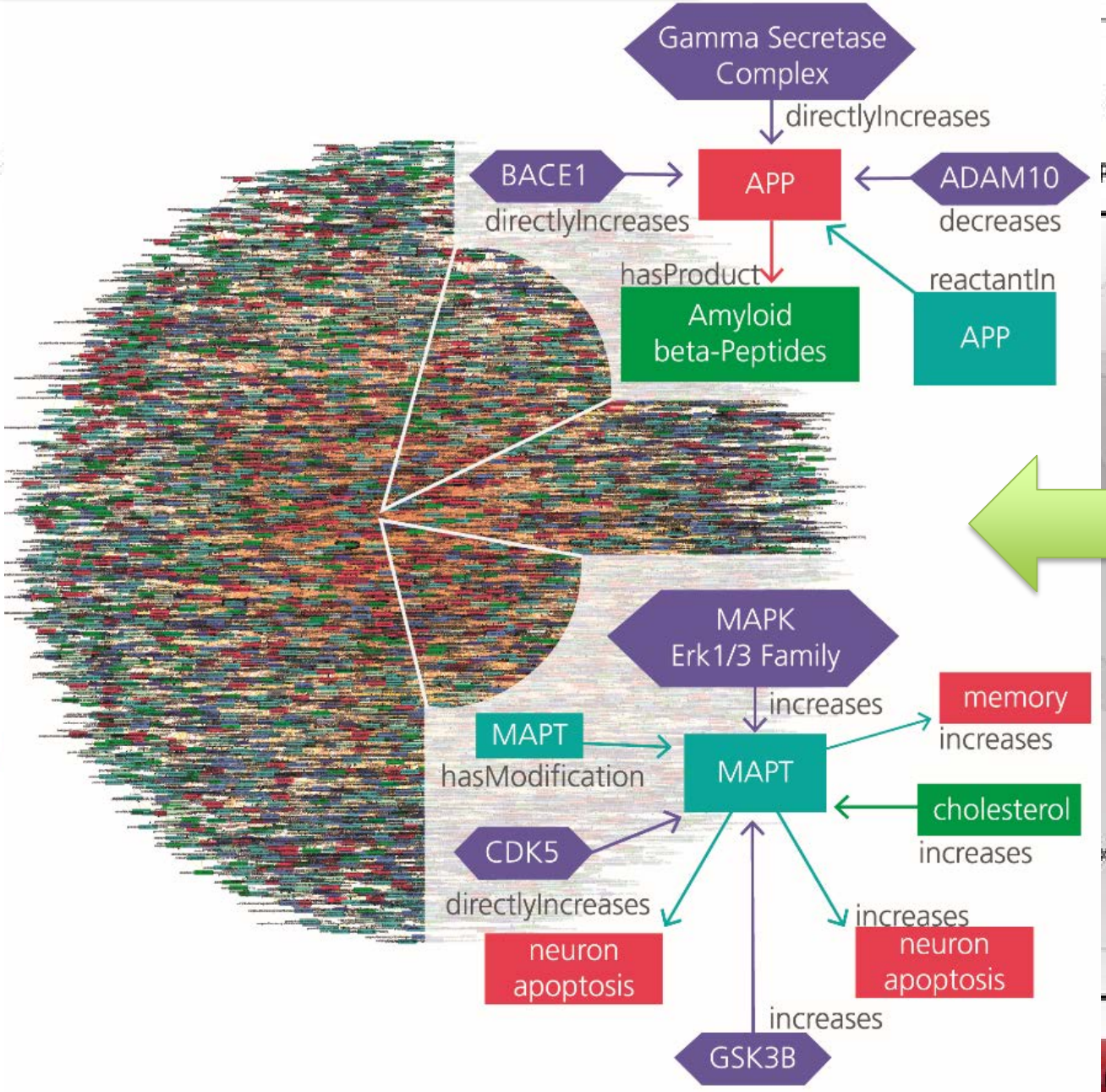
Prion-like diffusion

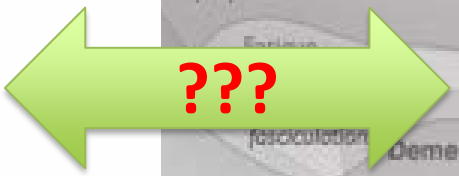
Neuronal death

Parkinson's disease

Alzheimer disease

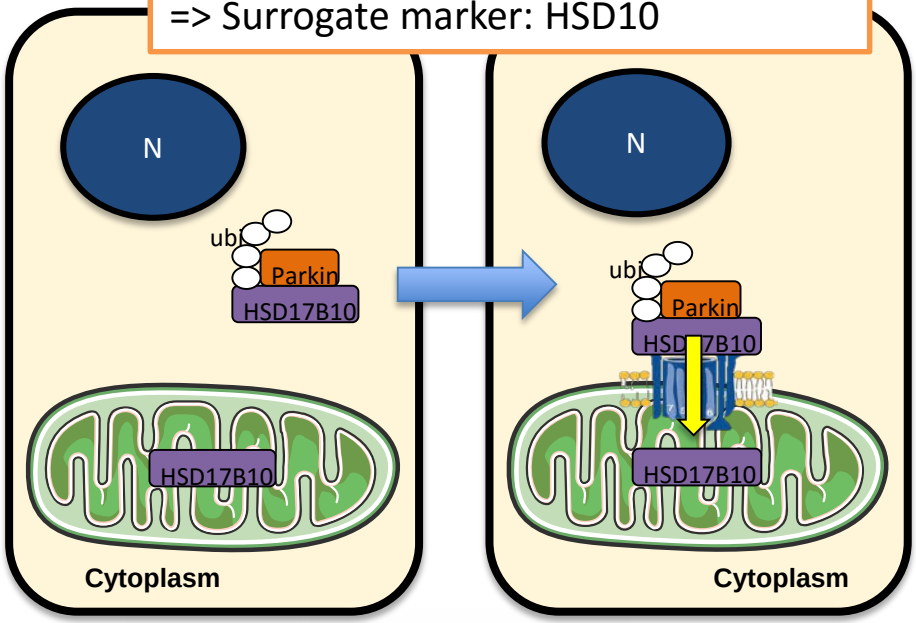
OpenBEL model for Alzheimer´s Disease

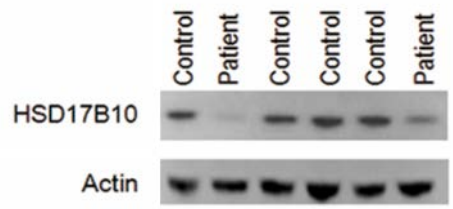




PD: Cross-talk mitophagy - neuroinflammation

Parkin-dependent mitophagy => PD
=> Surrogate marker: HSD10

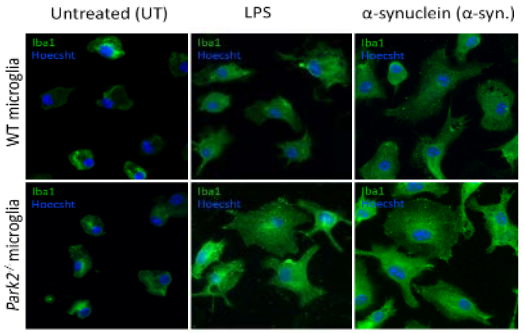


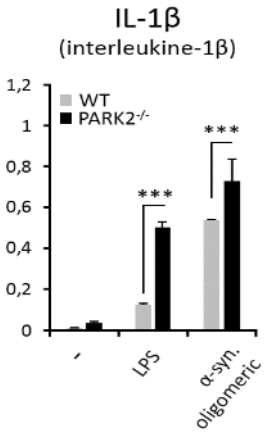


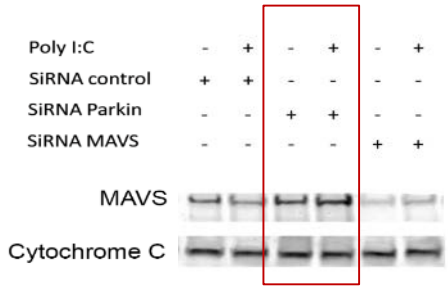
Bertolin et al., 2015

Parkin-dependent microglia over- activation
=> Surrogate marker: TFAM

1/ PARK2$^{-/-}$ microglia are over-actived





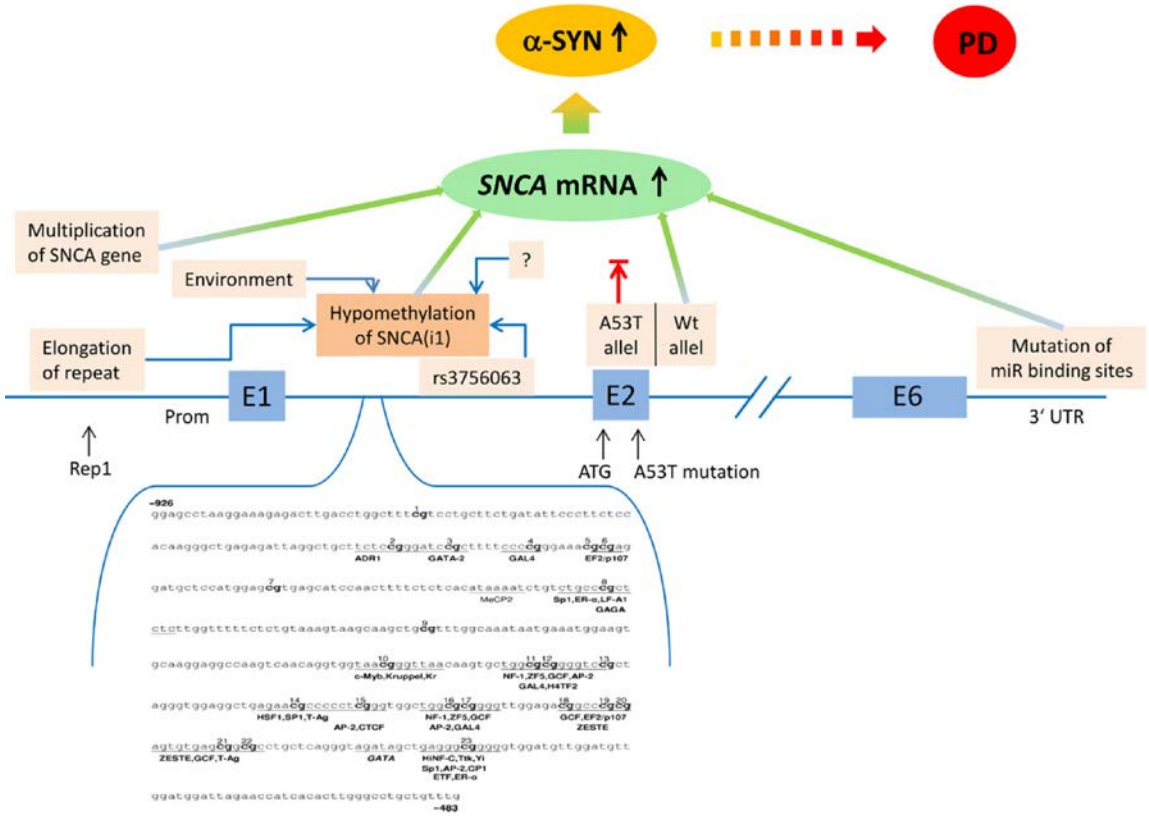


2/ Inflammasome-related cytokine over-production

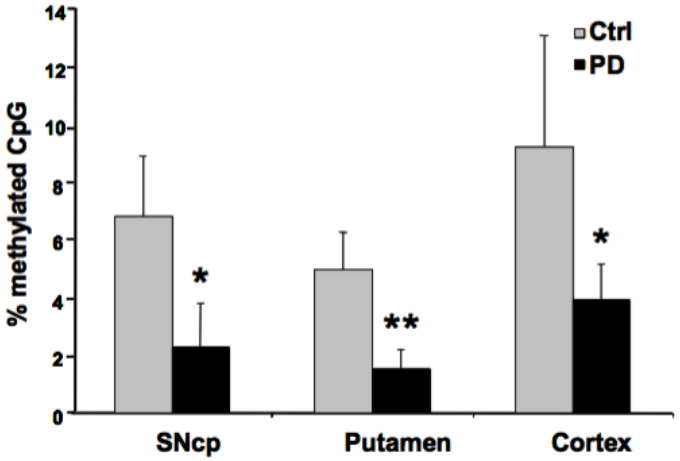
3/ Parkin contributes to MAVS degradation

Mouton-Liger, Glia 2018

PD: Epigenetics hypothesis

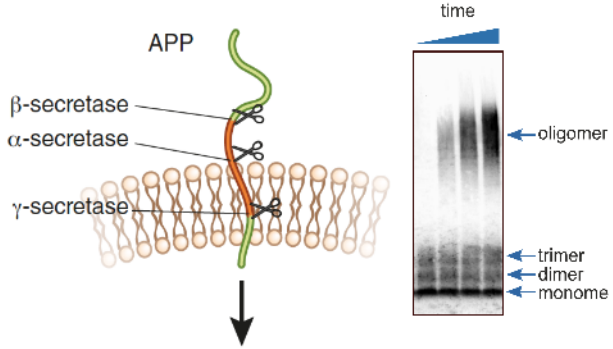


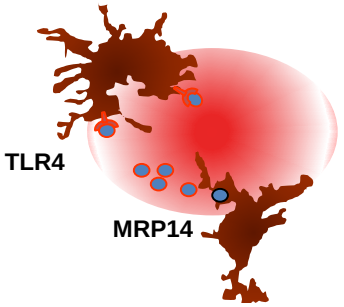
SNCA methylation in the CNS



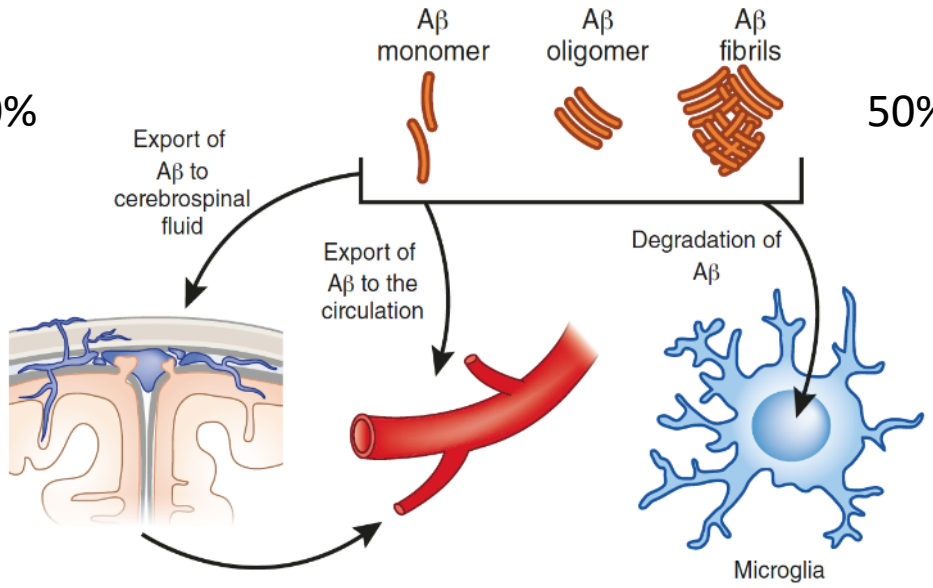
Wullner et al., J Neurochem 2016

AD: Neuroinflammation hypothesis





50%



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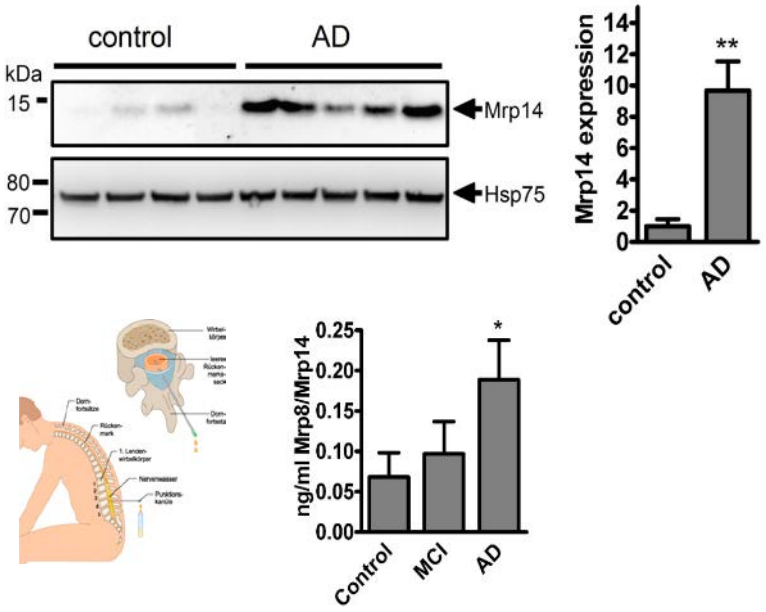


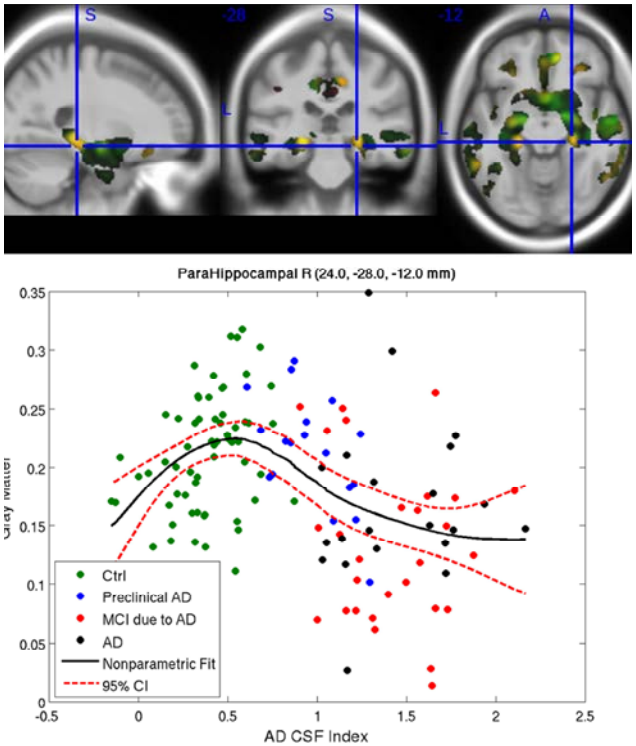
Heneka et al. Nat Immunol, 2015

Kummer et al. J. Neurosci. 2012

Heneka et al. *Lancet Neurol*, 2015

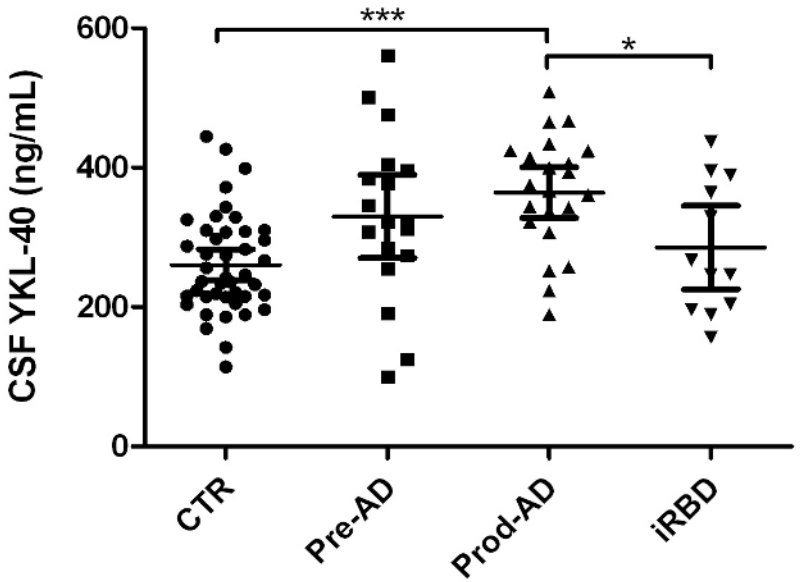
AD: glial inflammatory response, YKL40 as a biomarker

Nonlinear cerebral atrophy patterns across the Alzheimer's Disease continuum



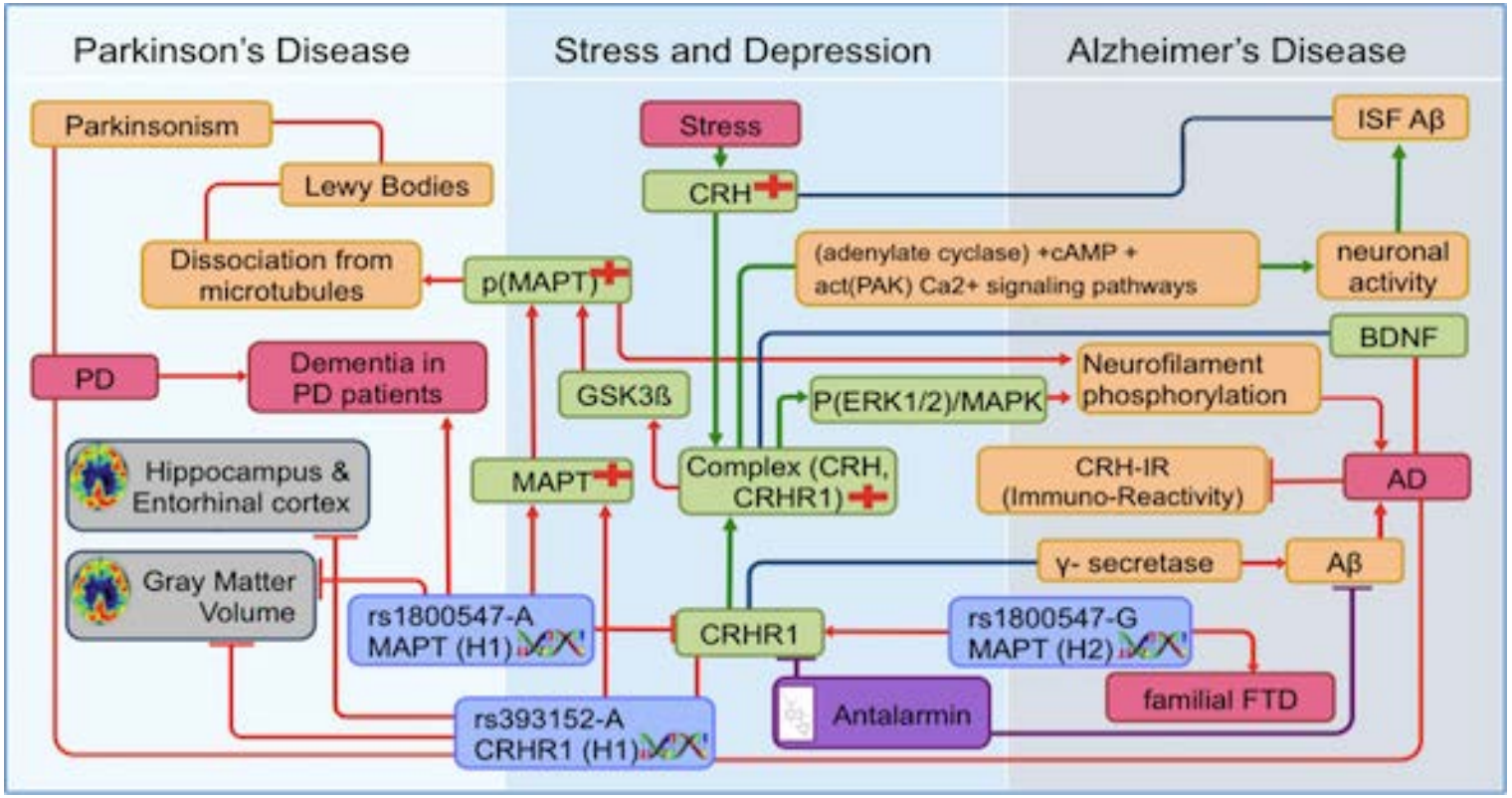
Gispert et al., Neurobiol Aging (2015)

YKL40: glial inflammatory response in AD



Novel mechanisms to be tested: WP3 mechanism graphs

Insuline pathway (**SARD**: **Luc Cannard, Eric Boitier, Delphine Ibghi**)
Stress-depression/CRH release linking AD and PD



European multicenter study – ECRIN

ICM, INSERM, Paris
Cécile Gaudebout
Stéphanie Carvalho

2 yrs of administrative/regulatory processes

2 yrs of recruitment

7th May 2014 — Submission to INSERM advisory board

5th Jun. 2014 — Submission to ECRIN advisory board

March 2015 — Protocol Finalisation and submission to Regulatory and Ethical Authorities **in France**

May 2015 — Protocol approval obtained in France

Sept 2015 — First subject included

Oct. 2015 — Protocol submission to Regulatory and Ethical Authorities **in Germany, and Sweden**

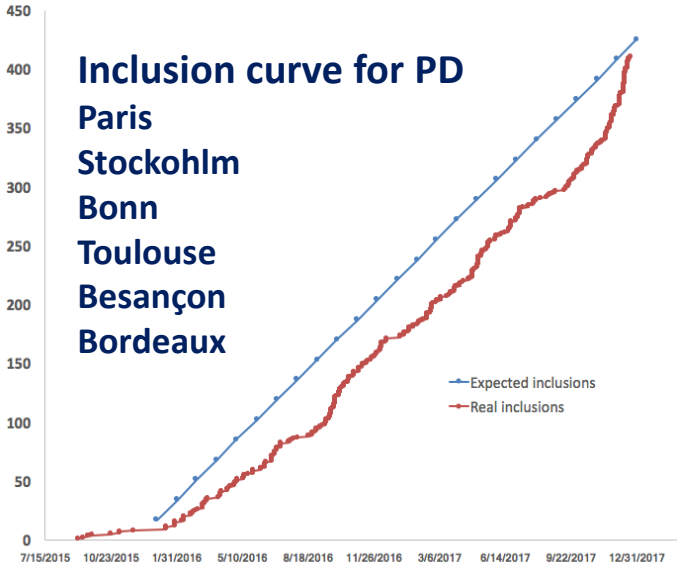
Dec. 2015 — First subject inclusion in all centers

Dec. 2017 — End of study

nspark

AETIONOMY: unique dataset across neurodegenerative diseases

		PD						AD		
Origin	**Total n**	**DNA**	**CSF**	**Plasma**	**Serum**	**Fibroblasts**	**MRI**	**DNA**	**CSF**	**MRI**
AETIONOMY-CS (PD group)	405	396	99	391	391	160	30			
External cohorts	1556	645	84	230			14	436	380	23
TOTAL samples		**1041** [0,1,4]	**183** [0,2,3,6]	**621** [0,3,5]	**391** [0]	**160** [0]	**44** [0,7]	**436** [0,1]	**380** [0,2,6]	**23** [0,7]



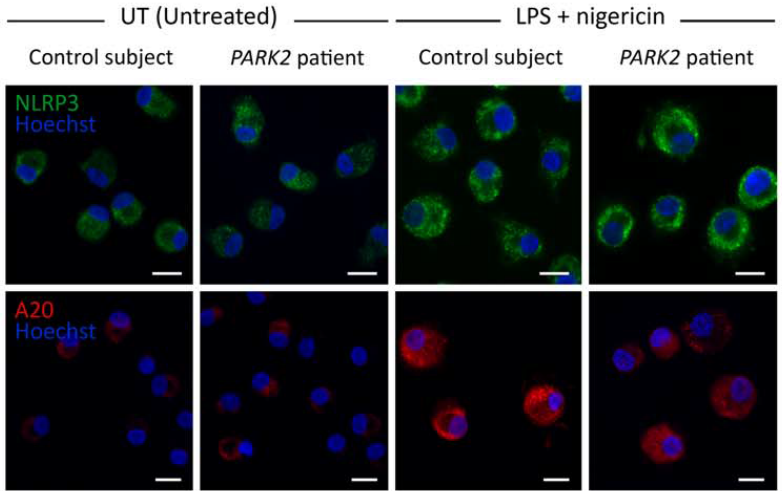
Available associated data:

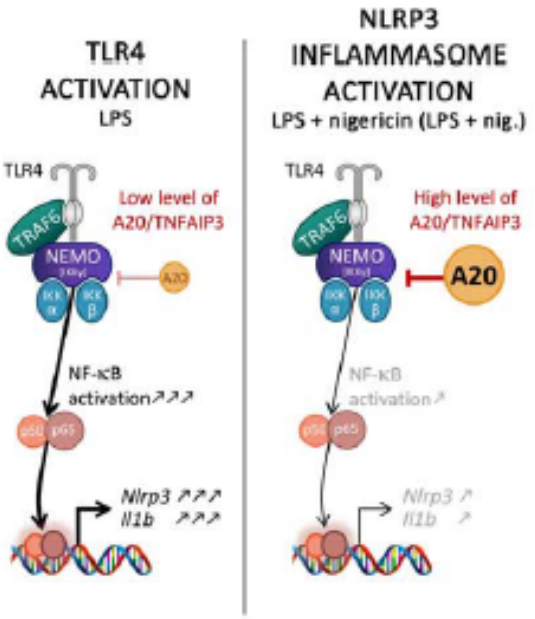
[0]Clinical Data
[1]Genomics (ICM)
[2]Inflammatory (IDIBAPS/UKB)
[3]Proteomics (KI)
[4]Methylation (UKB)
[5]Cholesterol (UKB)
[6]Isuline resistance pathway (SARD)
[7]Brain imaging (BBRC)

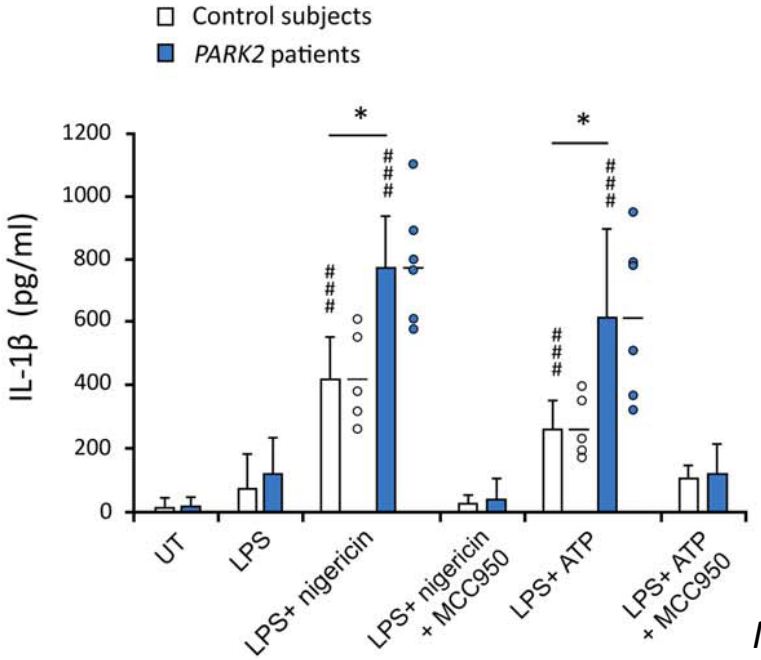
	Genetic PD (N = 25)	Idiopathic PD (N = 251)	At Risk for PD (N = 39)	Healthy Control (N = 90)
Age (years)*	**58.72 ± 14.89**	**64.07 ± 8.64**	**63.26 ± 11.05**	**62.83 ± 9.22**
Female, n (%)	11 (44.00)	80 (31.87)	13 (33.33)	59 (65.56)
Ethnicity, n (%)				
Caucasian/White	19 (76.0)	245 (97.61)	32 (80.0)	85 (93.41)
Black	1 (4.0)	3 (1.2)	2 (5.0)	1 (1.1)
Asian	1 (4.0)	0	1 (2.5)	2 (2.2)
North African/Arabic	4 (16.0)	3 (1.2)	3 (7.5)	1 (1.1)
Other	0	0	2 (5.0)	2 (2.2)
Weight (kg)*	67.42 ± 12.26	77.03 ± 15.51	74.33 ± 13.86	71.88 ± 14.46
Smoking, n (%)				
Current	3 (12.00)	17 (6.85)	5 (12.82)	7 (7.95)
Past	7 (28.00)	101 (40.37)	18 (46.15)	40 (45.45)
Never	15 (60.00)	130 (52.42)	16 (41.03)	41 (46.59)
Age at onset (years)*	45.42 ± 15.78	60.47 ± 8.71	N/A	N/A
Disease duration (months)$^{+}$	28.5 (43.0)	144.0 (125.0)	N/A	N/A
MDS-UPDRS Score*				
Part I	12.72 ± 6.56	8.73 ± 4.91	7.13 ± 3.44	3.48 ± 3.33
Part II	15.0 ± 9.05	8.99 ± 5.38	1.14 ± 1.59	0.58 ± 1.21
Part III	**45.16 ± 17.75**	**30.4 ± 14.51**	**9.64 ± 5.36**	**2.13 ± 3.17**
Part IV	5.56 ± 4.28	1.39 ± 2.61	0 ± 0	0 ± 0
HADS*				
Anxiety Score	**7.77 ± 4.25**	**5.68 ± 3.72**	**6.92 ± 3.37**	**4.87 ± 3.29**
Depression Score	**4.77 ± 3.25**	**4.03 ± 3.45**	**3.18 ± 2.99**	**2.21 ± 3.02**
NMSS total score*	9.9 ± 5.35	9.18 ± 4.67	7.59 ± 4.30	2.89 ± 3.42
MMSE total score *	**28.43 ± 1.69**	**28.38 ± 1.68**	**29.18 ± 0.9**	**28.93 ± 1.33**
MoCA total score*	**25.74 ± 4.28**	**26.07 ± 2.9**	**26.95 ± 2.55**	**26.69 ± 2.75**
RBANS total score*	92.57 ± 20.4	91.95 ± 16.51	102.11 ± 13.63	100.9 ± 15.57
Family history of PD, n (%)	16 (64.00)	14 (5.62)	15 (39.47)	5 (5.81)

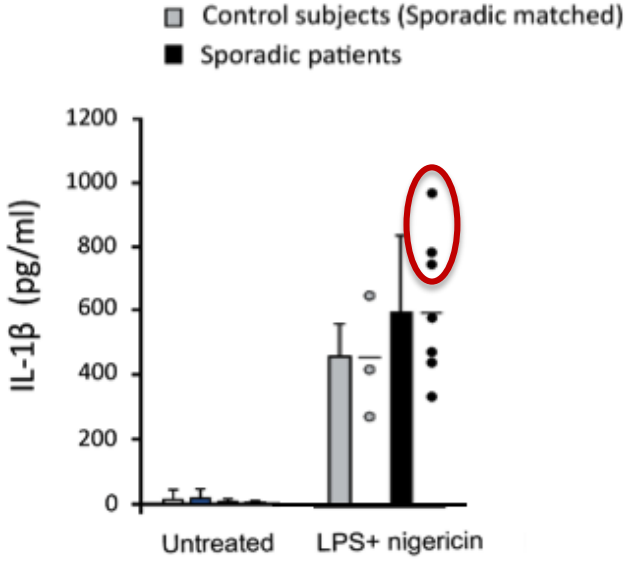
Thanks to UCB: S Bujac, B Clarke, C Firkle

Crosstalk between mitochondria dysfunction and inflammation in PD



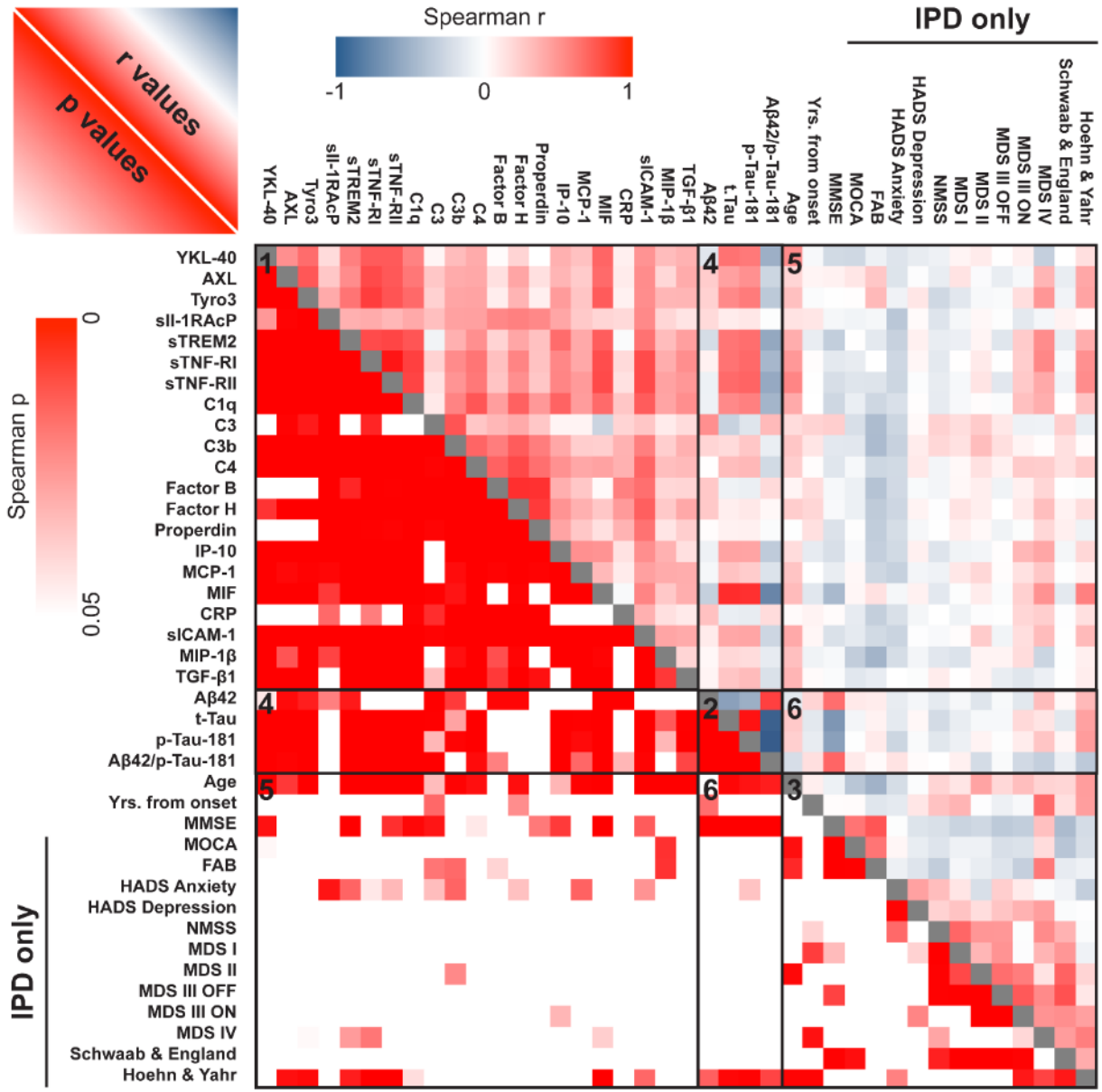






Mouton-Liger et al., Glia 2018

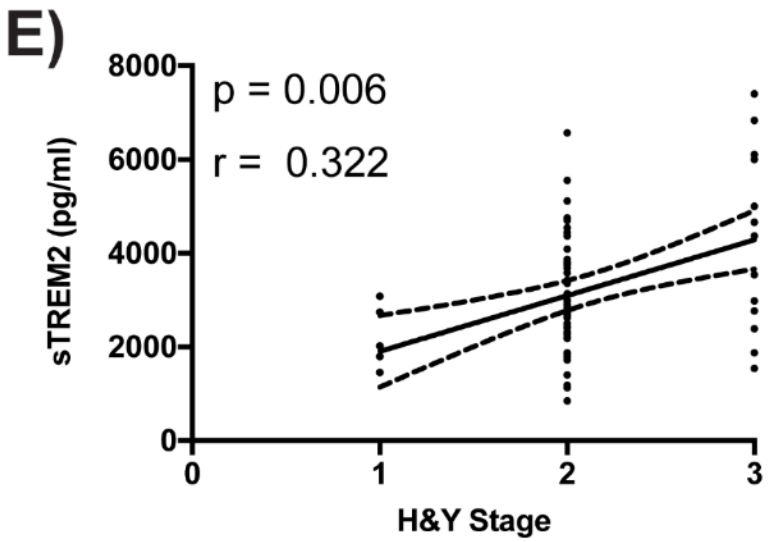
Immune biomarkers associates with AD markers and symptoms

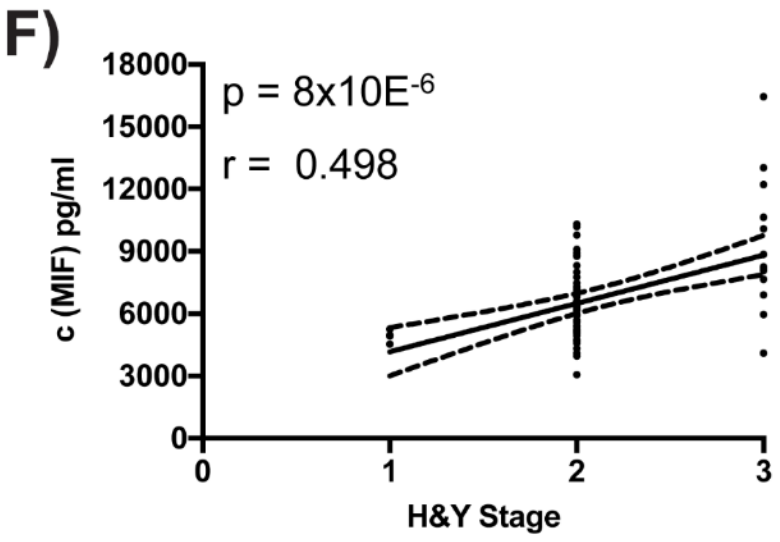


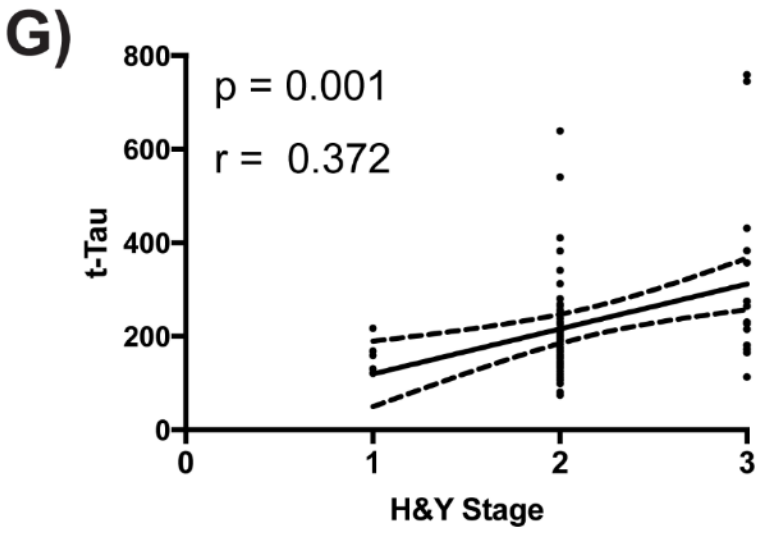
UKB, Bonn
Micheal Heneka
Frederic Brosseron

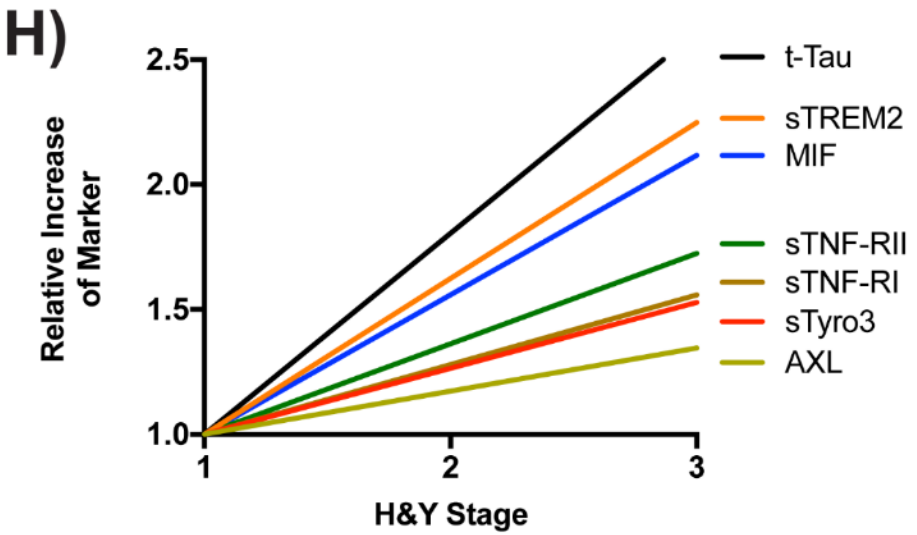
Brosseron et al., in prep.

Immune response depends on neuronal damage independently of the disease







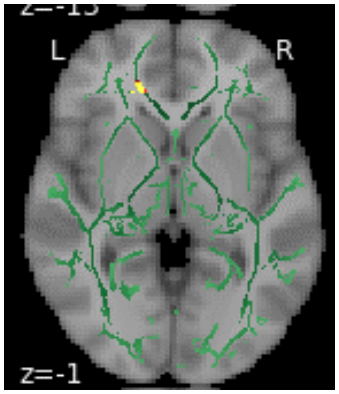


Brosseron et al., in prep.

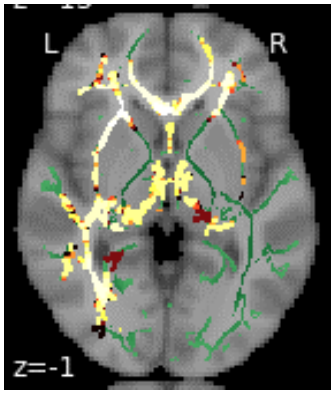
WM microstructure gets altered with age and amyloid markers whatever the underlying pathology

Age

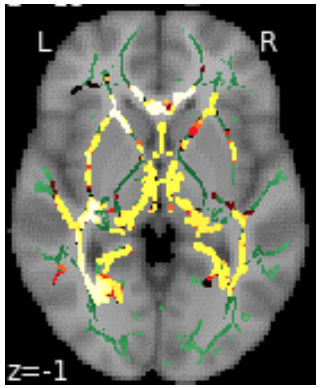
↘FA



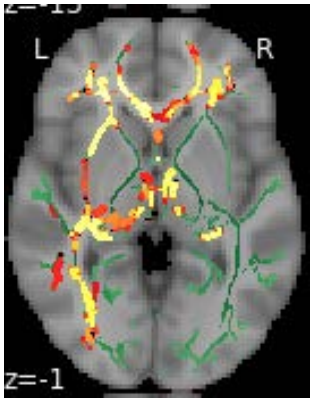
↗MD



↗AxD

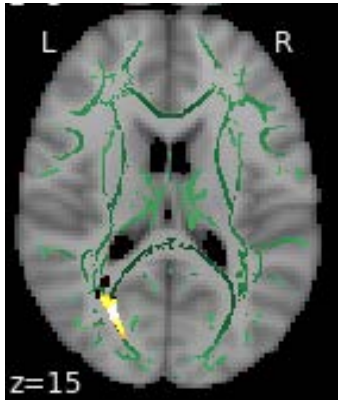


↗RD

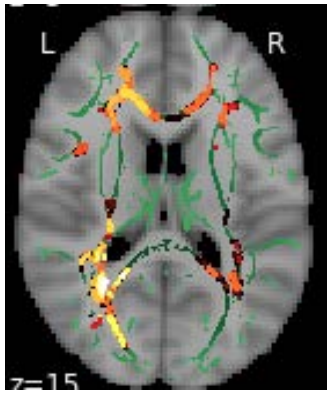


Aβ42

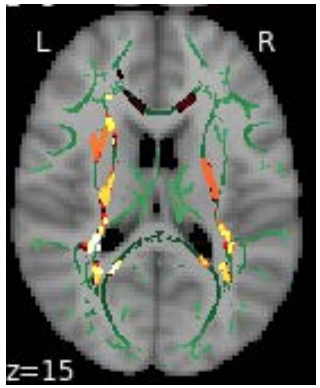
Positive with FA



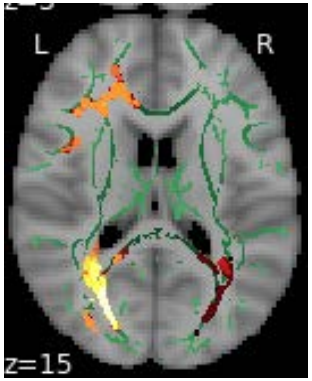
Negative with MD



Negative with AxD

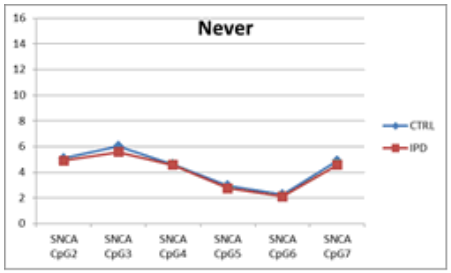


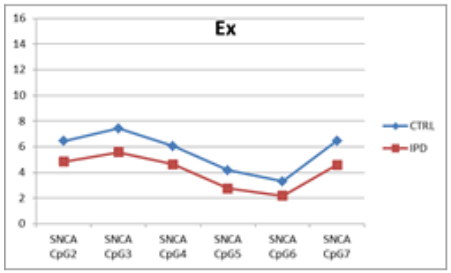
Negative with RD

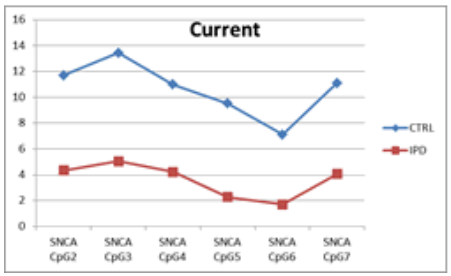


IDIBAPS/BBRC, Barcelona: JL Molinuevo, R Sanchez-Valle, B Bosch, A Antonell, G Operto

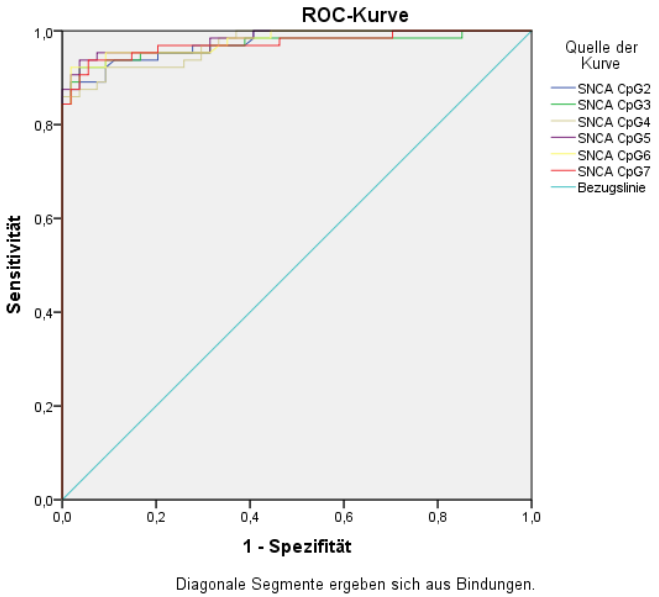
α-Synuclein: methylation *and smoking*







ROC curve IPD vs. HC (current smokers)



Diagonale Segmente ergeben sich aus Bindungen.

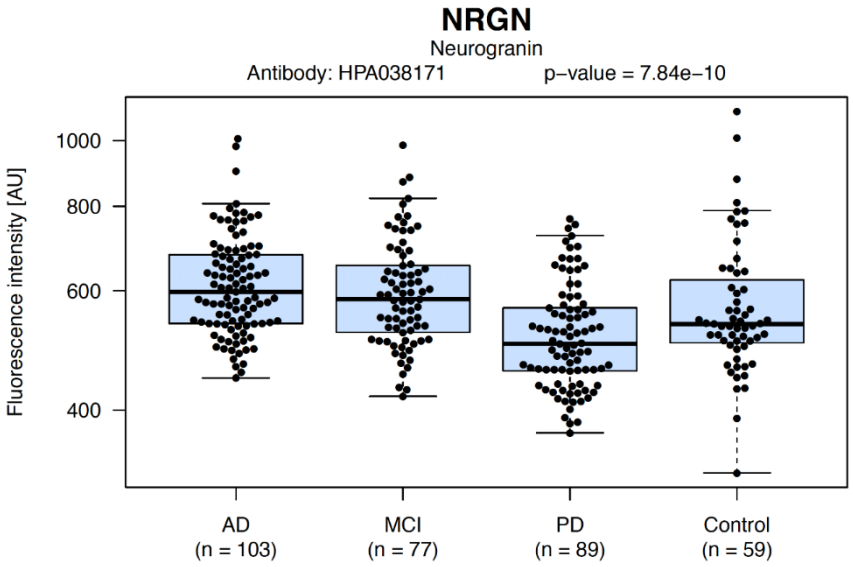
AUC IPD vs. HC (current smokers)

Variable(n) für Testergebnis	Fläche
SNCA CpG2	,975
SNCA CpG3	,970
SNCA CpG4	,971
SNCA CpG5	,981
SNCA CpG6	,978
SNCA CpG7	,973

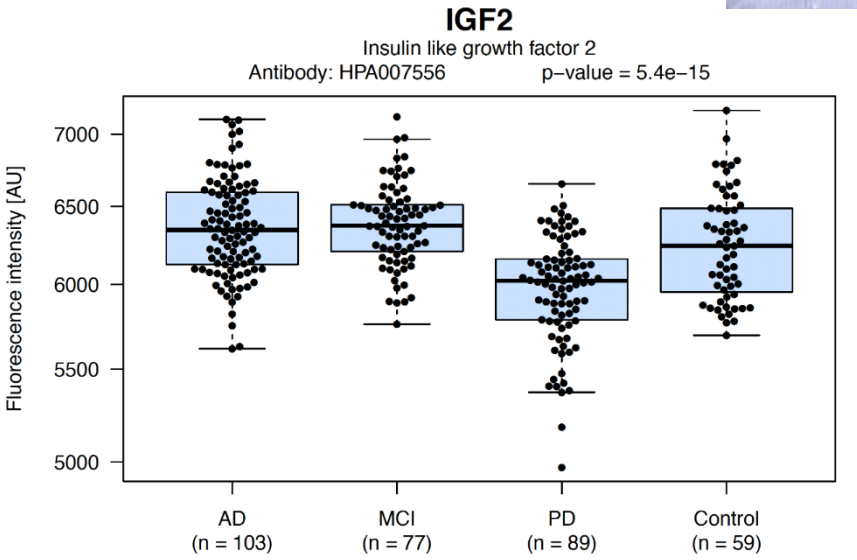
UKB, Bonn
Ullrich Wuellner
Ina Schmitt
Sandra Roeske

Proteomic analysis in CSF

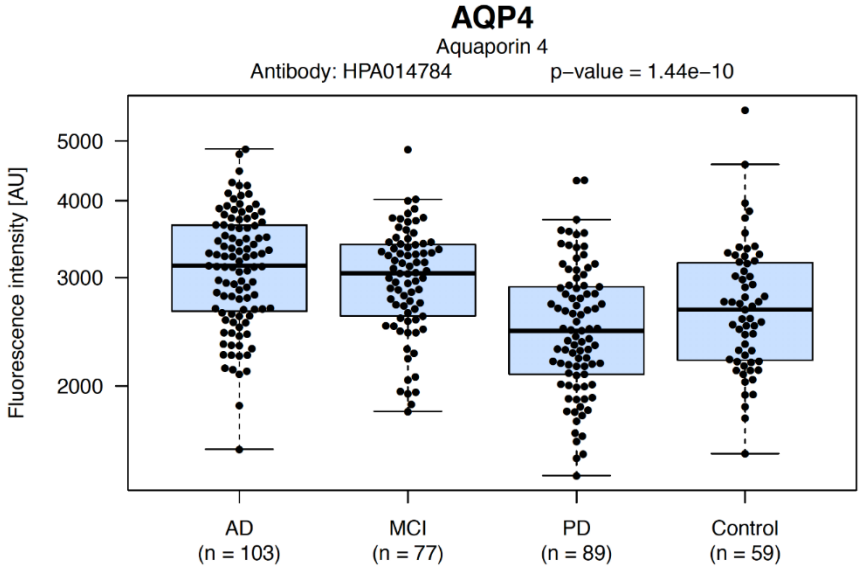
NRGN
Neurogranin



IGF2
Insulin like growth factor 2

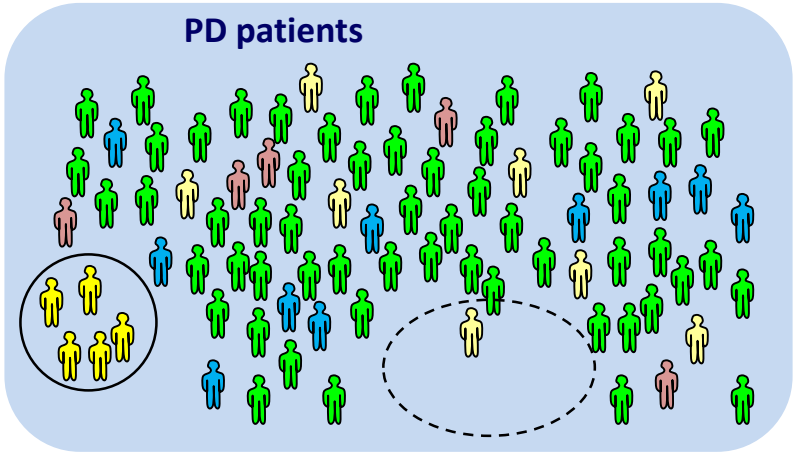


AQP4
Inflammation



KI, Stockohlm
P Svenningsson
I Markaki
P Tsitsi
P Nilsson
S Berström

Is it possible to stratify patients according to their underlying mechanism ?



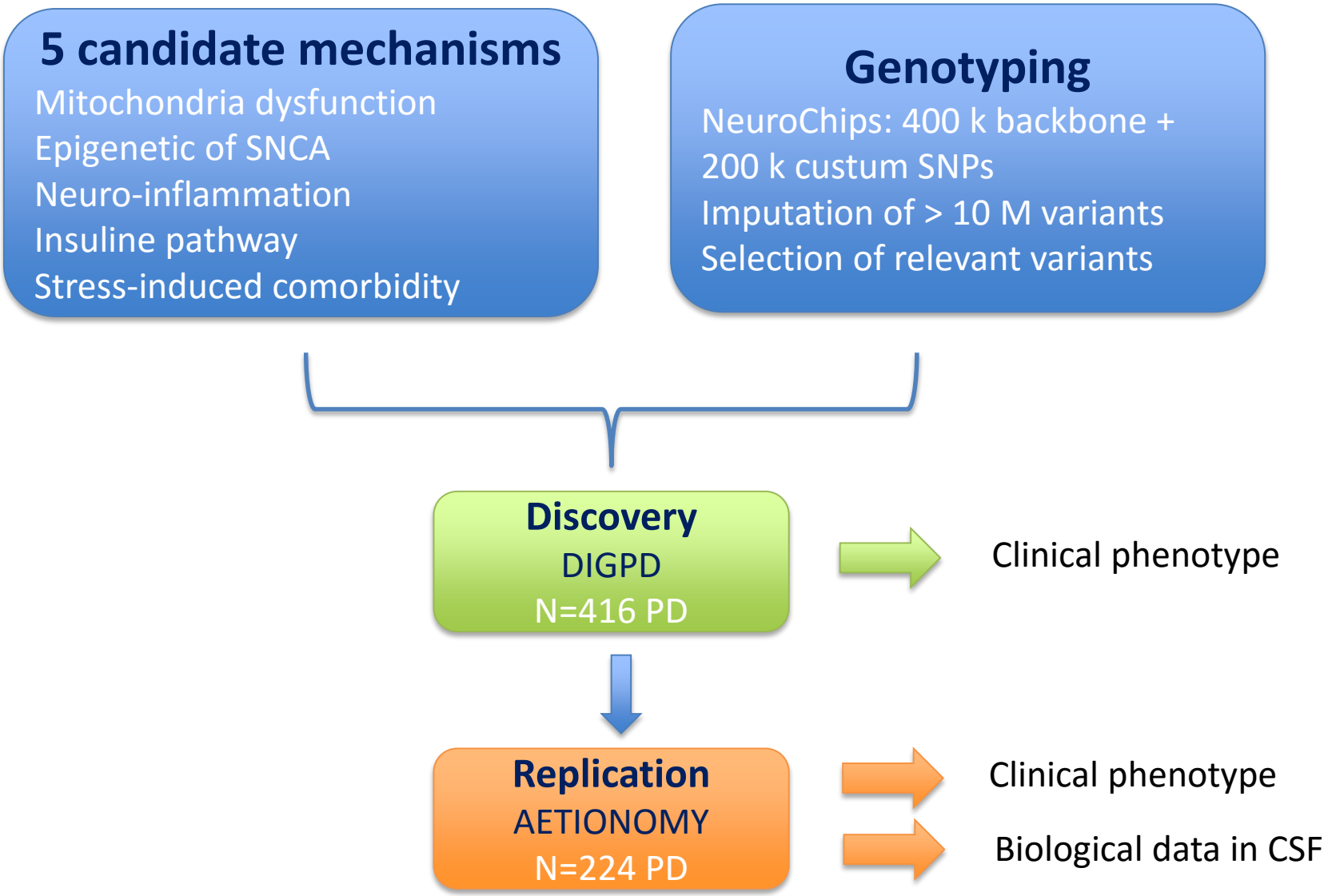
Genomic-based stratification

Biological validation

Replication in independant cohorts

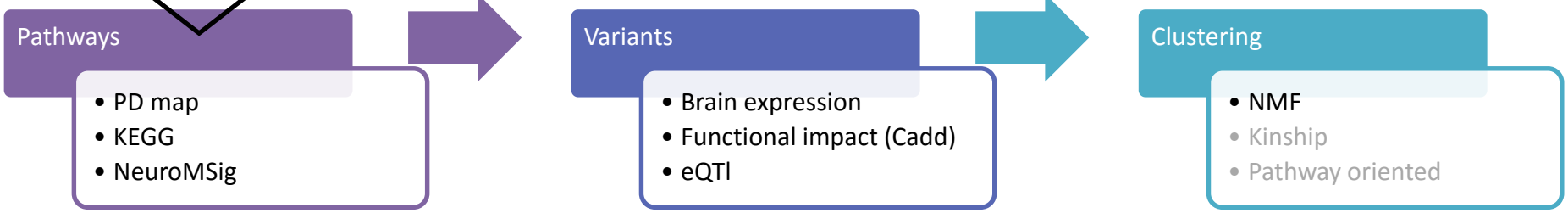
PD subpopulation ready for therapeutic intervention targeting specific mechanisms

Analysis pipeline



Genetic variant selection and clustering

5 candidate MECHANISMS



	N	Astroglial Inflammation	Insulin Signal Transduction	Mitochondrial Dysfunction	SNCA Methylation	Stress Induced Comorbidity
Total number of variants	956	354	221	285	237	76
Not shared		303	142	168	113	22
Common in 2 mechanisms		27	0	22	19	28
Common in 3 mechanisms		10	79	81	91	12
Common in 4 mechanisms		14	0	14	14	14

Non-negative Matrix Factorisation method

- NMF provides a parts-based representation of data:

$$H_{1j} \times Part_1 + H_{2j} \times Part_2 + \ldots = Image_j$$

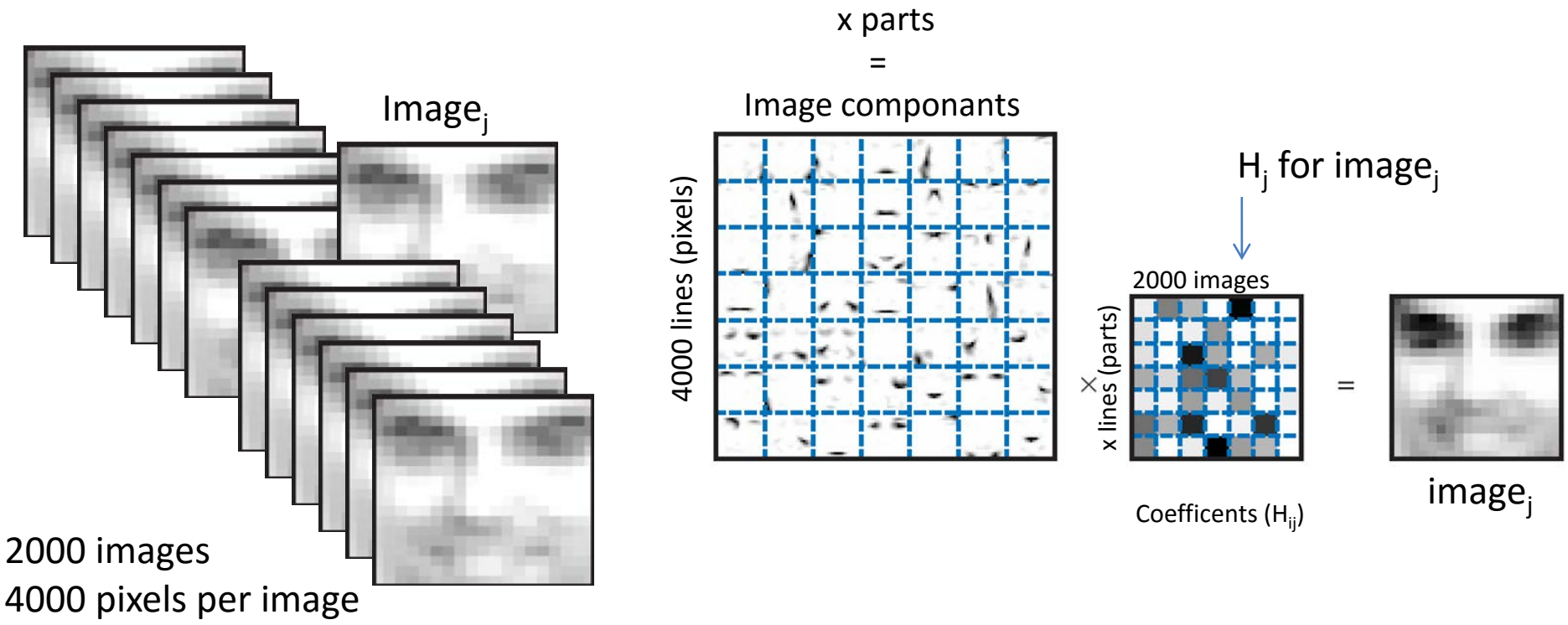


Illustration Lee and Seung 1999

NMF: application to AETIONOMY

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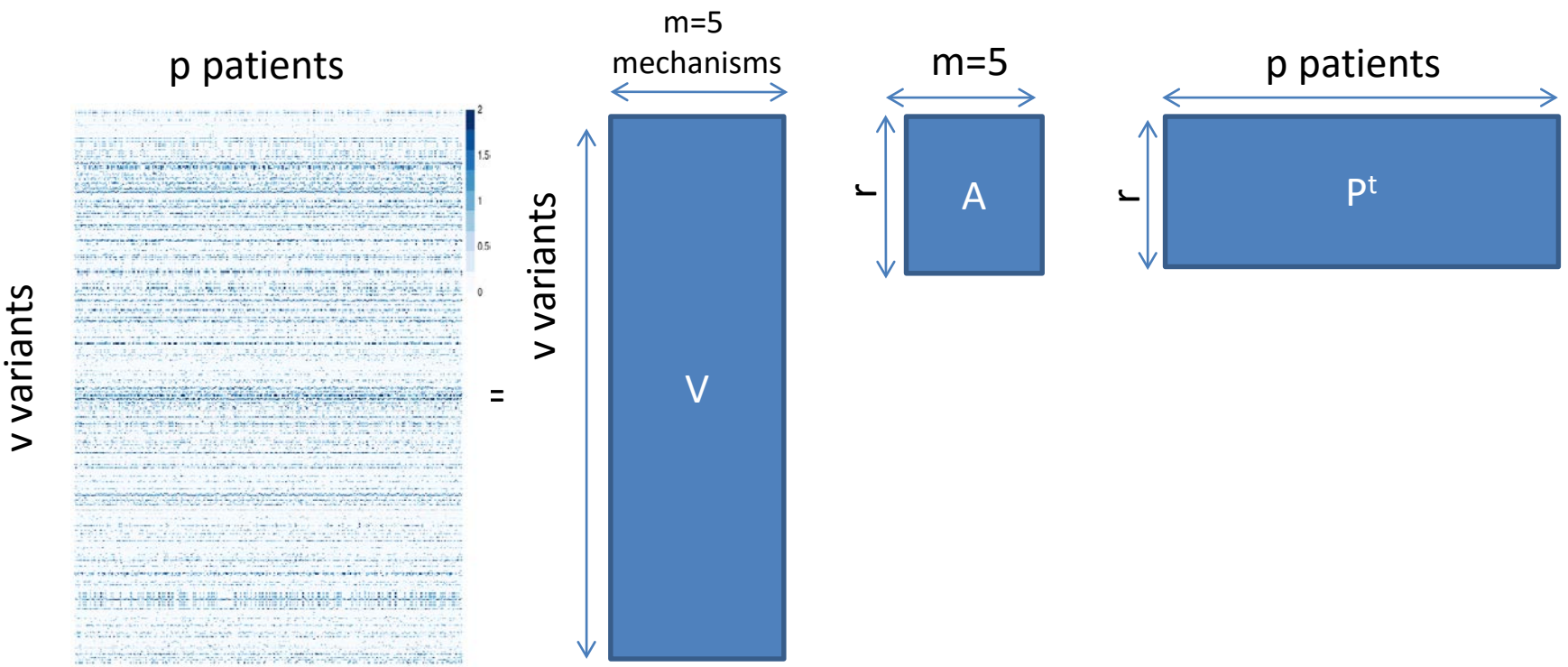
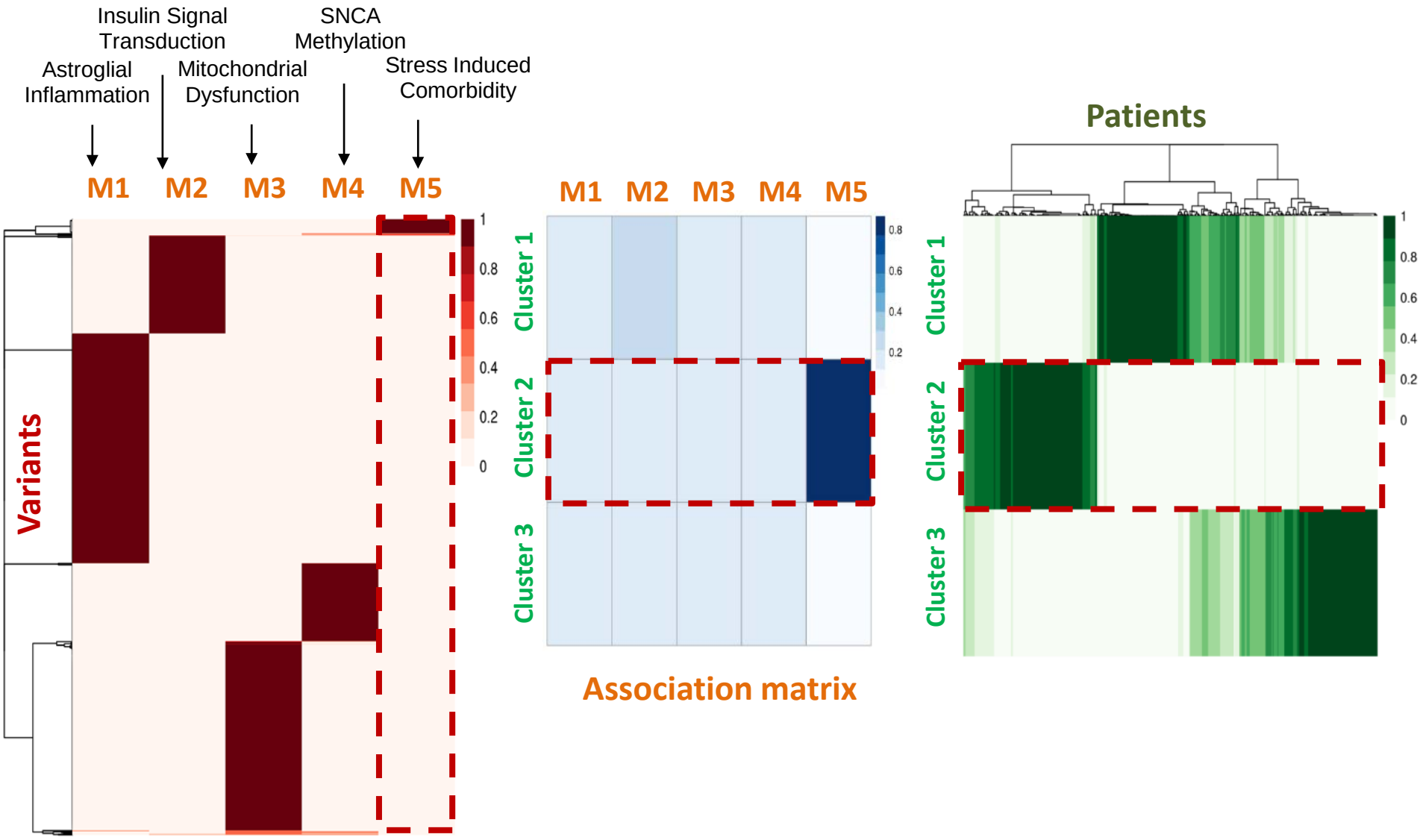
$$X \approx V \times A \times P^t$$

$$(v,p) = (v,m) \times (m,r) \times (r,p)$$

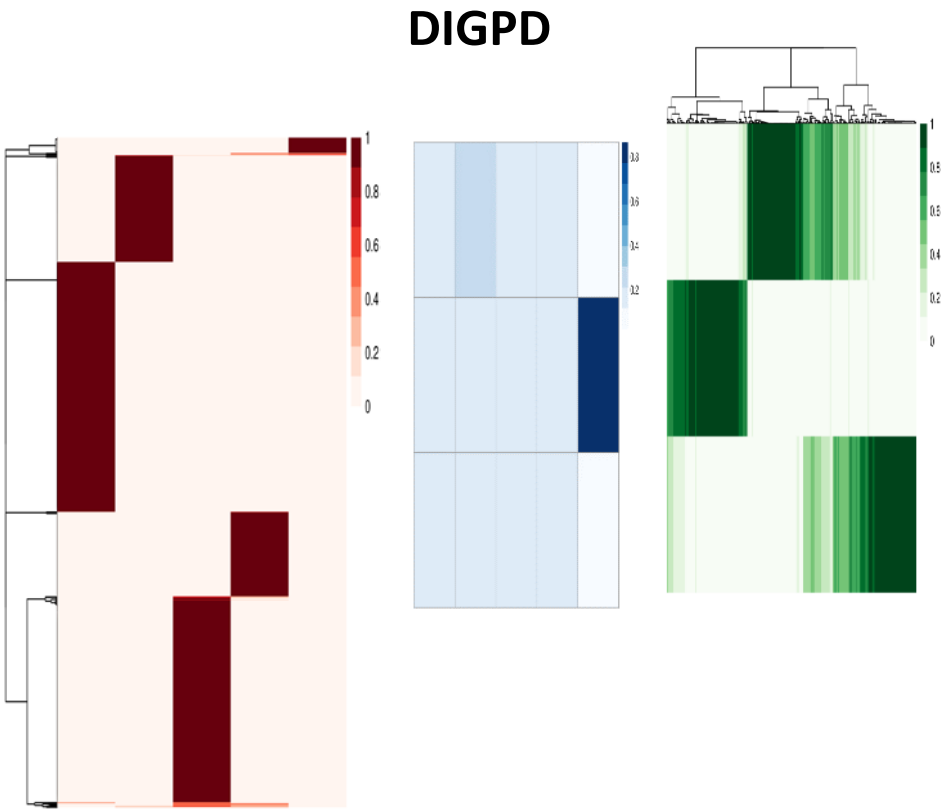


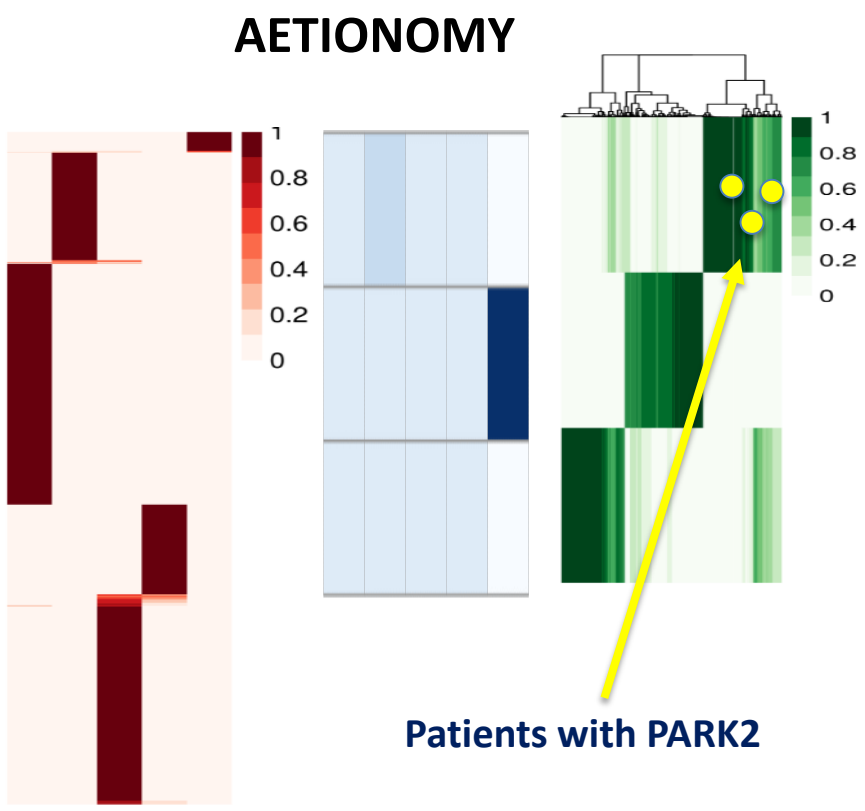
$$\min_{V,A,P} F(V, A, P) = \min_{V,A,P} ||X - V A P^t||^2 + Pen(V)$$

NMF in PD patients from the DIGPD cohort



Replication in the AETIONOMY cohort





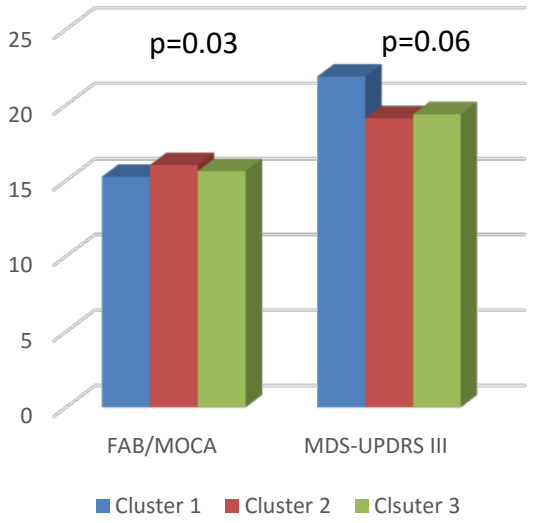
Similar variant map profile

Similar number of patients in clusters

Similar relationship with mechanisms

DIGPD (n=407)

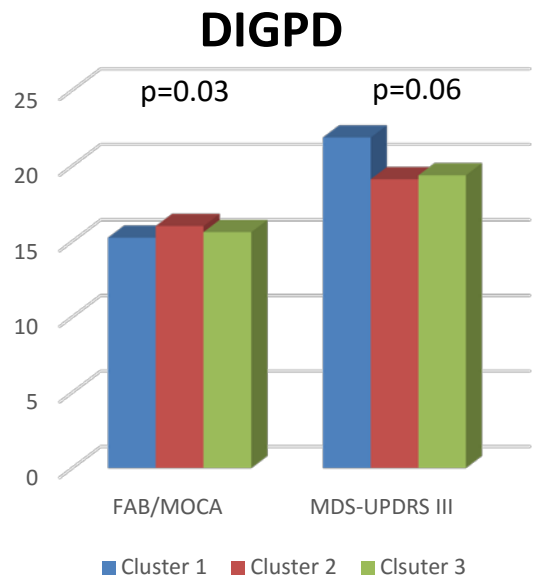
	Cluster 1	Cluster 2	Cluster 3	P-value
N	130 (32)	145 (36)	132 (32)	
Age	62.59 ± 10.64	61.8 ± 10.17	62.62 ± 8.63	0.79
Female (%)	52 (40%)	55 (37.93%)	58 (43.94%)	0.59
FAB/MOCA	**15.25 ± 2.66**	**16.02 ± 2.15**	**15.62 ± 2.19**	**0.03**
MMSE	28.2 ± 1.82	28.3 ± 1.84	28.08 ± 2.01	0.68
Non motor	7.41 ± 4.66	7.66 ± 4.8	7.24 ± 4.35	0.87
MDS-UPDRS I	8.27 ± 5.07	7.87 ± 4.94	7.82 ± 4.31	0.81
MDS-UPDRS II	8 ± 4.75	7.08 ± 4.47	7.68 ± 4.67	0.3
MDS-UPDRS III	**21.88 ± 10.85**	**19.12 ± 9.2**	**19.38 ± 10.76**	**0.06**
MDS-UPDRS IV	0.7 ± 1.99	0.49 ± 1.33	0.51 ± 1.62	0.79
Anxiety/depression	4.77 ± 3.11	4.63 ± 3.35	4.51 ± 3.03	0.77

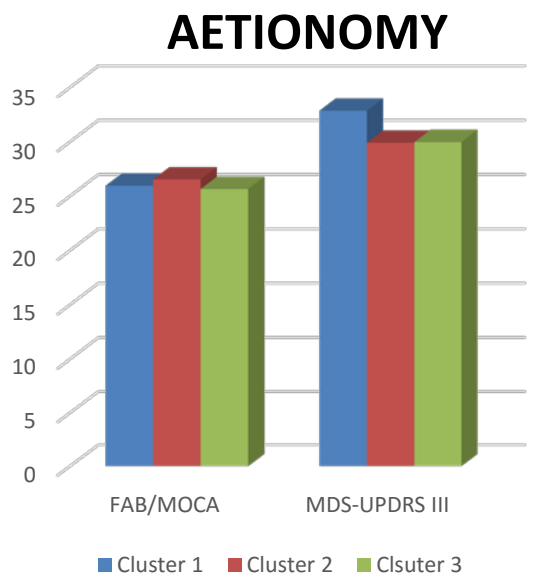


Regression model

Variable	Age inclusion	Age diagnosis	Sexe	Groupe
MDS-UPDRS III	<0.0001 *	<0.0001 *	0.7645	0.0385*
FAB	0.0066*	0.0426*	0.1947	0.0246*

	DIGPD (n=407)				AETIONOMY (n=224)			
	Cluster 1	**Cluster 2**	**Cluster 3**	**P-value**	**Cluster 1**	**Cluster 2**	**Cluster 3**	**P-value**
N	130 (32)	145 (36)	132 (32)		81 (36)	63 (28)	80 (35)	
Age	62.59 ± 10.64	61.8 ± 10.17	62.62 ± 8.63	0.79	63.52 ± 7.88	65 ± 7.57	63.89 ± 10.02	0.45
Female (%)	52 (40%)	55 (37.93%)	58 (43.94%)	0.59	25 (30.86%)	17 (26.98%)	26 (32.5%)	0.77
FAB/MOCA	**15.25 ± 2.66**	**16.02 ± 2.15**	**15.62 ± 2.19**	**0.03**	**25.95 ± 3.09**	**26.53 ± 2.58**	**25.65 ± 3.04**	**0.29**
MMSE	28.2 ± 1.82	28.3 ± 1.84	28.08 ± 2.01	0.68	28.28 ± 1.73	28.72 ± 1.44	28.25 ± 1.86	0.25
Non motor	7.41 ± 4.66	7.66 ± 4.8	7.24 ± 4.35	0.87	10.39 ± 4.47	8.4 ± 4.77	8.49 ± 4.55	0.01
MDS-UPDRS I	8.27 ± 5.07	7.87 ± 4.94	7.82 ± 4.31	0.81	9.04 ± 5.12	8.35 ± 4.67	8.24 ± 4.9	0.54
MDS-UPDRS II	8 ± 4.75	7.08 ± 4.47	7.68 ± 4.67	0.3	9.53 ± 5.68	8.5 ± 5.03	9.21 ± 5.45	0.52
MDS-UPDRS III	**21.88 ± 10.85**	**19.12 ± 9.2**	**19.38 ± 10.76**	**0.06**	**32.85 ± 14.81**	**29.91 ± 16.07**	**29.97 ± 12.71**	**0.29**
MDS-UPDRS IV	0.7 ± 1.99	0.49 ± 1.33	0.51 ± 1.62	0.79	1.54 ± 2.82	1.18 ± 2.33	1.13 ± 2.3	0.81
Anxiety/depression	4.77 ± 3.11	4.63 ± 3.35	4.51 ± 3.03	0.77	4.96 ± 3.97	3.79 ± 3.05	3.42 ± 3.3	0.03

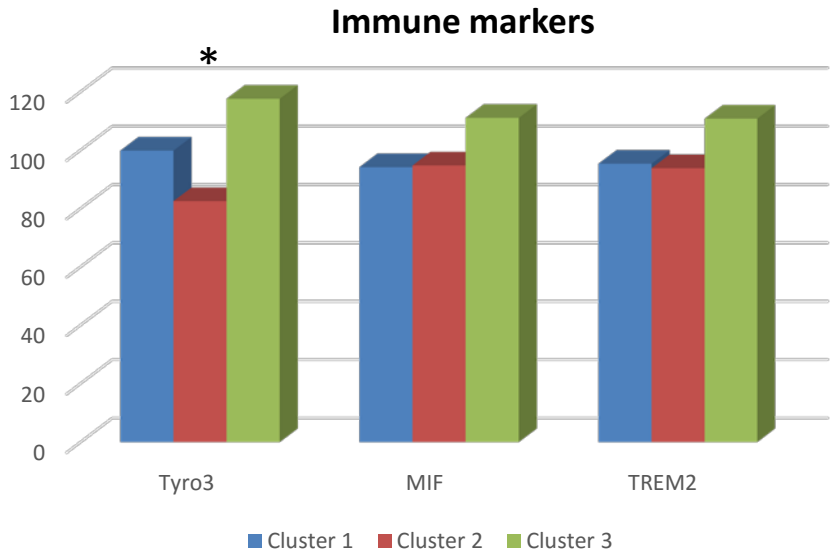


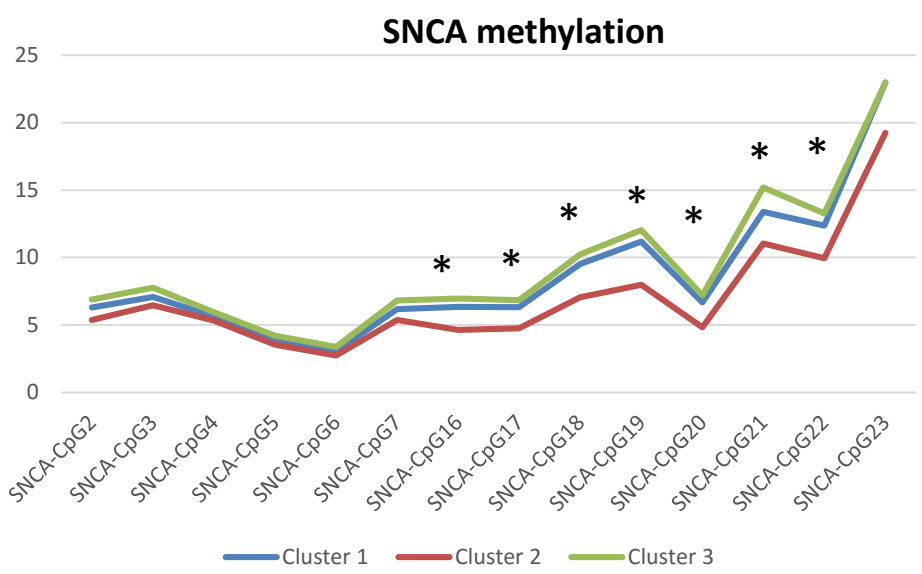


Immune markers and methylome profiles

	Cluster 1	Cluster 2	Cluster 3	p-value
n	22 (36,07%)	16 (26,23%)	23 (37,7%)	
Tyro3	2858.06 ± 987.28	2362.4 ± 831.82	3367.07 ± 1068.86	0.01
Properdin	18.73 ± 13	19.05 ± 10.75	13.16 ± 6.89	0.07
MIF	9167.03 ± 2328.36	9224.26 ± 4205	10812.88 ± 3653.66	0.1
C4	683.47 ± 364.5	827.27 ± 283.79	666.36 ± 279.18	0.12
TNFR_I	273.18 ± 71.21	253.45 ± 70.07	289.12 ± 70.45	0.16
Factor_B	670.86 ± 374.49	683.91 ± 287.24	559.48 ± 288.86	0.18
CRP	9036.66 ± 13345.2	8097.73 ± 18559.51	3579.72 ± 2926.23	0.22
TREM2	5823.23 ± 3142.85	5730.11 ± 2672.96	6766.13 ± 2842.98	0.26
Factor_H	673.45 ± 282.12	688.45 ± 262.09	588.84 ± 186.11	0.33
TNFR_II	147.36 ± 43.81	134.96 ± 44.52	147.43 ± 40.97	0.35
TGF_b1	36.58 ± 6.51	34.65 ± 4.54	36.56 ± 5.18	0.35
MCP_1	309.77 ± 93.16	333.11 ± 79.55	303.51 ± 76.08	0.42
C3	1354.68 ± 1579.78	1315.42 ± 1484.42	1075.14 ± 1069.76	0.7
IP_10	253.85 ± 121.72	309.51 ± 211.77	305.06 ± 200.79	0.72
AXL	19.1 ± 4.25	18.42 ± 4.78	19.46 ± 4.77	0.76
C1q	290.88 ± 90.9	274.76 ± 81.2	285.09 ± 80.39	0.79
ICAM_1	2915.91 ± 1074.36	2830.26 ± 1221.11	2722.75 ± 714.47	0.84
Il1RAcP	1342.47 ± 877.63	1216.78 ± 776.73	1312.15 ± 836.71	0.9
C3b	834.5 ± 1293.52	744.68 ± 648.18	581.53 ± 265.22	0.91
MIP_1b	10.08 ± 4.07	9.93 ± 3.7	9.28 ± 2.74	0.91

	Cluster 1	Cluster 2	Cluster 3	p-value
n	24 (32%)	30 (40%)	21 (28%)	
SNCA-CpG2	6.29	5.38	6.9	0.09
SNCA-CpG3	7.09	6.47	7.77	0.38
SNCA-CpG4	5.63	5.33	5.94	0.68
SNCA-CpG5	3.92	3.54	4.21	0.52
SNCA-CpG6	3.04	2.74	3.38	0.45
SNCA-CpG7	6.18	5.38	6.82	0.11
SNCA-CpG16	6.35	4.64	6.97	0.0002
SNCA-CpG17	6.32	4.76	6.84	0.003
SNCA-CpG18	9.52	7.06	10.23	0.0001
SNCA-CpG19	11.18	7.99	12.04	0.00003
SNCA-CpG20	6.68	4.83	7.2	0.0006
SNCA-CpG21	13.4	11.03	15.19	0.0004
SNCA-CpG22	12.37	9.95	13.28	0.004
SNCA-CpG23	22.97	19.25	22.98	0.08





Conclusions and perspectives

- Neurodegenerative & neuro-immune **biomarkers are associated with neurodegeneration (and aging) across diseases**
- **Specific profiles** of biomarkers can however be found to **discriminate AD from PD** and/or **patients from controls**
- **Mechanism-based stratification** may be achieved by using genomic information, but association with **relevant biomarkers must be further explored**
- **Prospective longitudinal datasets are needed** for testing their association with disease progression
- **AETIONOMY: unique dataset** combining clinical, biological, and genetic data made available for the scientific community

Thank you for your attention

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