

Supplementary material

Associations of cortical *SPP1* and *ITGAX* with cognition and common neuropathologies in older adults

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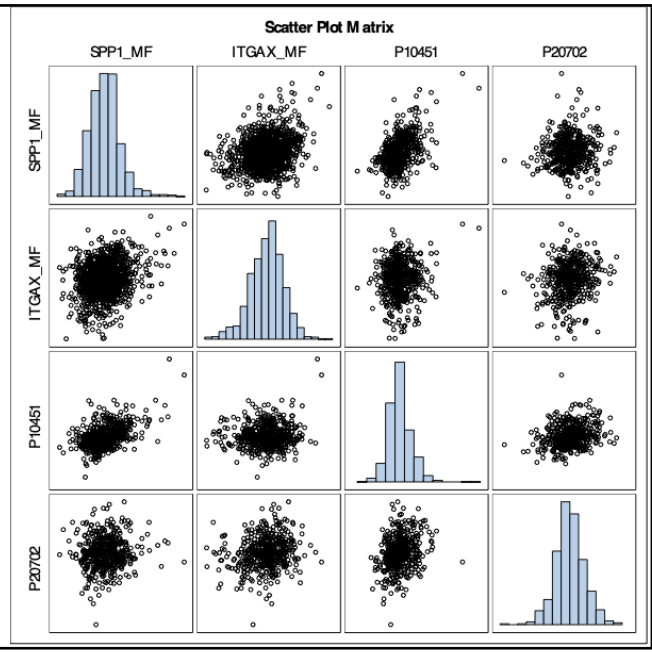
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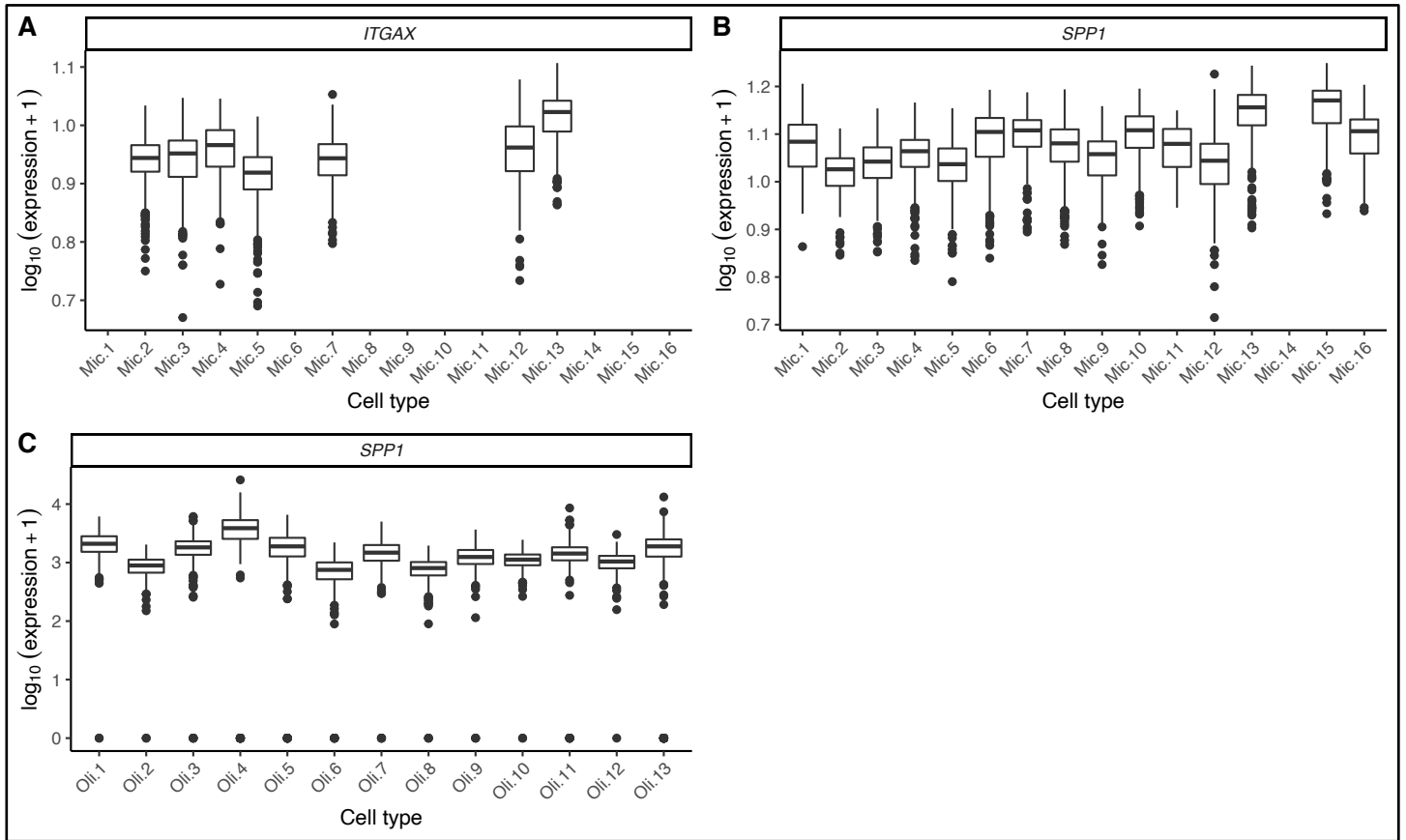
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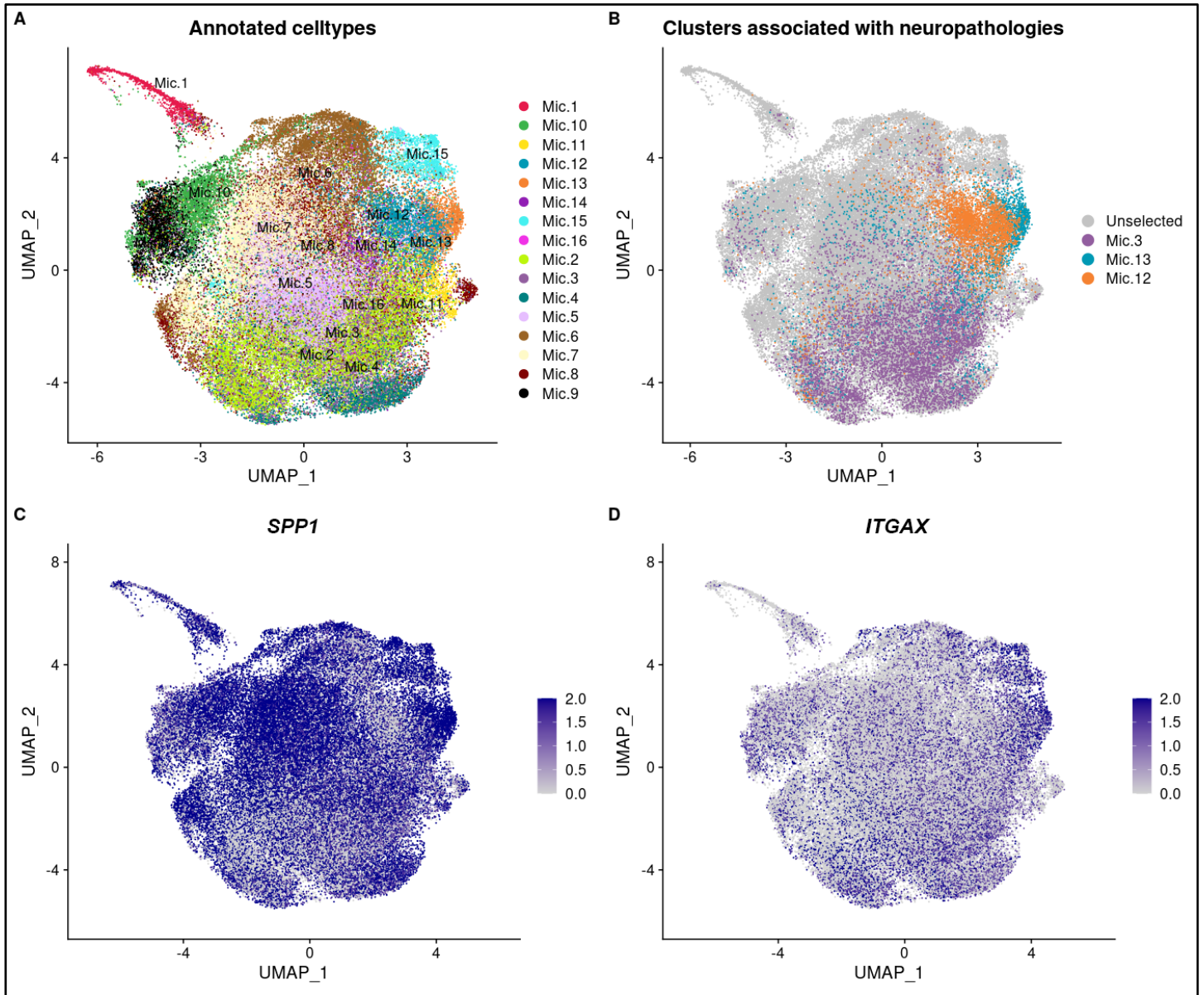
Pearson Correlation Coefficients Prob > r under H0: Rho=0 Number of Observations				
	SPP1_MF	ITGAX_MF	P10451	P20702
SPP1_MF	1.00000 1216	0.25473 <.0001 1216	0.48657 <.0001 541	0.07852 0.0887 471
ITGAX_MF	0.25473 <.0001 1216	1.00000 1216	0.08557 0.0467 541	0.16631 0.0003 471
P10451	0.48657 <.0001 541	0.08557 0.0467 541	1.00000 580	0.26142 <.0001 489
P20702	0.07852 0.0887 471	0.16631 0.0003 471	0.26142 <.0001 489	1.00000 505



Supplementary Figure 1 - Correlations of *SPP1* and *ITGAX* expression from bulk RNASeq. The results are for RNA and protein levels. P10451 = OPN, P20702 = CD11c.



Supplementary Figure 2 - *ITGAX* and *SPP1* expression in the snRNASeq data. A) *ITGAX* expression in the microglial subpopulation. B) *SPP1* expression in the microglial subpopulation. C) *SPP1* expression in the oligodendrocytes clusters. Cells nomenclature: Mic = microglia and Oli = oligodendrocytes.



Supplementary Figure 3 - *SPP1* and *ITGAX* expression in the microglial subpopulations. A) Microglial sub-clusters visualized in an UMAP reduction. Annotations from Green et al, 2023 and Fujita et al, 2022^{1,2}. B) Selected clusters associated with neuropathologic indices for better visualization. C) *SPP1* expression across the microglial sub-clusters. D) *ITGAX* surface protein expression across the microglial subpopulations. In these plots, each dot is a cell, so we can visualize the gene expression across the distinct cell clusters. Dark blue represents high expression, and gray no expression (C-D).

Supplementary Table 01 – Associations of *SPP1* and OPN with clinical diagnosis at death.

Variables	<i>SPP1</i> (N=1,205)	OPN (N=580)
Age at death,	1.0672 (1.0489,1.0857)	1.0932 (1.0653,1.1218)
Male sex	1.0330 (0.8160,1.3075)	1.0536 (0.7500,1.4801)
Educational	1.0087 (0.9781,1.0404)	1.0219 (0.9752,1.0708)
<i>SPP1</i> expression	1.3629 (1.2072,1.5387)	
OPN expression		1.3012 (1.1101,1.5252)

The results for *SPP1*, and separately OPN, were obtained from a logistic regression model with a 3-level ordinal outcome of no cognitive impairment (reference), mild cognitive impairment and dementia. The statistics in each cell are odds ratio (95% confidence interval).

Supplementary Table 02 – The associations with the MSBB RNASeq dataset. CERAD = Test from the Consortium to Establish a Registry for Alzheimer's Disease, Braak refers to the AD score for progression of neurofibrillary pathology, CDR = Clinical dementia rating scale, plaqueMean = density of neuritic plaques ³.

pheno	Estimate	Std. Error	df	t value	Pr(> t)	gene
CERAD	0.037653501	0.0614423	299.7822056	0.612826969	0.540455366	<i>SPP1</i>
Braak	0.099004344	0.03015903	302.9530329	3.282742649	0.001148289	<i>SPP1</i>
CDR	0.125009888	0.03435023	306.0363784	3.639273326	0.000320839	<i>SPP1</i>
plaqueMean	0.017723861	0.00818247	213.7553285	2.166076854	0.031411825	<i>SPP1</i>
CERAD	-0.035957882	0.03909985	297.5154299	-0.919642513	0.35850462	<i>ITGAX</i>
Braak	0.125168845	0.01824624	304.0141866	6.859981894	3.86093E-11	<i>ITGAX</i>
CDR	0.123132451	0.02131791	308.0457942	5.776008856	1.86966E-08	<i>ITGAX</i>
plaqueMean	0.023543896	0.00493446	208.5736712	4.7713196	3.43755E-06	<i>ITGAX</i>

Supplementary Table 03 – The associations with the Mayo Clinic RNASeq dataset. Braak refers to the AD score for progression of neurofibrillary pathology, PSP = progressive supranuclear palsy ⁴.

pheno	Estimate	Std. Error	df	t value	Pr(> t)	gene
AD diagnosis	0.307570139	0.185600408	499	1.657163056	0.098115056	<i>SPP1</i>
Pathological aging diagnosis	0.190206151	0.256856691	499	0.740514682	0.459336043	<i>SPP1</i>
PSP diagnosis	-0.236916037	0.2004781	499	-1.181755198	0.237865712	<i>SPP1</i>
Braak	0.106960571	0.044332514	364	2.412689043	0.016328988	<i>SPP1</i>
Thal	0.091376596	0.044360377	284	2.059869686	0.040322097	<i>SPP1</i>
AD diagnosis	-0.138084235	0.131774779	499	-1.047880603	0.295200896	<i>ITGAX</i>
Pathological aging diagnosis	0.295747153	0.18236616	499	1.62172167	0.105494592	<i>ITGAX</i>
PSP diagnosis	-0.443004548	0.142337819	499	-3.112346047	0.001962499	<i>ITGAX</i>
Braak	0.061267428	0.030956667	364	1.979135143	0.048553966	<i>ITGAX</i>
Thal	0.075218418	0.030707532	284	2.449510383	0.014909154	<i>ITGAX</i>

Supplementary Table 04 – The associations with the TMT proteins from MSBB. CERAD = Test from the Consortium to Establish a Registry for Alzheimer's Disease, Braak refers to the AD score for progression of neurofibrillary pathology, CDR = Clinical dementia rating scale, plaqueMean = density of neuritic plaques ⁵

pheno	Estimate	Std. Error	t value	Pr(> t)	protein
CERAD	0.009657771	0.024736194	0.390430767	0.696682279	ITGAX_P20702
Braak	0.084896821	0.011311835	7.505132235	2.77835E-12	ITGAX_P20702
CDR	0.082060625	0.013610941	6.029019336	9.20806E-09	ITGAX_P20702
plaqueMean	0.0217182	0.003276788	6.627893605	7.76197E-10	ITGAX_P20702
CERAD	0.050384217	0.035962956	1.401003238	0.16294438	SPP1_P10451
Braak	0.058424912	0.01844173	3.168081899	0.001804642	SPP1_P10451
CDR	0.046929212	0.021530326	2.179679607	0.030586966	SPP1_P10451
plaqueMean	0.012752548	0.005189532	2.457360098	0.015283687	SPP1_P10451

Supplementary Table 05 - Annotation of the microglial subpopulations. Annotation from Fujita et al, 2022 and Gilad Green et al, 2023. In bold, the clusters associated with neuropathologic indices, in our study.

State	Description
Mic.1	Proliferating
Mic.2	Homeostatic
Mic.3	Homeostatic/ tau-associated
Mic.4	Homeostatic
Mic.5	Homeostatic
Mic.6	Reactive
Mic.7	Reactive
Mic.8	Reactive
Mic.9	Homeostatic-Redox
Mic.10	Reactive-Redox
Mic.11	Stress-Response
Mic.12	Disease-Elevated/ lipid-associated
Mic.13	Disease-Elevated/ lipid-associated
Mic.14	Interferon-Response
Mic.15	Mic.15
Mic.16	Mic.16

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