Open Source Tools to De-risk AD Target Predictions

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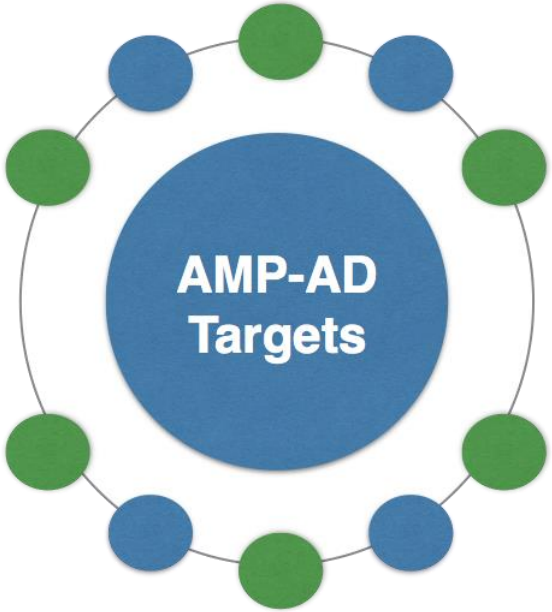
SageBionetworks


INTERNATIONAL AMUSEMENT



Identification of target predictions catalyzed by systems biology

Evaluation of target predictions catalyzed by open science

In the absence of prior knowledge, how do you distinguish poor target predictions from dark target predictions?

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Open Science

Open data to increase confidence in predictions

60,000 files shared by **42 investigators** across **22 institutions**
representing samples from **36 research studies**

3 rat models

15 genomic data modalities

17 mouse models

10 drosophila models

7043 human samples

22 model system studies

13 human cell models

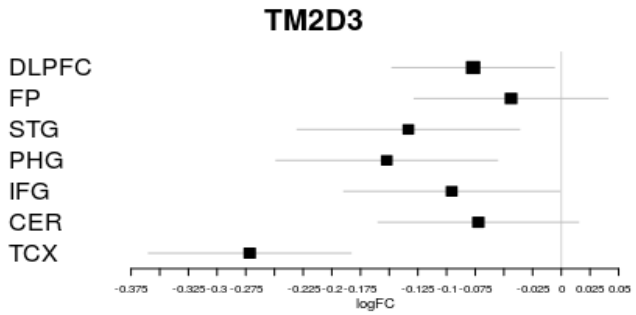
14 diagnoses

15 human studies

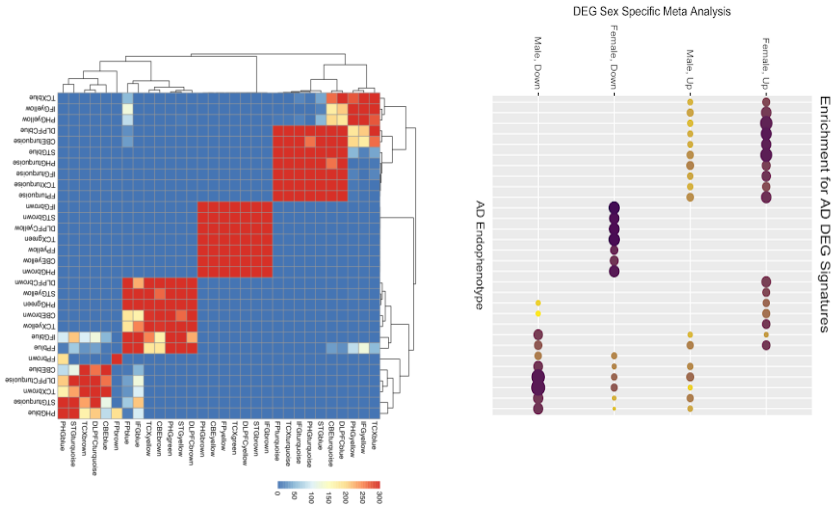
ADNI
Alzheimer's Disease Neuroimaging Initiative

RADC Research Resource Sharing Hub

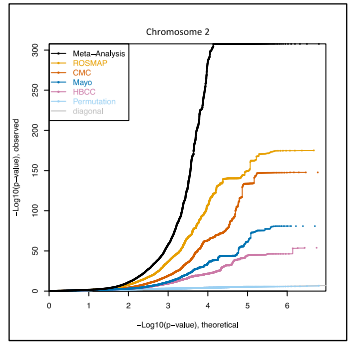
Identify generalizable observations from across the consortium



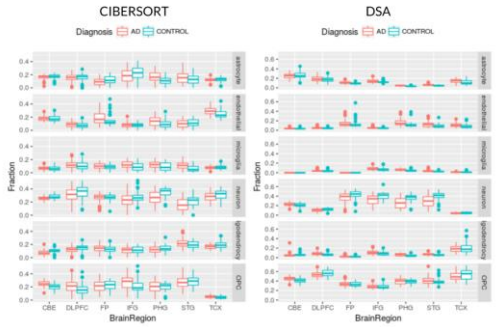
RNAseq Working Group



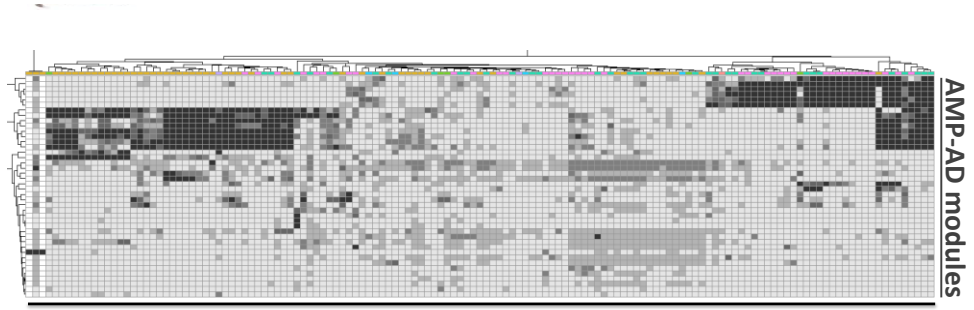
Network Working Group



eQTL Working Group



Deconvolution Working Group



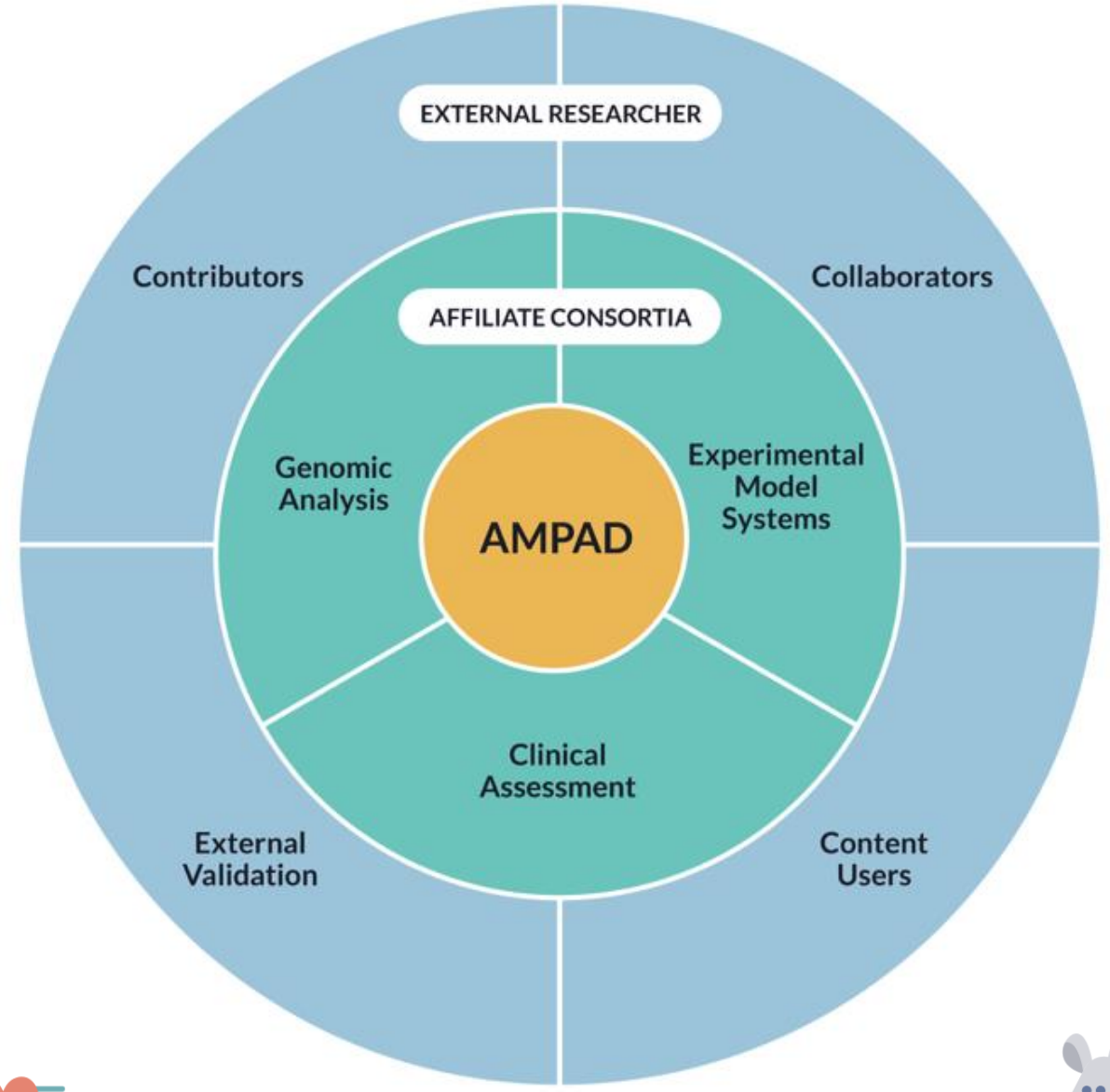
139 mouse model Differentially Expressed Genes (DEGs) in Brain

Cross-Species Working Group

Accumulate evidence for target predictions from across AMP-AD

geneSymb	Region	Layer1	Layer2	Layer3	Layer4	Layer5	Layer6	RankScore	k_in_top_	pubmedC	pubmedID	Worm.ort	Fly.ortho	Mouse.or	mean_Ast	mean_Enc	mean_Mic	mean_Ne	mean_Oli	mean_iPS	mean_hN	mean_iPS	mean_pA	mean_iPS	is.immun
PLXNB3	BM22	7	38	100	217	374	515	0.480795	85	0		plx-1,plx-	FBgn0025	Plxnb3	1.842249	1.101031	0	0.205399	0.62108	0.90444	1.785239	54.56941	30.88928	19.15856	NA
ATP6V1A	BM36	8	50	131	240	363	478	0.806245	9	0		vha-13	FBgn0265	Atp6v1a	168.6346	138.8499	442.2963	831.0098	268.1563	366.6274	369.0135	64.95847	63.53446	65.58719	NA
PREPL	BM36	7	45	141	254	368	465	0.824514	7	1	23485813		FBgn0032	Prepl	98.13387	85.54561	150.9547	580.8568	278.4382	30.46931	23.08672	78.71727	54.92785	76.61298	NA
GABRB2	BM36	19	79	162	269	357	450	0.84909	5	1	20888417	gab-1	FBgn0010	Gabrb2	31.26505	28.65796	0.239217	642.1141	25.99352	1.486837	2.565852	0.038538	1.771879	0.687589	NA
OAT	BM36	17	70	158	236	332	431	0.462744	100	2	25764435,	C16A3.10,	FBgn0022	Oat	565.2447	459.8682	337.2439	546.2507	289.4883	79.205	81.07979	65.72522	58.51719	60.36607	NA
CLTC	BM36	16	64	129	192	284	392	0.53951	54	0		chc-1	FBgn0000	Cltc	415.4341	317.1852	570.6399	572.7174	421.5224	763.8088	775.5931	630.998	512.2617	247.7109	TRUE
CLSTN3	BM36	19	63	145	232	288	315	0.50401	69	3	27018282,	casy-1	FBgn0039	Clstn3	33.78531	0.668914	0	48.01558	1.201666	5.900816	4.793786	23.82711	32.47991	89.92683	NA
STAT3	BM36	33	103	162	211	251	273	0.61382	29	39	27306655,	sta-1	FBgn0016	Stat3	134.9197	95.69395	75.26738	69.83217	81.21607	162.236	194.9765	225.313	200.5993	294.4464	TRUE
SCN2A	BM22	15	60	136	190	225	252	0.996808	2	1	19056495		FBgn0264	Scn2a1	36.48317	97.77494	0.144283	964.4424	53.71501	NA	NA	20.32981	2.044302	17.32819	NA
ST8SIA3	BM36	14	36	61	112	188	230	0.495659	73	0				St8sia3	1.361451	44.1992	0	161.3374	12.39321	NA	NA	0.469425	0.634031	2.934088	NA
LAPTM5	BM22	13	53	122	178	205	221	0.537875	56	0			FBgn0040	Laptm5	0.100606	0	801.343	12.77265	11.73214	2170.205	2111.734	0.57717	0.155815	0.179616	NA
TLN1	BM22	12	44	94	142	181	205	0.616022	27	0		Y71G12B.1	FBgn0260	Tln1	60.93569	89.3179	96.74341	34.10808	35.1842	1005.908	1272.093	649.9724	509.1263	210.1413	NA
PLXNB1	BM36	16	49	100	140	160	177	0.654468	19	0		plx-1,plx-	FBgn0025	Plxnb1	131.9302	19.53324	0.202008	12.00693	88.60671	0.853873	2.675884	94.09172	128.0527	208.5335	NA
SYT1	BM36	11	27	59	94	126	162	0.738114	11	4	27036734,	snt-1,snt-	FBgn0004	Syt1	111.9558	188.0778	2.084353	1959.427	216.5924	1.361645	0.883898	66.91156	6.516135	43.2029	NA
SNRPN	BM36	5	20	47	88	139	162	0.478157	88	0		snr-2	FBgn0262	Snrpn	34.13056	28.31835	23.94988	274.006	63.49879	2.026755	1.31533	10.44817	4.625719	25.74816	NA
STXBP5L	BM36	9	49	108	140	150	152	1	1	0		tom-1	FBgn0030	Stxbp5l	22.15779	7.74618	0	257.2706	14.68663	0.0709	0.181893	10.75764	0.613963	4.07375	NA
IPCEF1	BM36	7	31	68	98	125	151	0.543313	51	0		cnk-1	FBgn0021	Ipcef1	1.319019	0.93587	313.2563	56.90519	0.133593	43.85008	5.274469	0.197529	0.302051	6.856131	NA
PTPRC	BM36	21	48	79	105	117	122	0.534285	58	4	25904803,	clr-1	FBgn0014	Ptprc	0.126108	0	840.8779	5.857045	0.087377	556.3699	542.732	0.050719	0.027689	0.121665	TRUE
PGM2L1	BM36	6	19	41	73	110	119	0.606495	32	0		Y43F4B.5	FBgn0033	Pgm2l1	41.33417	62.66841	0.244454	549.8055	58.20443	69.16821	24.62011	23.31106	30.43922	48.74624	NA
OXR1	BM36	15	48	81	97	108	108	0.4944	74	0		F52E1.13	FBgn0013	Oxr1	111.158	73.84945	487.8827	895.2432	229.8183	83.59503	50.31907	37.77577	32.24421	40.78274	NA
ITPKB	BM36	14	45	66	81	84	84	0.615469	28	4	27485122,	lfe-2	FBgn0266	Itpkb	170.5094	15.20195	0.368404	7.746039	84.14657	131.9887	52.09112	52.38168	48.46014	199.4926	NA
BEX2	BM36	5	22	46	63	77	84	0.549253	48	0					37.38837	15.96159	1.661769	388.6237	85.76364	0.183965	0.303398	0.571604	3.559767	21.89887	NA
YAP1	BM36	12	31	51	63	69	72	0.573063	40	0		F13E6.4	FBgn0034	Yap1	65.80892	16.44811	0.159675	2.715589	0	0.782943	1.278804	105.2838	115.0456	105.0383	NA
FLJ00418	BM36	14	38	56	59	68	72	0.510465	67	NA					NA	NA	NA	NA	NA	NA	NA	0.697908	0.426866	1.121088	NA
NHSL1	BM36	8	32	55	66	70	70	0.565568	41	0					925.9085	116.2174	351.5957	15.84129	2.089532	10.34856	16.20556	81.84442	38.33485	95.15214	NA
GPR158	BM10	5	19	33	49	64	67	0.47997	87	0		F39B2.8	FBgn0051	Gpr158	2.480375	1.739343	7.664397	91.00083	2.980566	NA	NA	31.29134	2.014838	1.97662	NA
LRP10	BM36	15	37	61	66	66	66	0.740791	10	1	22734645			Lrp10	41.82685	93.50068	0.105327	0.459694	34.93363	211.7742	261.5741	201.9834	108.5608	144.574	NA
INPP5D	BM36	9	34	52	64	66	66	0.563574	42	9	28054028,	TZ589.10		Inpp5d	2.754021	2.898906	15.26649	0.108337	0.030922	141.3368	132.0936	1.753459	0.784304	8.941674	NA
WWTR1	BM36	5	27	52	58	58	58	0.589341	34	0			FBgn0034	Wwtr1	4.203612	191.0391	1.631813	31.10212	5.938066	3.937605	2.018107	281.4129	310.3445	124.3911	NA
RP11-553	BM36	12	32	50	56	57	57	0.480068	86	NA					138.5842	77.06258	23.32954	32.66445	60.52765	0.394813	2.574166	8.608285	14.67634	12.77521	NA

Drugability Index



AMP-AD

M2OVE-AD Consortium

189 investigators

Model AD Program

Resilience-AD Program


ENTER
AIR-GAP
0-59

Agora

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- broadcast target predictions
- aggregate target evidence
- disseminate tools
- communicate independent evaluations

Early sharing of target predictions from systems evaluation of human disease

View all nominated targets

Gene name	Nominations	Teams
ABCA7	1	Duke
ADAM9	1	Duke
AK4	1	Broad-Rush-Columbia
ALK	1	Mayo-UFL-ISB
AP2B1	1	Emory
ATP2B1	1	MSSM

http://agora.ampadportal.org

AMP-AD Evidence in Support of VGF

MSSM

The Icahn School of Medicine at Mount Sinai team, led by Eric Schadt, Bin Zhan

Why was the target selected?

VGF was selected as a target because it was downregulated in AD cases. It was

Predicted therapeutic direction

VGF activation is hypothesized to rescue diseases. In human postmortem brai
improves neurogenesis in the subgranular zone of hippocampus, and partially re

The type of data used and analyses done to identify target

Bayesian network analysis derived from RNAseq and SNP genotypes.

[link to MSSM team]

Emory

The Emory team, led by Allan Levey, focuses on the generation and analysis of prote

Why was the target selected?

VGF was identified as both a potential driver and a protein linking different group
negatively correlated with the two hallmark pathologies of AD, namely CERAD as a

Predicted therapeutic direction

Don't know. Possibly activate (promote neurogenesis/homing), since reduced in AD.

The type of data used and analyses done to identify target

Discovery quantitative proteomics of FrCx WPCNA of multiple and consensus cohor

[link to Emory team]

Broad-Rush-Columbia

The Broad-Rush-Columbia team, led by Philip De Jager and David E
from two prospective cohort studies of aging and dementia. They us
decline in older age, as well as resilience to the brain pathologies. Fi

Why was the target selected?

This gene was found to have large correlations with AD status in the

Predicted therapeutic direction

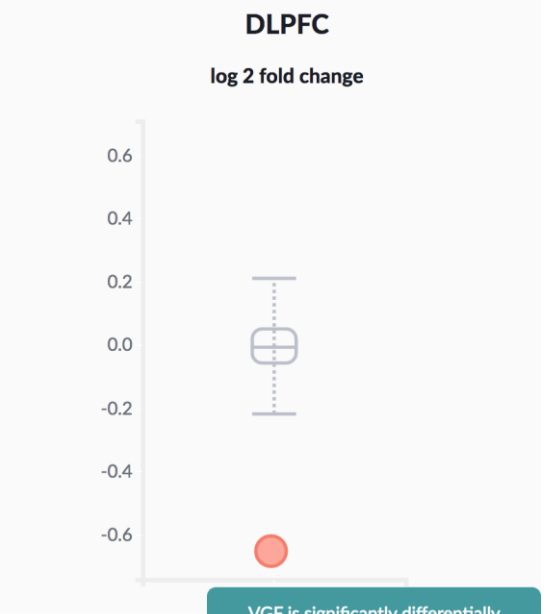
Upregulate

The type of data used and analyses done to identify target

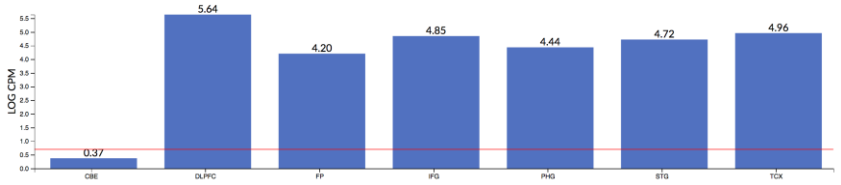
SRM protein levels.

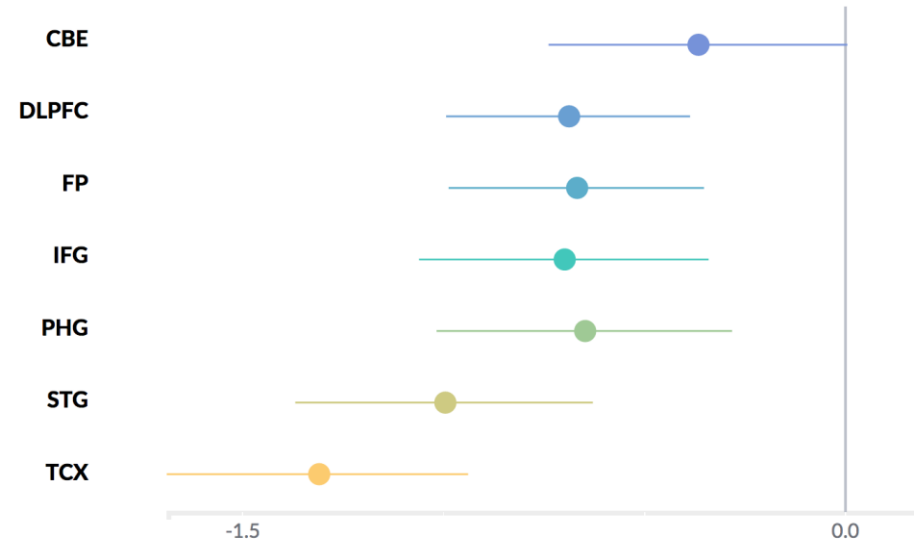
[link to Broad-Rush-Columbia team]

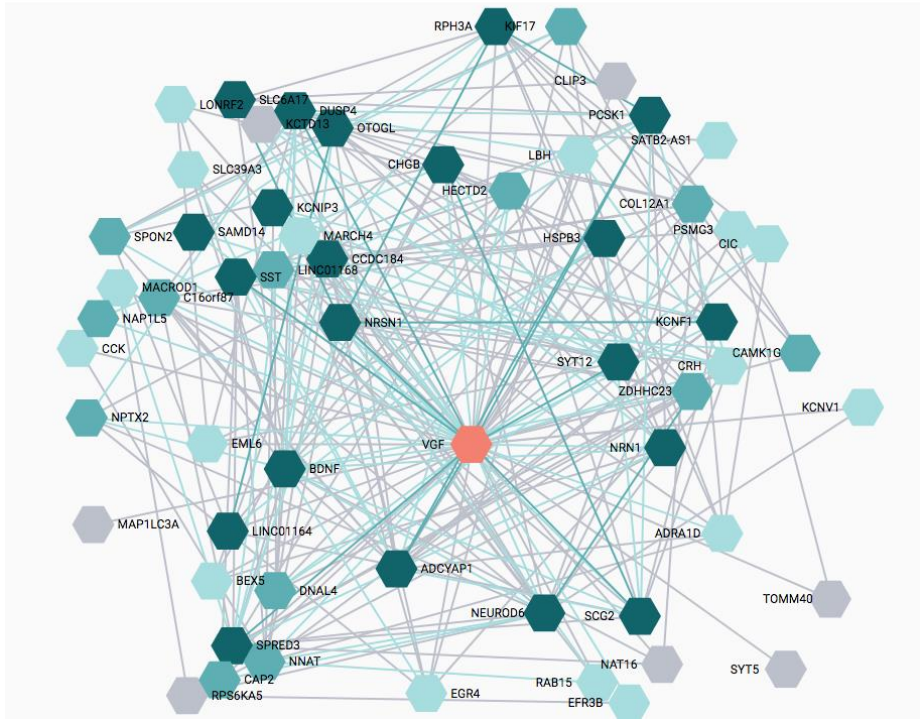
AMP-AD Evidence in Support of VGF



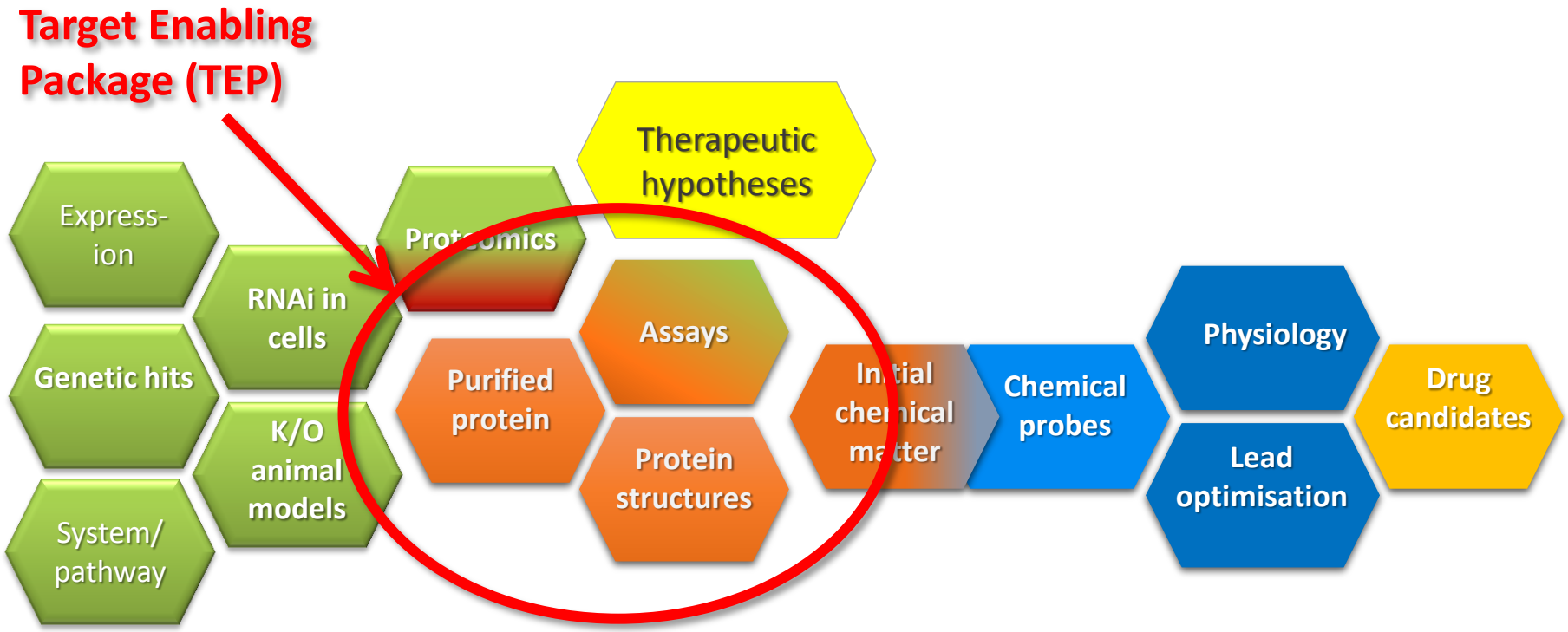
VGF is significantly differentially expressed in DLPFC with a log fold change value of -0.686 and an adjusted p-value of 0.001.







Open experimental tools for target evaluation



The SGC: A public-private partnership that supports the discovery of new medicines through open access research

SGC

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Nathan Price and Cory Funk – ISB
Paul Brenna and Opher Gileadi – Oxford
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Suzana Petanceska and the National Institute of Aging

ACCELERATING MEDICINES PARTNERSHIP (AMP)

ALZHEIMER'S DISEASE

AMP-AD Knowledge Portal

synapse.org/ampad

Access data and
learn more about AMP-AD

Agora

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and explore results

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