Integrative Biology Approach to Complexity of Alzheimer's Disease and Novel Target Discovery and Validation

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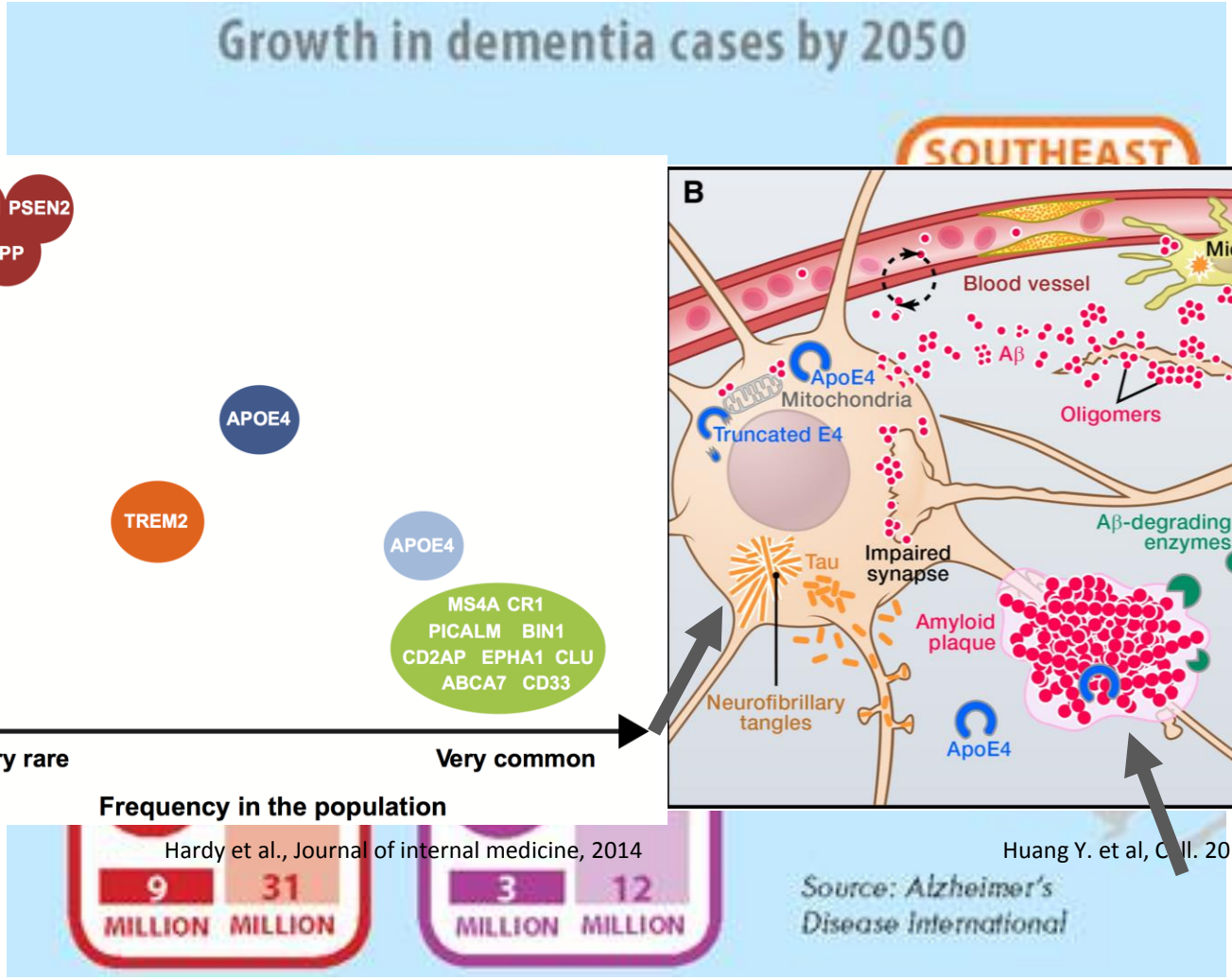
Alzheimer's Disease (AD)



Hardy et al., Journal of internal medicine, 2014

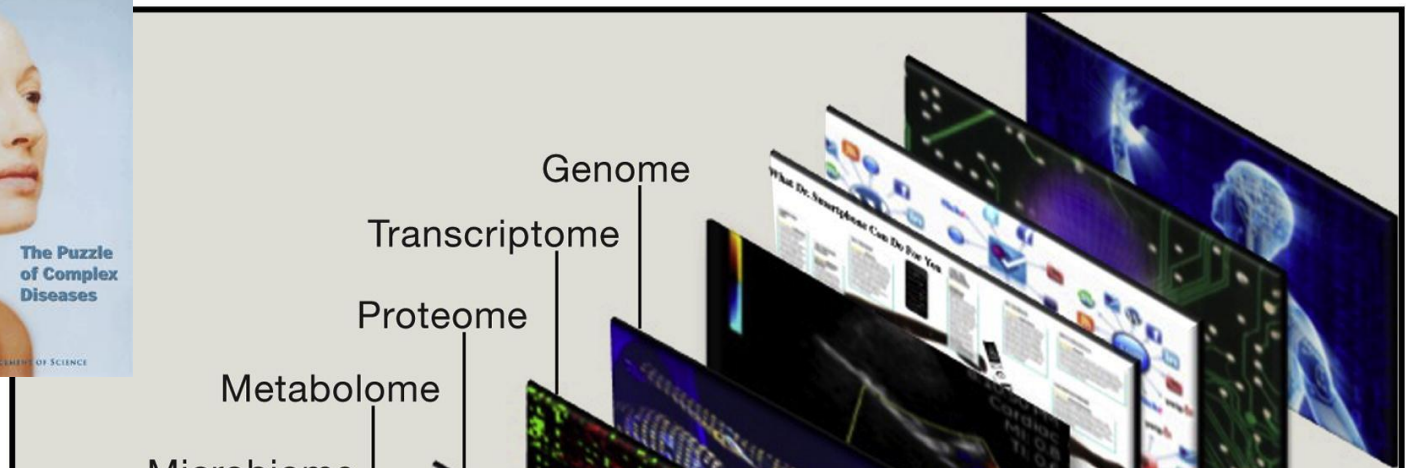
Huang Y. et al, Cell. 2012 Mar 16;148(6):1204-22

https://www.fic.nih.gov/news/globalhealthmatters/march-april-2015/pages/nih-alzheimers-research-summit.aspx

AD is complex

- No perfect characterization
- No precise diagnosis
- Mechanisms and causes largely unknown
- No cure

Multi-omics are increasingly widespread



How can we learn more by integrating omics?

Cell, Volume 157, Issue 1, 27 March 2014, Pages 241–253

Systems based functional approach

Resource

Cell

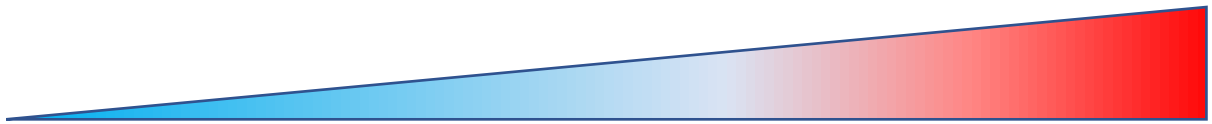
Constructing multiscale models to further AD understanding

Manikandan Narayanan,[6] Christine Suver,[4] Hardik Shah,[1,2] Milind Mahajan,[1,2,3] Tammy Gillis,[9] Jayalakshmi Mysore,[9] Marcy E. MacDonald,[9] John R. Lamb,[10] David A. Bennett,[11] Cliona Molony,[6] David J. Stone,[7] Vilmundur Gudnason,[12] Amanda J. Myers,[13] Eric E. Schadt,[1,2,3] Harald Neumann,[5] Jun Zhu,[1,2,3] and Valur Emilsson[12,*]

Zhang et al, Cell, 2013

AMP-AD dataset

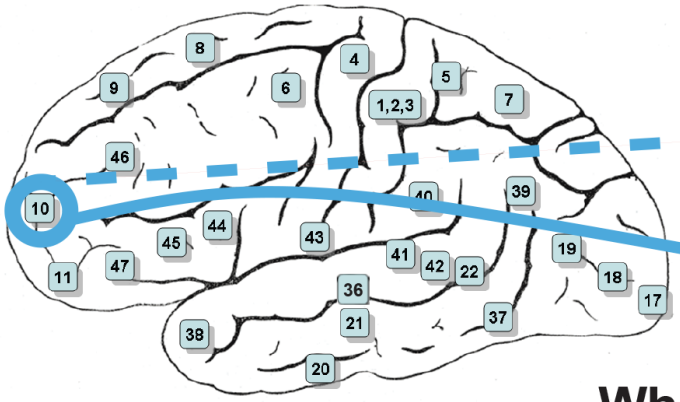
No disease



Definite AD

N=315

BM10: Anterior Prefrontal Cortex



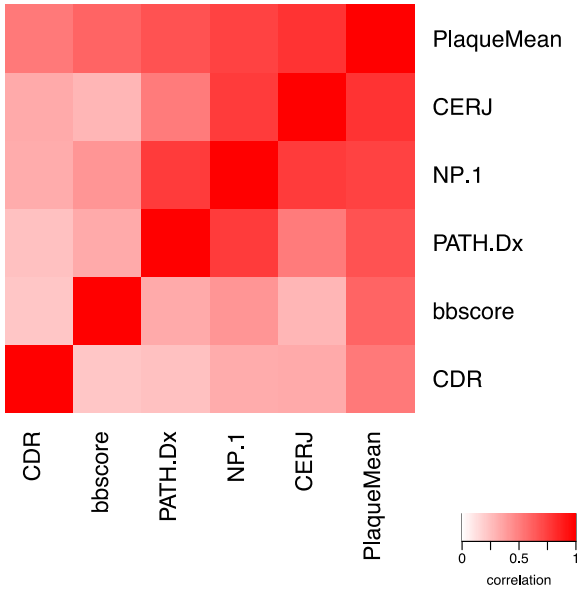
Protein Expression

RNA Sequencing

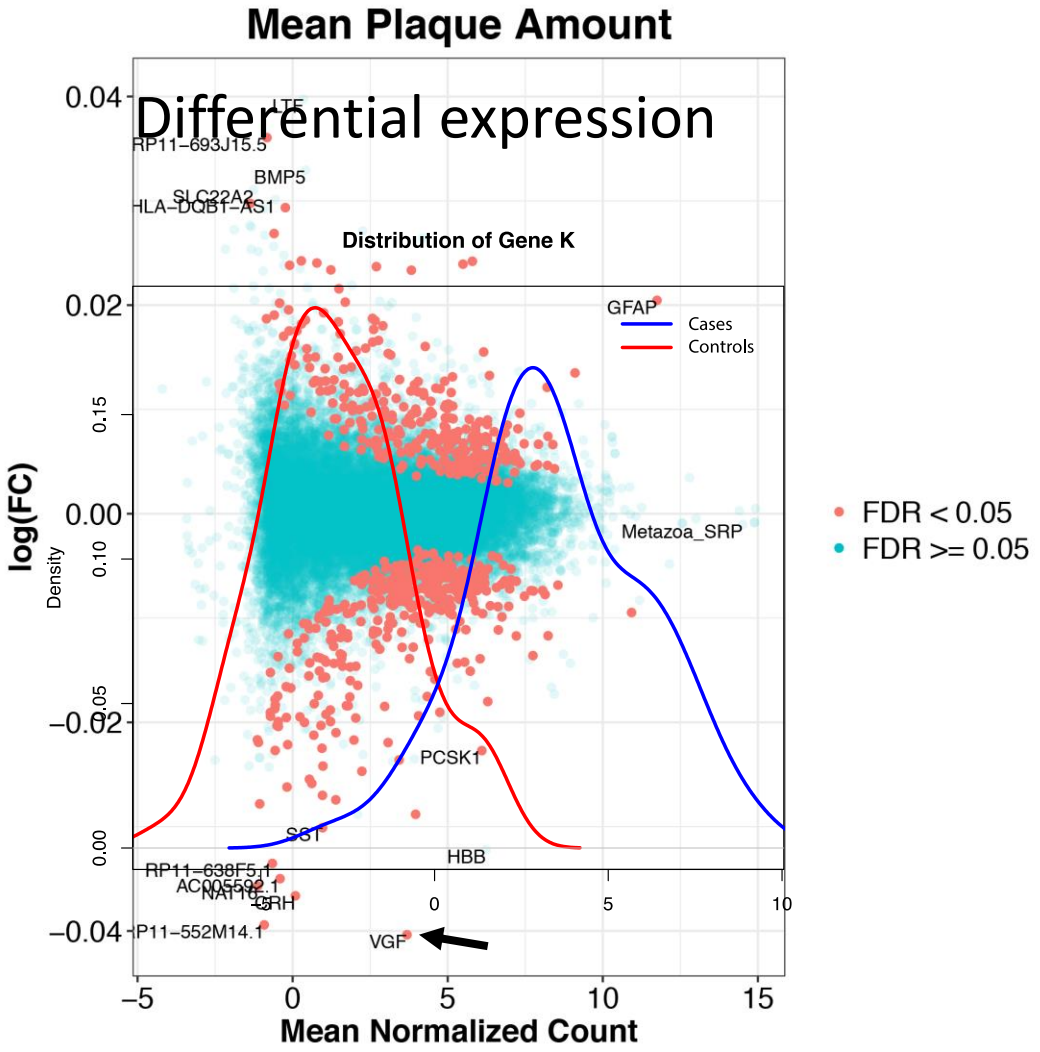
Whole Exome Sequencing

Clinical and neuropathological traits represent different aspects of AD

CDR	clinical dementia rating
bbscore	braak score
PATH Dx	clinical neuropathology
NP-1	neuropathology category
CERJ	CERAD neuropath Criteria
PlaqueMean	mean neocortical plaque density (number of plaques/mm2)

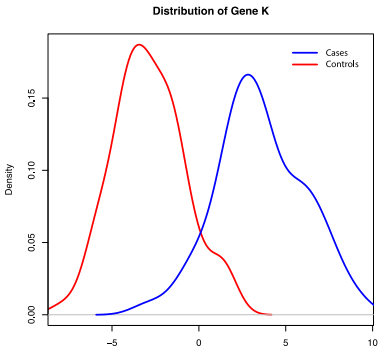


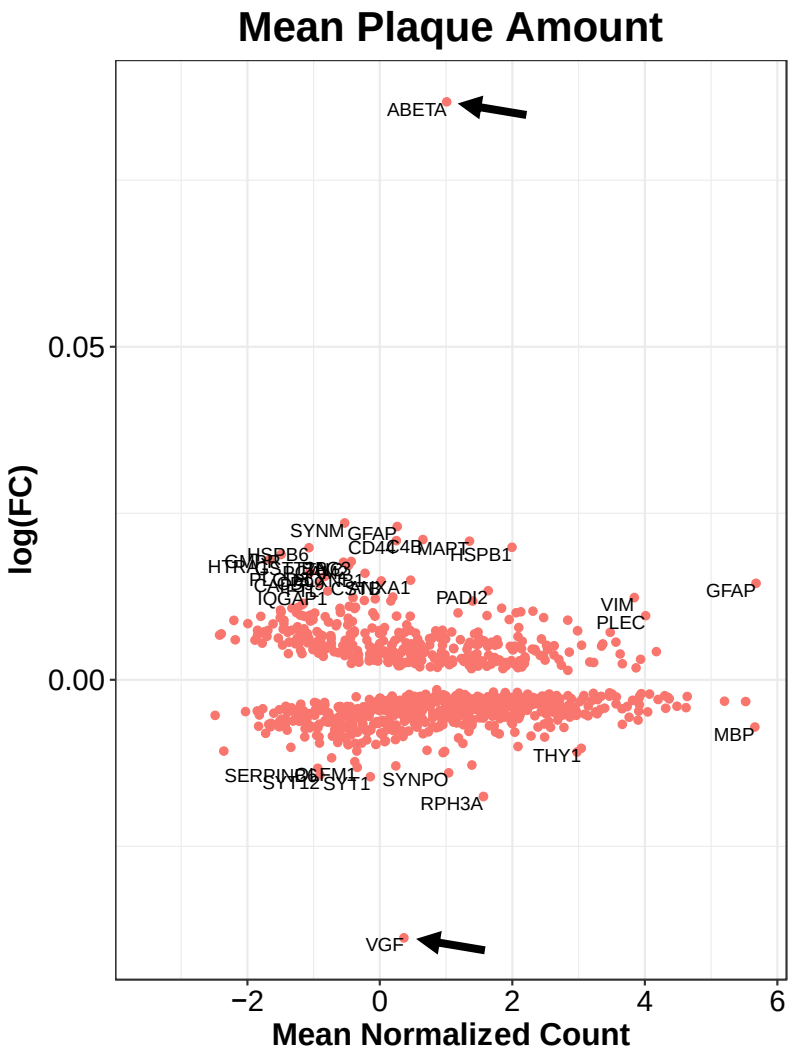
VGF transcript has the largest log Fold Change (FC) for AD



VGF protein has the largest logFC after ABeta

Differential expression

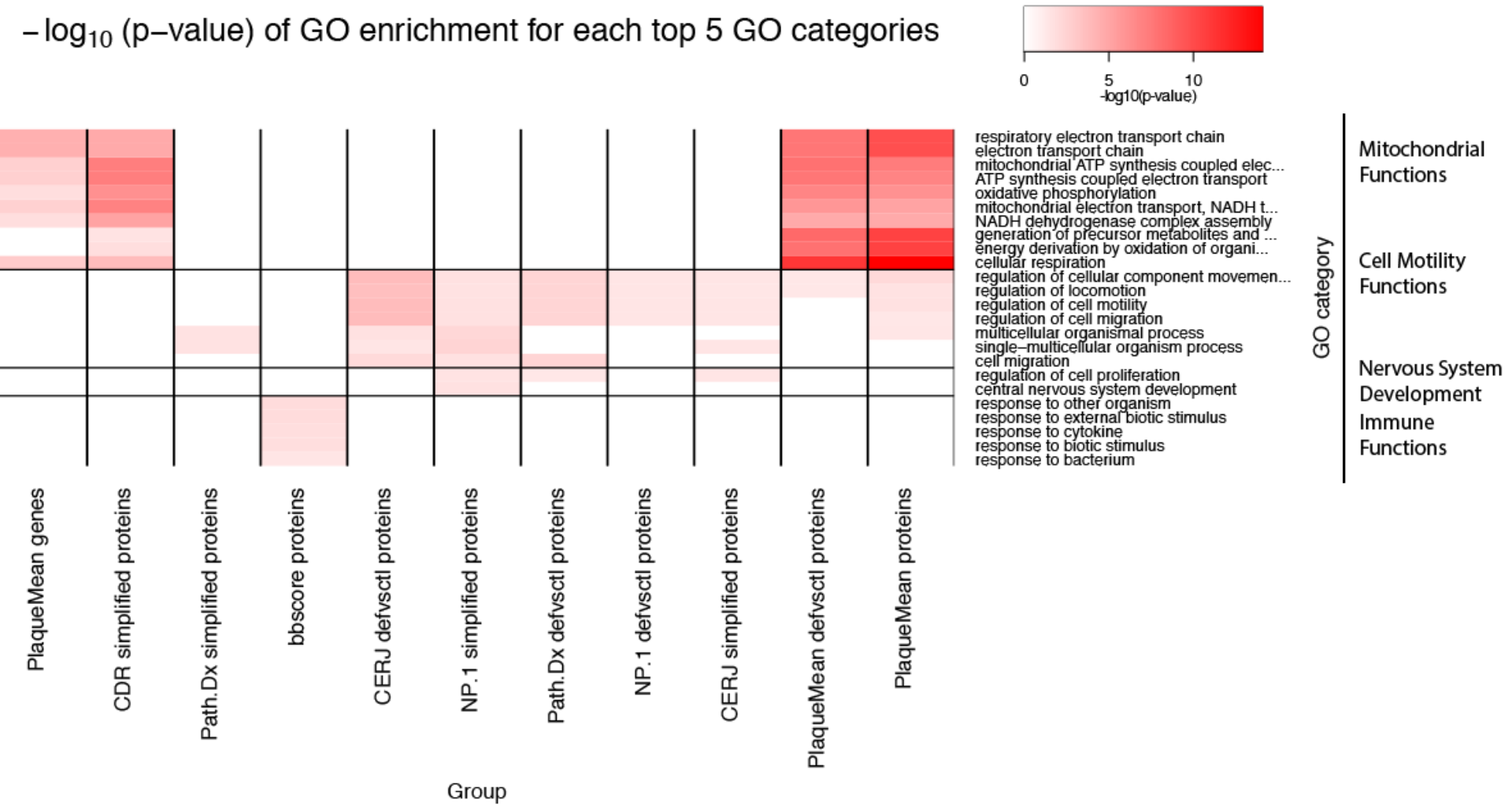




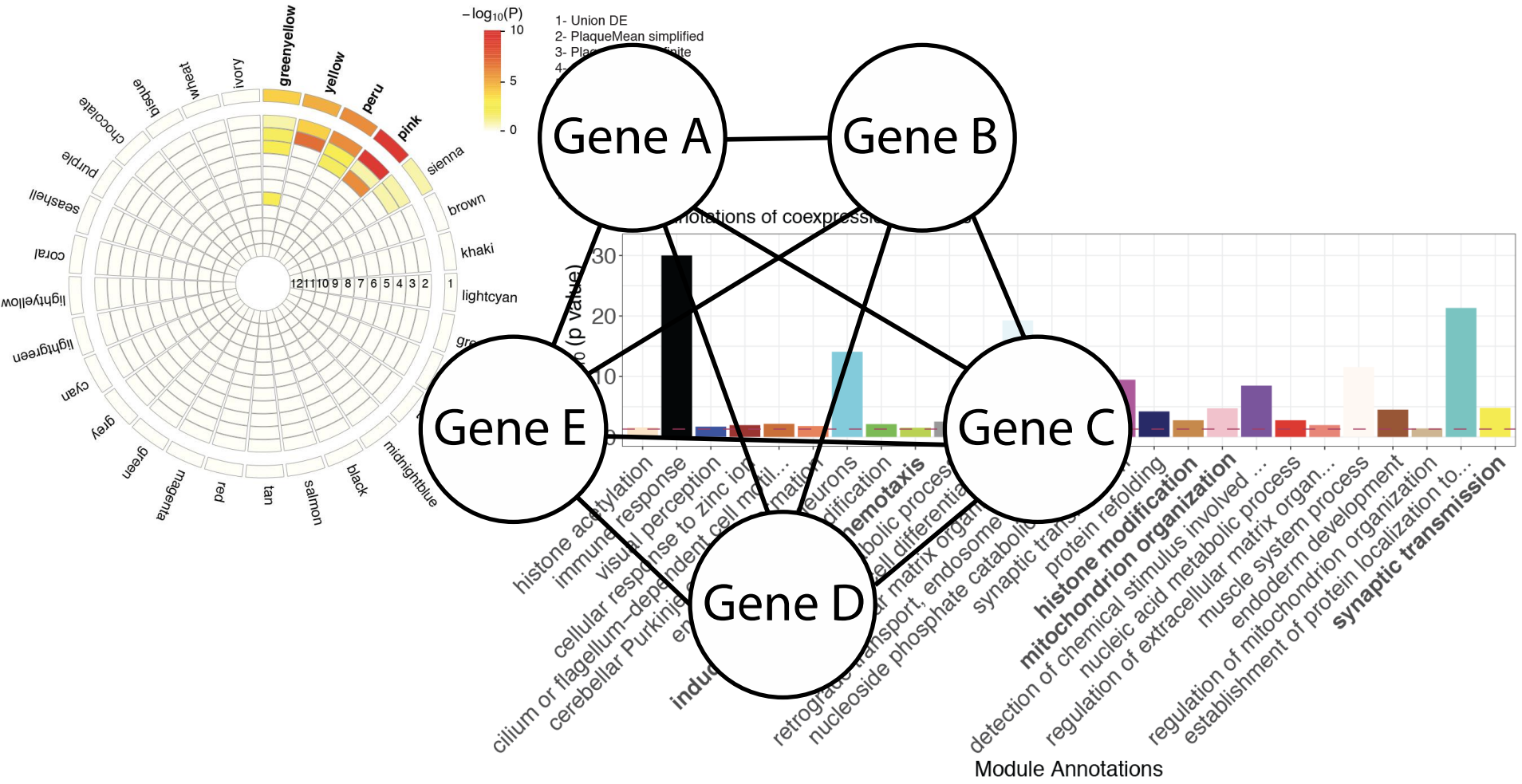
- FDR < 0.05
- FDR >= 0.05

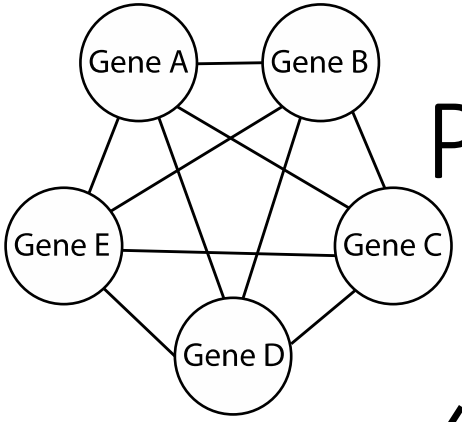
VGF is DE in all traits

Gene Ontology (GO) enrichments are coherent with known AD pathways

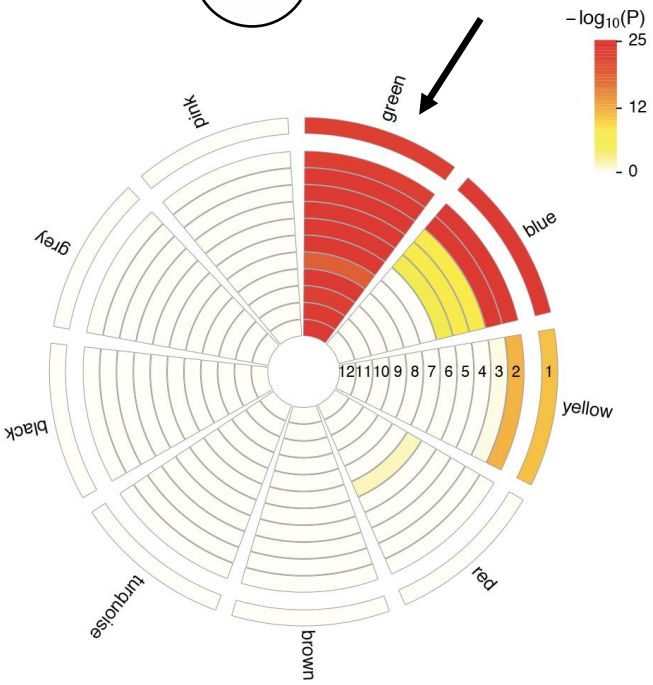


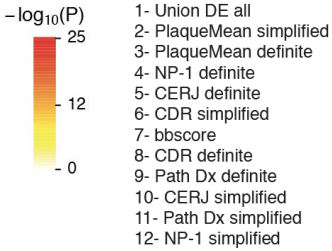
Gene co-expression network

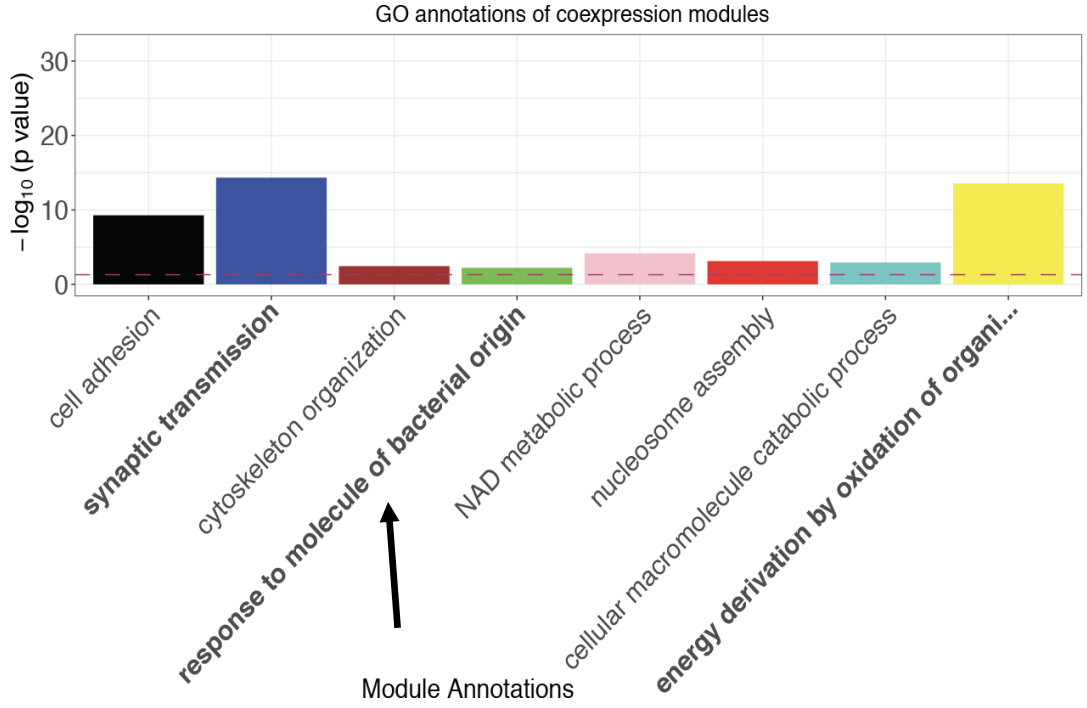




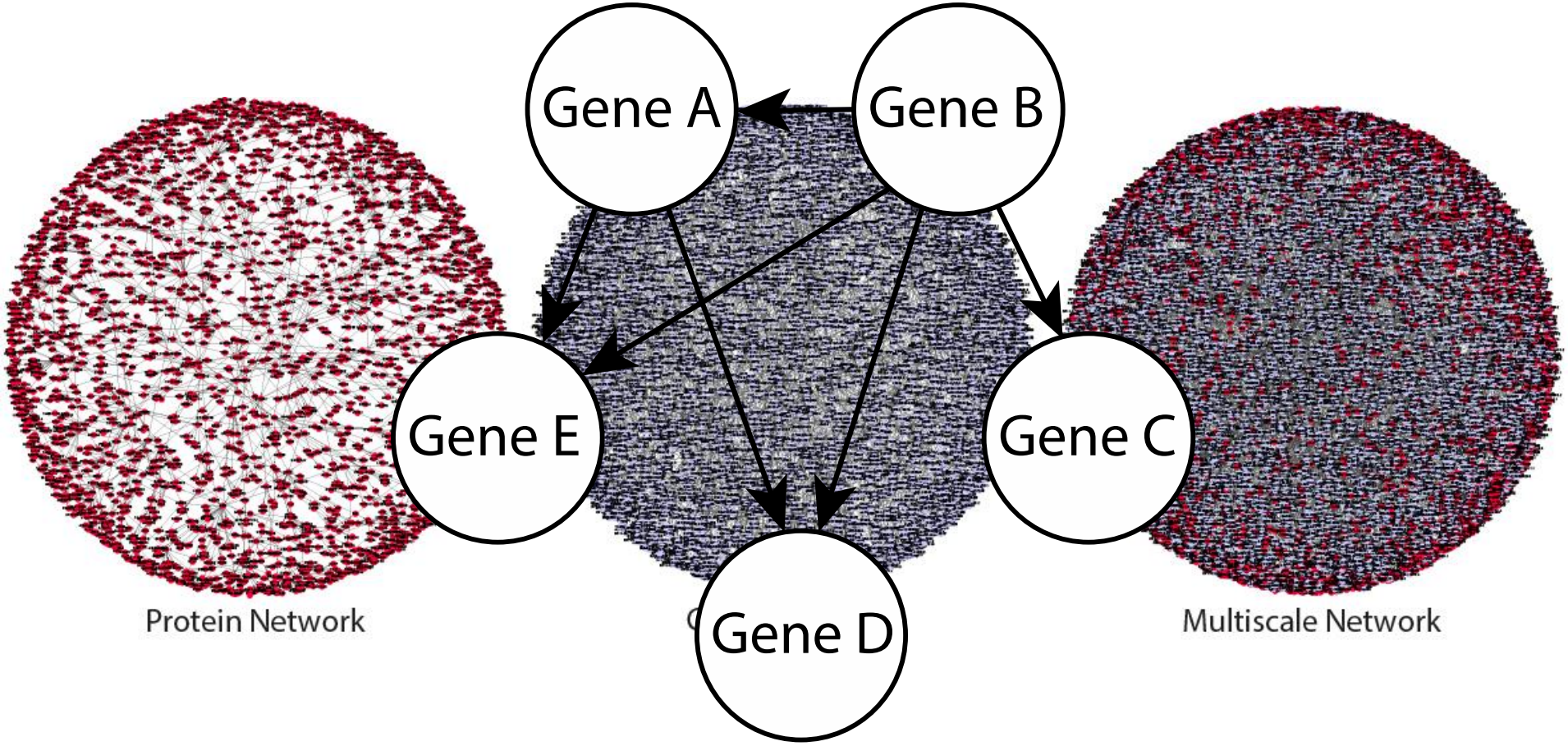
Protein co-expression network





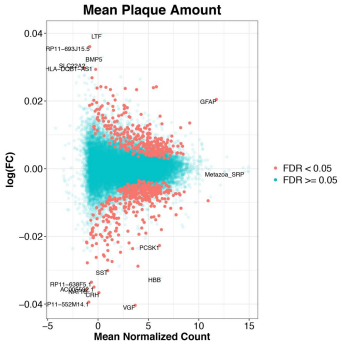


Bayesian Networks

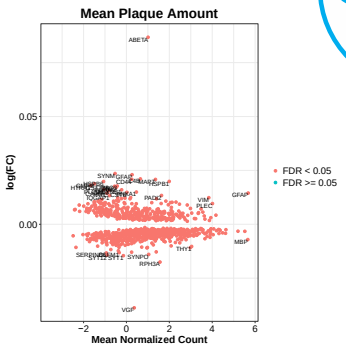


Key driver (KD) analysis

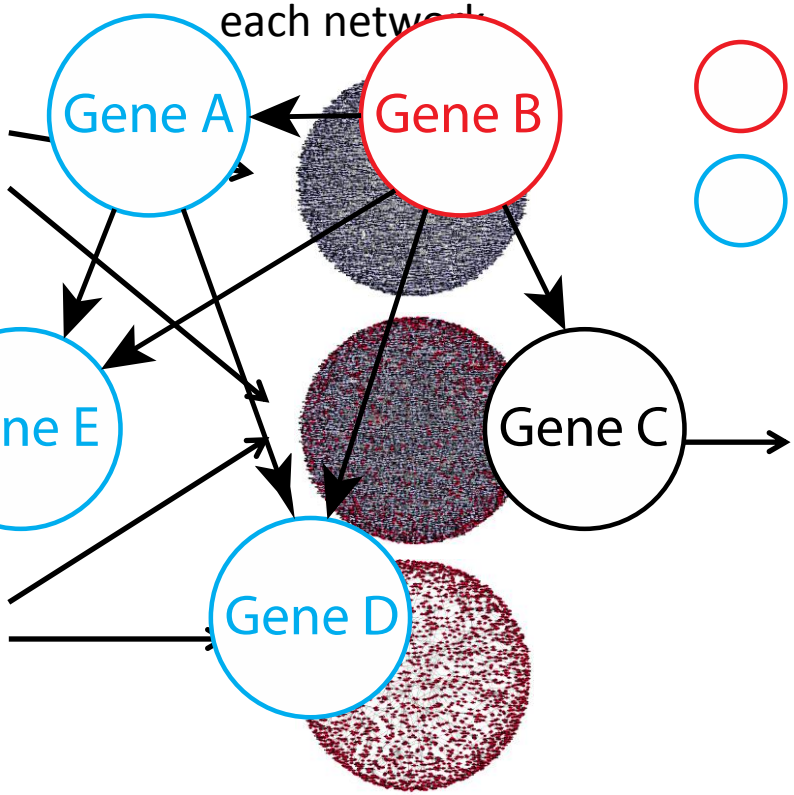
DE genes



DE proteins



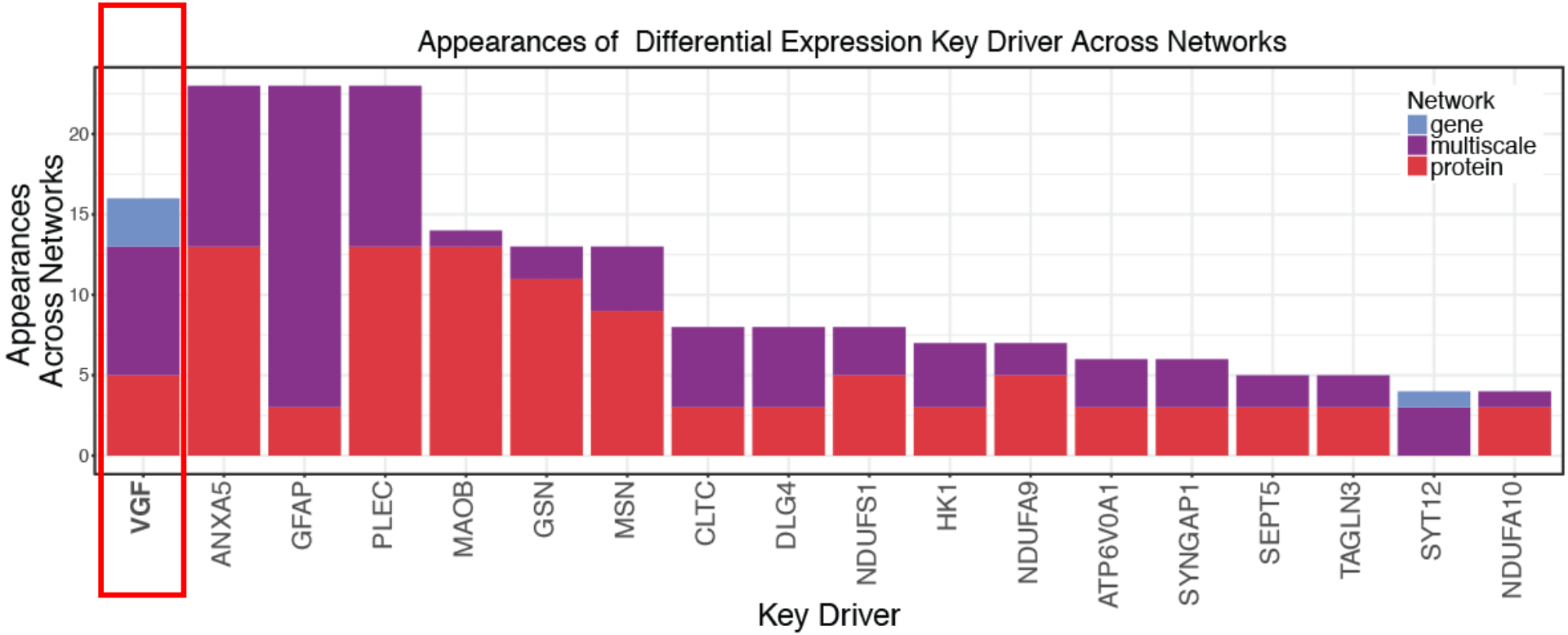
Detect key drivers in each network



Key Driver

Target List

VGF is a KD of AD



VGF replicated as a KD in:

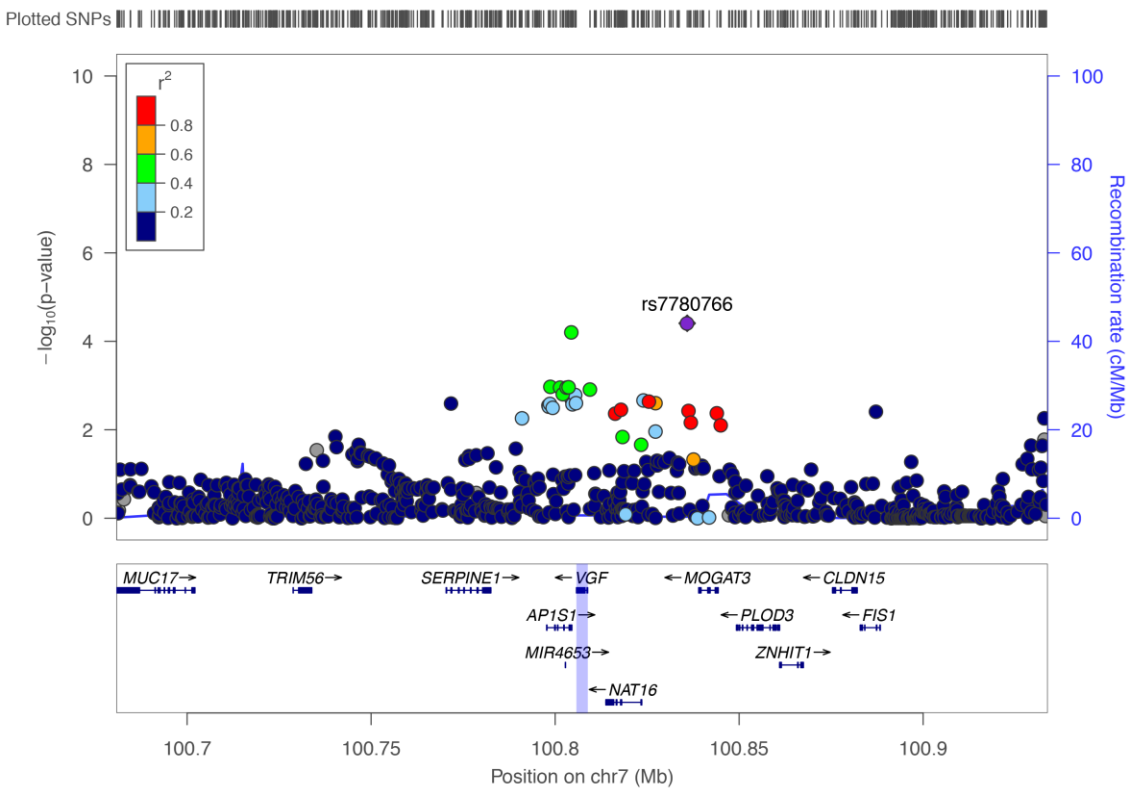
- MSSM
  - superior temporal gyrus
  - pars opercularis
- ROSMAP
  - dorsolateral prefrontal cortex

VGF (nerve growth factor inducible)

- 615 AA precursor protein
- Regulates neural activity and survival
  - Peptide TLPQ-62 regulates memory formation and depression
- Involved in energy balance
  - Peptide TLPQ-21 binds to C3aR1 and has anti-obesity functions
- Downregulated in cerebrospinal fluid of AD patients (potential biomarker)

Levi, A., et al., Cell Mol Neurobiol, 2004. 24(4): p. 517-33.
Thakker-Varia, S. and J. Alder, Behav Brain Res, 2009. 197(2): p. 262-78.
Lin, W.J., et al., J Neurosci, 2015. 35(28): p. 10343-56.
Fairbanks, C.A., et al., Pain, 2014. 155(7): p. 1229-37.
Hannedouche, S., et al., J Biol Chem, 2013. 288(38): p. 27434-43.
Cero, C., et al., Structure, 2014. 22(12): p. 1744-1753.
Cero, C., et al., Mol Metab, 2017. 6(1): p. 148-158.
Hendrickson, R.C., et al., PLoS One, 2015. 10(8): p. e0135365.

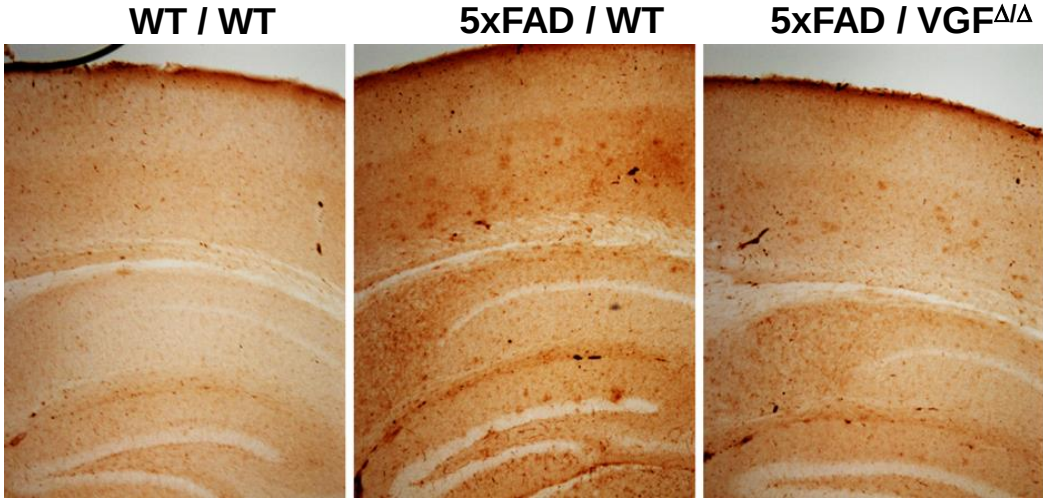
VGF locus shows signal in GWAS



- Lead SNP p-value: 3.91e-5 (significance-threshold: 6.9e-5)

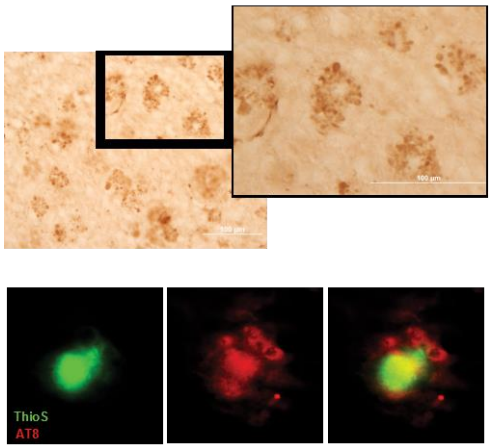
Nat Genet. 2013 Dec;45(12):1452-8. doi: 10.1038/ng.2802. Epub 2013 Oct 27.
http://locuszoom.org/

Reduced p-Tau and dystrophic neurite clusters in 5xFAD/VGF germline overexpression brains

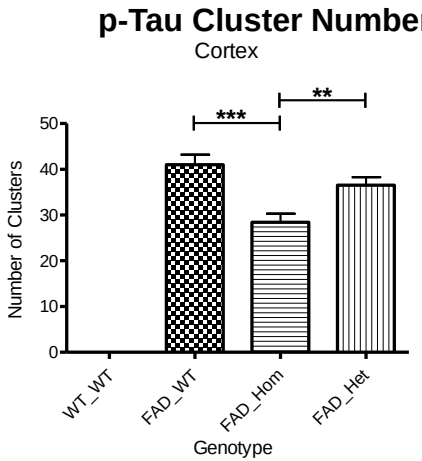


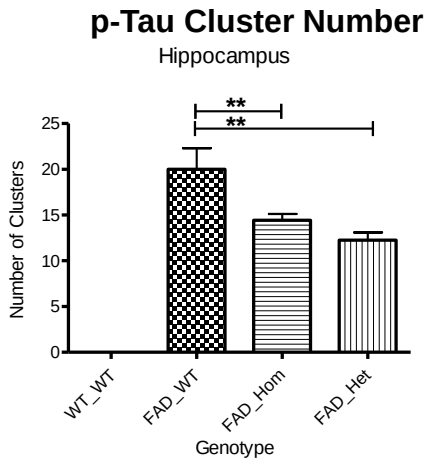
p-Tau(AT8) staining

Dystrophic neurites
(crown-shaped staining)



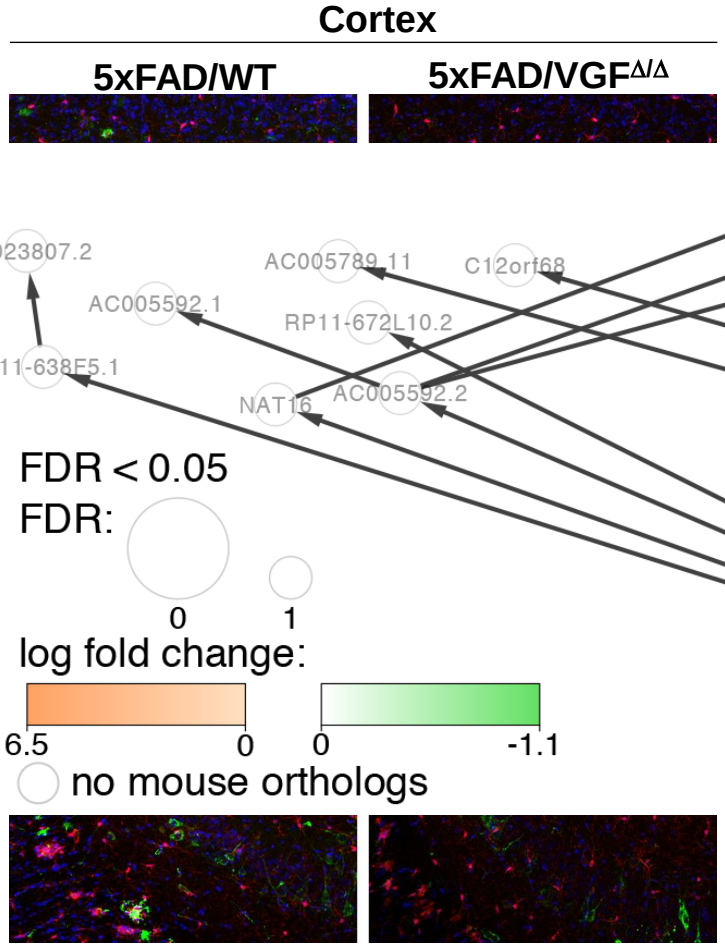
Green: ThioS (plaque)
Red: AT8 (p-Tau)





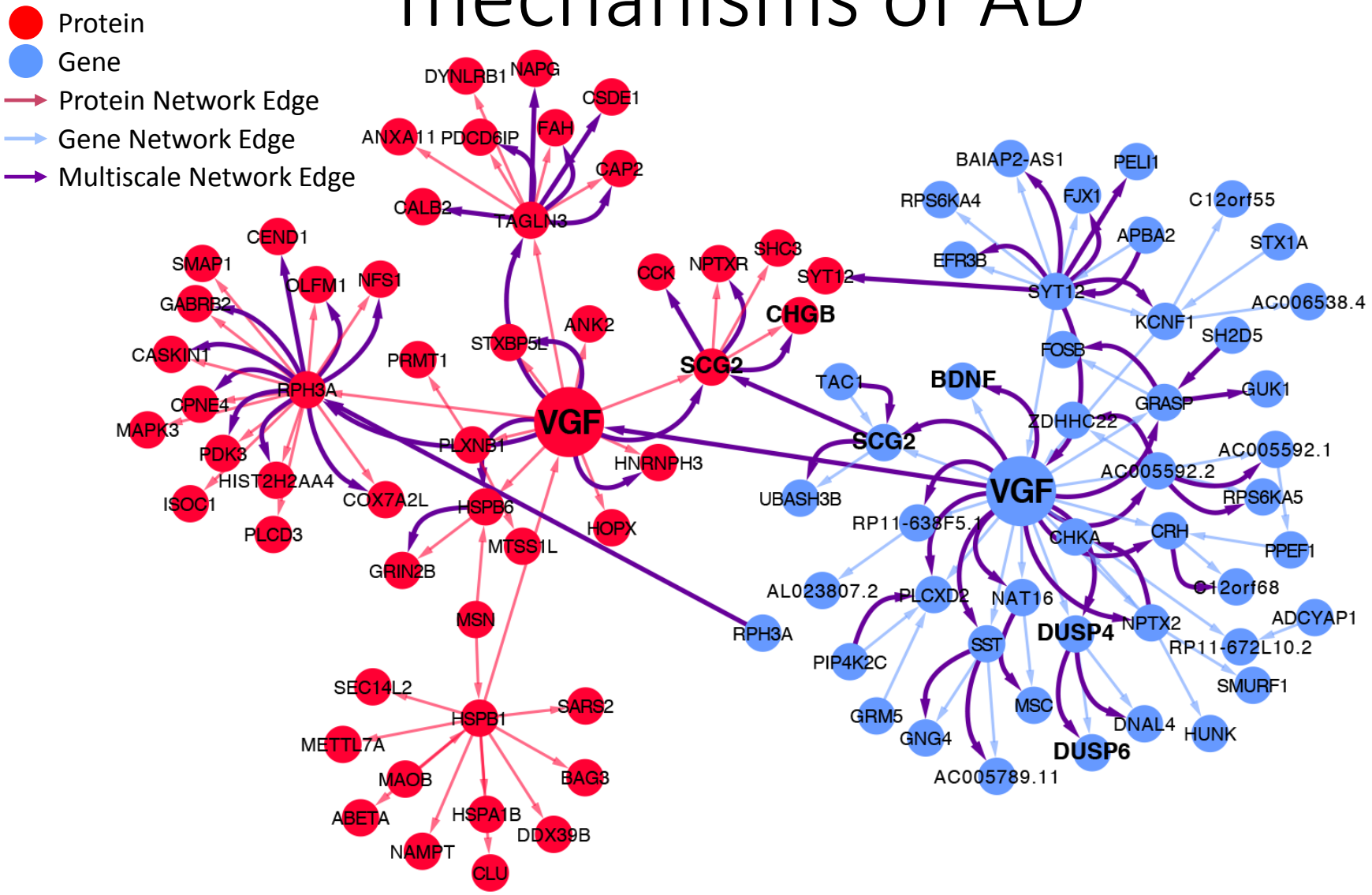
By Jay Lin & Mickael Audrain & Siddharth Hariharan

Functional and Molecular Validation of VGF



Green: Abeta (6E10)
Red: Iba-1
Blue: DAPI

VGF subnetworks may help inform mechanisms of AD



Conclusions

- VGF is a new KD of AD
- Most downregulated gene and protein in AD samples
- Replicated in other brain regions
- Replicated in other datasets
- Validated functionally and molecularly
- Subnetwork provides insights into mechanisms

Acknowledgments

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