Computational network analysis of spreader nodes reveals drug repurposing candidates for Alzheimer's Disease

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Supplementary Table 1. Relevant biological pathways identified for the spreader genes of the female DEG sample PC AD00103 vs AD00106.

Pathway name	Entities			Reactions	
	found	ratio	p-value / FDR*	found	ratio
Immune System	20 / 2,793	0.173	1.58e-08 / 1.03e-05	109 / 1,807	0.115
Signaling by Rho GTPases[1]	11 / 708	0.044	6.47e-08 / 1.75e-05	65 / 203	0.013
Signaling by Rho GTPases, Miro GTPases and RHOBTB3[1]	11 / 724	0.045	8.11e-08 / 1.75e-05	65 / 212	0.014
Neurodegenerative Diseases	4 / 30	0.002	4.15e-07 / 5.36e-05	3 / 22	0.001

Supplementary Table 2. Relevant biological pathways identified for the spreader genes of the female DEG sample SPL AD01206 vs AD01202.

Pathway name	Entities			Reactions	
	found	ratio	p-value / FDR*	found	ratio
Attenuation phase[2]	14 / 47	0.003	1.11e-16 / 1.30e-14	4 / 5	3.19e-04
HSF1 activation[2,3]	13 / 43	0.003	1.11e-16 / 1.30e-14	5 / 7	4.47e-04
HSF1-dependent transactivation[2,3]	14 / 59	0.004	1.11e-16 / 1.30e-14	5 / 8	5.11e-04
Cellular response to heat stress[4]	15 / 135	0.008	1.11e-16 / 1.30e-14	18 / 29	0.002
Regulation of HSF1-mediated heat shock response[2,3]	13 / 113	0.007	1.11e-16 / 1.30e-14	8 / 14	8.93e-04
Cellular responses to stimuli[5-8]	24 / 1,166	0.072	1.11e-16 / 1.30e-14	82 / 613	0.039
Cellular responses to stress[9,10]	22 / 1,039	0.065	4.44e-16 / 4.44e-14	77 / 521	0.033
Cytokine Signaling in Immune system[11]	17 / 1,095	0.068	4.40e-10 / 3.87e-08	52 / 791	0.05

Supplementary Table 3. Relevant biological pathways identified for the spreader genes of the male DEG sample EC AD00205 vs AD00201.

Pathway name	Entities			Reactions	
	found	ratio	p-value / FDR*	found	ratio
Attenuation phase[2]	13 / 47	0.003	1.11×10^{-16} / 1.98×10^{-14}	4 / 5	3.19e-04
HSF1-dependent transactivation[2,3]	13 / 59	0.004	1.11×10^{-16} / 1.98×10^{-14}	5 / 8	5.11e-04
HSF1 activation[2,3]	11 / 43	0.003	1.11×10^{-16} / 1.98×10^{-14}	4 / 7	4.47e-04
Cellular response to heat stress[4]	13 / 135	0.008	2.22×10^{-16} / 2.95×10^{-14}	16 / 29	0.002
Regulation of HSF1-mediated heat shock response[2,3]	12 / 113	0.007	1.33×10^{-15} / 1.41×10^{-13}	7 / 14	8.93e-04
Cellular responses to stimuli[5-8]	17 / 1166	0.072	3.97×10^{-8} / 3.53×10^{-6}	74 / 613	0.039
Cellular responses to stress[9,10]	16 / 1039	0.065	5.33×10^{-8} / 4.05×10^{-6}	60 / 521	0.033
Cytokine Signaling in Immune system[11]	16 / 1095	0.068	1.10×10^{-7} / 7.24×10^{-6}	12 / 791	0.050

Supplementary Table 4. Relevant biological pathways identified for the spreader genes of the male DEG sample PC AD00803 vs AD00801.

Pathway name	Entities			Reactions	
	found	ratio	p-value / FDR*	found	ratio
Attenuation phase[2]	9 / 47	0.003	1.49×10^{-14} / 8.20×10^{-12}	4 / 5	0.000328
HSF1-dependent transactivation[2,3]	9 / 59	0.004	1.13×10^{-13} / 3.10×10^{-11}	5 / 8	0.000524
IGF2BPs bind RNA[12]	6 / 13	0.000824	2.49×10^{-12} / 4.55×10^{-10}	2 / 3	0.000197
HSF1 activation[2,3]	7 / 43	0.003	4.64×10^{-11} / 6.36×10^{-9}	4 / 7	0.000459
Cytokine Signaling in Immune system[11]	18 / 1095	0.069	3.87×10^{-10} / 2.63×10^{-8}	30 / 791	0.052

Supplementary Table 5. Relevant biological pathways identified for the spreader genes of the male DEG sample PC AD00102 vs AD00101.

Pathway name	Entities			Reactions	
	found	ratio	p-value / FDR*	found	ratio
Chaperone Mediated Autophagy[13]	4 / 23	0.001	8.29e-08 / 3.76e-05	19 / 19	0.001
Peptide chain elongation[14]	5 / 97	0.006	6.94e-07 / 1.34e-04	4 / 5	3.19e-04
Eukaryotic Translation Elongation[14]	5 / 102	0.006	8.87e-07 / 1.34e-04	7 / 9	5.74e-04
Protein methylation[15]	3 / 19	0.001	5.26e-06 / 5.95e-04	4 / 9	5.74e-04
Translation	7 / 450	0.028	9.39e-06 / 8.45e-04	54 / 126	0.008

Supplementary Table 6. Relevant biological pathways identified for the spreader genes of the male DEG sample PC AD00104 vs AD00101.

Pathway name	Entities			Reactions	
	found	ratio	p-value / FDR*	found	ratio
CASP4 inflammasome assembly[16]	3 / 13	8.07e-04	3.68e-06 / 8.60e-04	2 / 7	4.47e-04
VEGFR2 mediated vascular permeability[17]	4 / 48	0.003	4.31e-06 / 8.60e-04	10 / 15	9.57e-04
Interleukin-4 and Interleukin-13 signaling[18]	6 / 211	0.013	7.03e-06 / 8.60e-04	2 / 47	0.003
Signaling by Receptor Tyrosine Kinases[19]	9 / 634	0.039	8.12e-06 / 8.60e-04	99 / 759	0.048
Microbial factors inhibit CASP4 activity[16]	3 / 17	0.001	8.18e-06 / 8.60e-04	3 / 4	2.55e-04
Non-canonical inflammasome activation[20]	3 / 18	0.001	9.70e-06 / 8.60e-04	2 / 17	0.001
Cytokine Signaling in Immune system[11]	11 / 1,095	0.068	1.75e-05 / 0.001	10 / 791	0.005

Supplementary Table 7. Relevant biological pathways identified for the spreader genes of the male DEG sample PC AD00108 vs AD00101.

Pathway name	Entities			Reactions	
	found	ratio	p-value / FDR*	found	ratio
Cellular responses to stimuli[5-8]	16 / 1,166	0.072	1.11e-10 / 1.07e-07	70 / 613	0.039
Regulation of TP53 Degradation[21]	6 / 43	0.003	3.10e-10 / 1.13e-07	25 / 30	0.002
Regulation of TP53 Expression and Degradation[21]	6 / 46	0.003	4.62e-10 / 1.13e-07	25 / 35	0.002
Amyloid fiber formation[22]	7 / 89	0.006	4.70e-10 / 1.13e-07	13 / 33	0.002
Regulation of CDH1 Expression and Function[23]	8 / 192	0.012	3.33e-09 / 4.30e-07	12 / 92	0.006
Regulation of CDH1 Function[23]	6 / 65	0.004	3.58e-09 / 4.30e-07	9 / 16	0.001

Supplementary Table 8. Relevant biological pathways identified for the spreader genes of the male DEG sample SPL AD01203 vs AD01201.

Pathway name	Entities			Reactions	
	found	ratio	p-value / FDR*	found	ratio
Interleukin-4 and Interleukin-13 signaling[18]	14 / 211	0.013	$1.22e^{-15}$ / $7.90e^{-13}$	6 / 47	0.003
Cytokine Signaling in Immune system[11]	23 / 1,095	0.069	$6.55e^{-15}$ / $2.12e^{-12}$	55 / 791	0.052
Cellular responses to stress[9,10]	21 / 1,039	0.066	$3.40e^{-13}$ / $7.32e^{-11}$	87 / 521	0.034
Attenuation phase[2]	8 / 47	0.003	$1.72e^{-12}$ / $2.64e^{-10}$	4 / 5	3.26e-04
Signaling by Interleukins[18]	17 / 646	0.041	$2.05e^{-12}$ / $2.64e^{-10}$	29 / 505	0.033
Cellular responses to stimuli[5-8]	21 / 1,166	0.074	$3.10e^{-12}$ / $3.32e^{-10}$	94 / 613	0.040
Cellular response to heat stress[4]	10 / 135	0.009	$7.93e^{-12}$ / $7.29e^{-10}$	16 / 29	0.002
HSF1-dependent transactivation[2,3]	8 / 59	0.004	$1.03e^{-11}$ / $8.25e^{-10}$	5 / 8	5.21e-04

Supplementary Table 9. List of repurposed drug candidates identified for females and males utilizing DGIdb data.

Gender	Drug Name	Drug ID	Literary evidence
Female	Acetazolamide	DB00819	24,25
	Amlexanox	DB01025	26
	Acetylsalicylic Acid / Aspirin	DB00945	27-31
	Ciclopirox Olamine	DB01188	32-36
	Clioquinol	DB04815	37-43
	Clotrimazole	DB00257	44
	Deferoxamine	DB00746	45
	Disulfiram	DB00822	46-49
	Epinephrine	DB00668	50
	Etanercept–SZZS	DB00005	51,52
	Ethinyl Estradiol	DB00977	53-57
	Estradiol Valerate	DB13956	58
	Fluconazole	DB00196	59
	Hexachlorophene	DB00756	60,61
	Histamine	DB05381	62
	Histidine	DB00117	63
	Ketoconazole	DB01026	64
	Methazolamide	DB00703	24,25
	Miconazole Nitrate	DB01110	65
	Resveratrol	DB02709	66
	Selenium	DB11135	67
	Tamoxifen	DB00675	68
	Tetracycline	DB00759	69,70
	Topiramate	DB00273	71
	Triclabendazole	DB12245	72
	Zonisamide	DB00909	73
Male	Genistein	DB01645	74-79
	Hexachlorophene	DB00756	60,61
	Ketoconazole	DB01026	64
	Masoprocol	DB00179	80,81
	Pentoxifylline	DB00806	82
	Progesterone	DB00396	83

Supplementary Table 10. List of repurposed drug candidates identified for females and males utilizing DrugBank data (alphabetically ordered).

Gender	Drug Name	Drug ID	Literary evidence
Female	Acetylsalicylic acid / Aspirin	DB00945	27-31
	Copper	DB09130	84
	NADH	DB00157	85,86
	Rifabutin	DB00615	87
	Xanthinol (Xanthinol Nicotinate)	DB09092	88
	Zinc	DB01593	89
	Zinc acetate	DB14487	89
	Zinc chloride	DB14533	90
Male	**Copper**	DB09130	84
	Zinc	DB01593	89
	Zinc acetate	DB14487	89
	Zinc chloride	DB14533	90

Supplementary Table 11. Spreader genes for Female DEG sample EC AD00204 vs AD00202

Gene	Regulation/Type
ACTB	down
ACTG1	down
CALM1	down
COX4I1	down
COX5B	down
FTH1	down
FTL	down
GAPDH	down
GFAP	Up/down
HSP90AA1	down
HSPA1A	down
KDM6A	up
LRP2	up
MT-ATP6	down
NFKBIA	up
PDE4D	down
PTPN11	up
RHOB	up
SLC1A2	down
SOD1	down

Supplementary Table 12. Spreader genes for Female DEG sample PC AD00103 vs AD00106

Gene	Regulation/Type
ACTB	down
APP	down
CALM3	down
CLTC	down
COX4I1	down
DLG4	down
FOS	down
GAPDH	down
H3-3B	new
HSP90AA1	down
HSP90AB1	down
HSPA5	down
NFKB1	up
PRKN	New Spreader
RAC1	down
RASA1	up
SNCA	up
SOD2	down
SRSF1	down
YWHAZ	down

Supplementary Table 13. Spreader genes for Female DEG sample SPL AD001206 vs AD01202

Gene	Regulation/Type
ACTB	down
B2M	up
CALR	down
CDC42	down
CTNNB1	Down
ENO1	down
GAPDH	down
GRB2	down
H3-3B	new
HNRNPU	New Spreader
HSP90AA1	up
HSP90AB1	down
HSPA1A	up
HSPA1B	up
JUN	up
NFKBIA	up
PCBP1	up
SOD1	up
TP53	new
YWHAE	down

Supplementary Table 14. Spreader genes for Male DEG sample EC AD00206 vs AD00201

Gene	Regulation/Type
ACTB	down
ANK2	down
ANK3	down
APOE	down
B2M	up
CALM1	down
CTNNB1	up
ELAVL1	up
ERBB4	down
FN1	up
FOS	down
GAPDH	down
GFAP	up
GRB2	up
HSP90AA1	up
HSP90AB1	down
HSPA8	up
SOD1	Up
SOD2	up
SUMO1	up

Supplementary Table 15. Spreader genes for Male DEG sample EC AD00205 vs AD00201

Gene	Regulation/Type
ANK2	down
ANK3	down
APP	down
B2M	up
CDH1	New spreader
DLG4	New spreader
EGR1	down
ERBB4	down
FOS	down
FTH1	down
FTL	down
H3-3B	new
HSP90AA1	Up
HSPA1A	down
HSPA1B	up
ITGB1	up
KCND2	down
NCAM1	up
SLC2A1	up
VWF	up

Supplementary Table 16. Spreader genes for Male DEG sample PC AD00803 vs AD00801

Gene	Regulation/Type
ACTB	down
ACTG1	down
B2M	up
CALM1	down
CD44	up
COX4I1	up
CSF1R	down
CYCS	up
ENO2	down
FOS	up
GFAP	up
H3-3B	new
HSP90AA1	up
HSP90AB1	down
HSPA1B	up
HSPA8	up
JUN	up
RAC1	down
SOD1	Up
SOD2	up

Supplementary Table 17. Spreader genes for Male DEG sample PC AD00102 vs AD00101

Gene	Regulation/Type
ACTB	down
ALDOA	down
CALM3	New spreader
CHI3L1	down
EEF1A1	down
GAPDH	down
GFAP	down
H3-3B	new
HSP90AA1	down
HSPA8	down
MAPT	New Spreader
MT-ATP6	down
PTGS1	New Spreader
RPL18A	down
RPLP2	up
RPS28	down
RPS3	New Spreader
SNCA	down
SRSF1	down
TARDBP	New Spreader

Supplementary Table 18. Spreader genes for Male DEG sample PC AD00104 vs AD00101

Gene	Regulation/Type
ACTB	down
AKT1	new
APP	down
CALM2	down
CALM3	New Spreader
DLG4	New Spreader
EGFR	new
ELAVL1	up
GAPDH	down
GFAP	down
HSP90AA1	down
HSP90AB1	down
HSPA5	down
MAPT	New Spreader
RBFOX1	up
SNCA	down
SRSF1	down
TARDBP	New Spreader
TP53	new
TUBA1A	**down**

Supplementary Table 19. Spreader genes for Male DEG sample PC AD00108 vs AD00101

Gene	Regulation/Type
ABL1	down
ACTB	down
ACTG1	down
BCL2	down
BRAF	down
CALM3	down
FYN	down
GAPDH	down
H3-3B	new
H4C6	New Spreader
HSPA5	up
HSPA8	up
MAPK8	down
MDM2	up
PPP2CA	up
PRKN	New Spreader
RAB11A	down
SNCA	down
SOX2	up
UBB	down

Supplementary Table 20. Spreader genes for Male DEG sample SPL AD01203 vs AD01201 ()

Gene	Regulation/Type
ACTB	down
AKT1	new
B2M	up
EGFR	new
GAPDH	down
HIF1A	up
HSP90AA1	up
HSP90AB1	down
HSPA1B	down
HSPA4	new
HSPA5	up
IL6	new
JUN	up
MDM2	down
MYC	new
PTEN	down
SOD2	up
SRC	new
TNF	new
TP53	new

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