Metabolic and Transcriptional Regulatory Network Models in Alzheimer’s Disease

Building models that provide biological insights and generate novel, testable hypotheses

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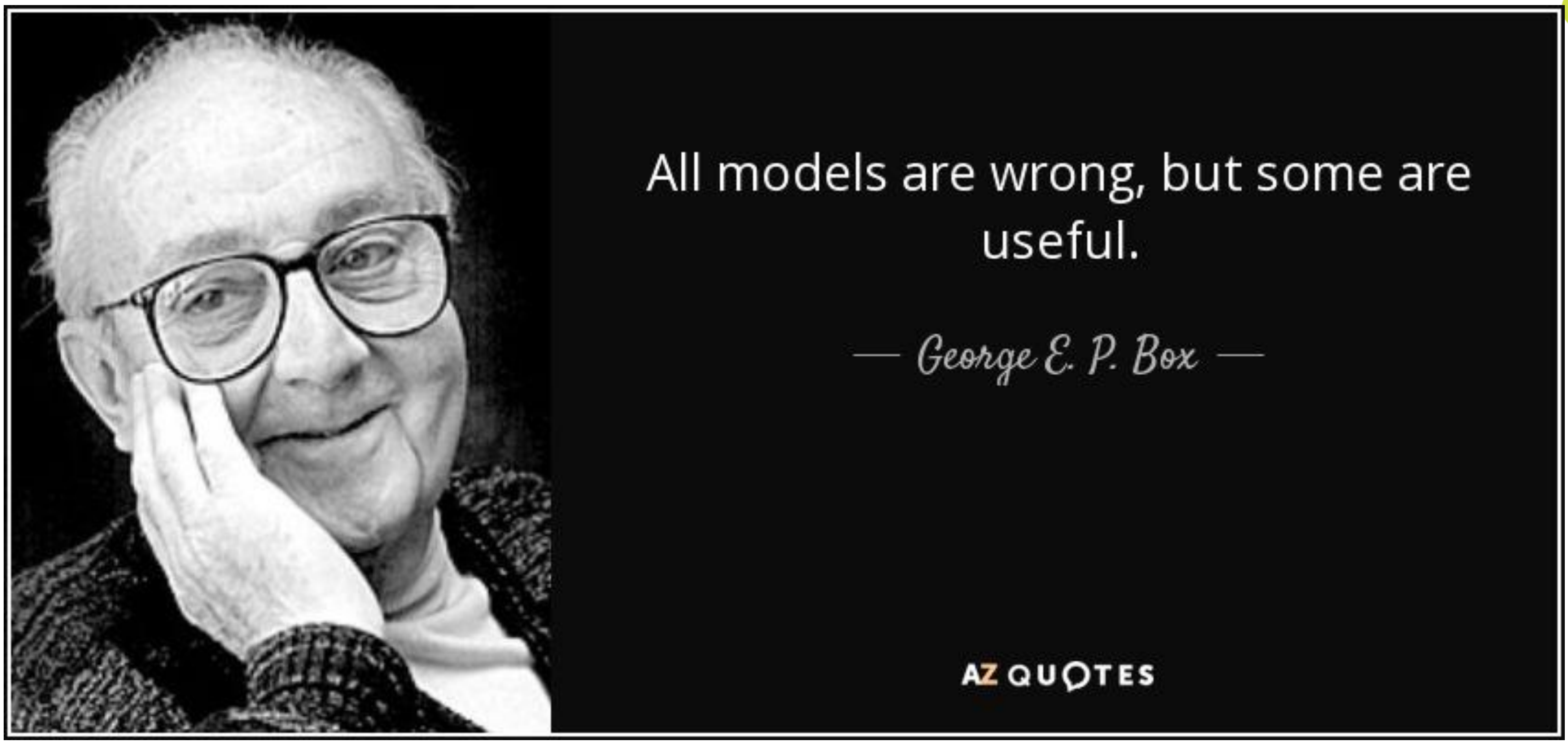


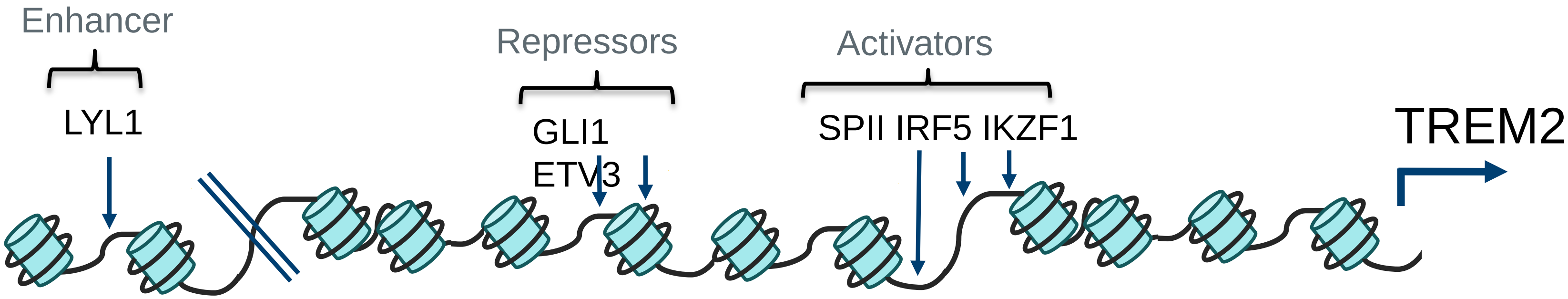
All models are wrong, but some are useful.

— George E. P. Box —

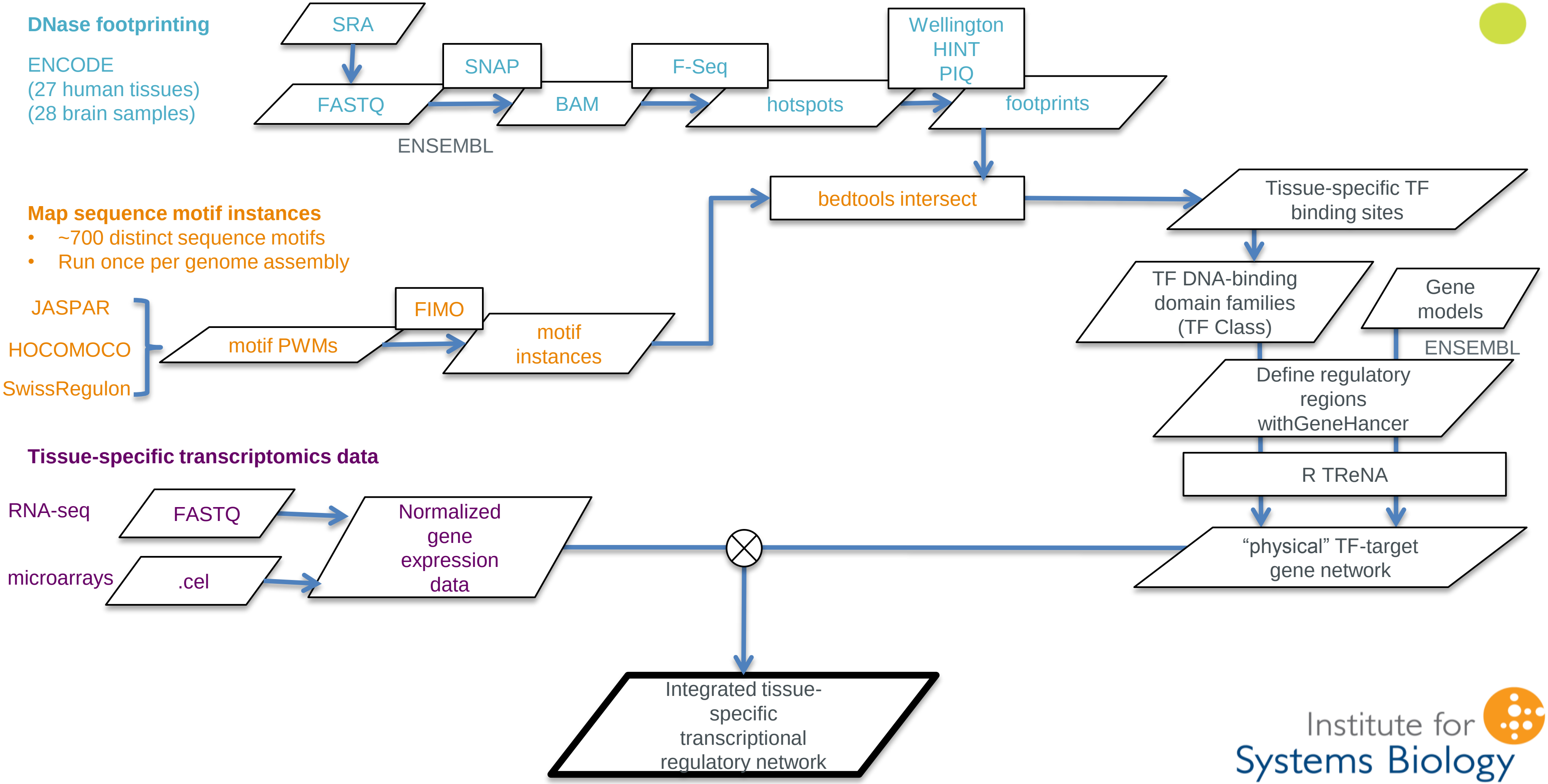
AZ QUOTES

Building a model of transcriptional regulation in the brain

- A single gene model consists of a list of transcription factors (TFs) and their footprints
- Inputs for a gene model
  - Brain-specific DHS data provides a list of putative binding sites (and TFs) that are potential regulators
  - Map between motifs and TFs
  - List of regulatory regions (GeneHancer)
  - Large RNA-seq dataset (>60 samples, can be microarray)
- Build a regression model between each individual TF and target gene using multiple LASSO approaches (and RF)



TReNA Workflow



DNase footprinting

ENCODE
(27 human tissues)
(28 brain samples)

SRA

FASTQ

SNAP

BAM

F-Seq

hotspots

Wellington
HINT
PIQ

footprints

ENSEMBL

Map sequence motif instances

- ~700 distinct sequence motifs
- Run once per genome assembly

JASPAR
HOCOMOCO
SwissRegulon

motif PWMs

FIMO

motif instances

bedtools intersect

Tissue-specific TF binding sites

TF DNA-binding domain families (TF Class)

Gene models

ENSEMBL

Define regulatory regions withGeneHancer

R TReNA

“physical” TF-target gene network

Tissue-specific transcriptomics data

RNA-seq

FASTQ

microarrays

.cel

Normalized gene expression data

Integrated tissue-specific transcriptional regulatory network

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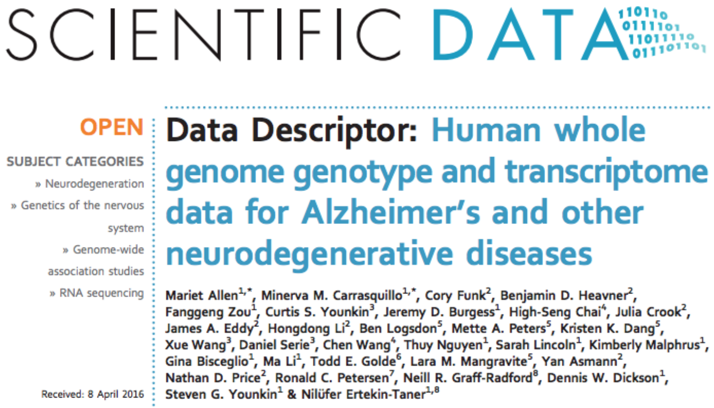
AMP-AD Postmortem RNA-seq Brain Samples



SCIENTIFIC DATA

OPEN

SUBJECT CATEGORIES
» Neurodegeneration
» Genetics of the nervous system
» Genome-wide association studies
» RNA sequencing

Received: 8 April 2016

Data Descriptor: Human whole genome genotype and transcriptome data for Alzheimer's and other neurodegenerative diseases

Mariet Allen[1,*], Minerva M. Carrasquillo[1,*], Cory Funk[2], Benjamin D. Heavner[2], Fanggeng Zou[1], Curtis S. Younkin[3], Jeremy D. Burgess[1], High-Seng Chai[4], Julia Crook[2], James A. Eddy[2], Hongdong Li[2], Ben Logsdon[5], Mette A. Peters[5], Kristen K. Dang[5], Xue Wang[3], Daniel Serie[3], Chen Wang[4], Thuy Nguyen[1], Sarah Lincoln[1], Kimberly Malphrus[1], Gina Bisceglio[1], Ma Li[1], Todd E. Golde[6], Lara M. Mangravite[5], Yan Asmann[2], Nathan D. Price[2], Ronald C. Petersen[7], Neill R. Graff-Radford[8], Dennis W. Dickson[1], Steven G. Younkin[1] & Nilüfer Ertekin-Taner[1,8]

Group	Number of Brains	Brain Regions	RNA-seq Library Method	Pathologies
Mayo Clinic, University of Florida, Institute for Systems Biology	~265	temporal cortex, cerebellum	poly-A enriched	AD, control
Religions Orders Study and Memory and Aging Project (ROSMAP)	~600	dorsolateral prefrontal cortex	strand-specific	AD, MCI, control, Parkinson's
Mount Sinai Brain Bank (MSBB)	~160	frontal pole, superior temporal gyrus, inferior frontal gyrus, parahippocamal gyrus	Ribo-zero	AD, MCI, control

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Available Genome-scale Models

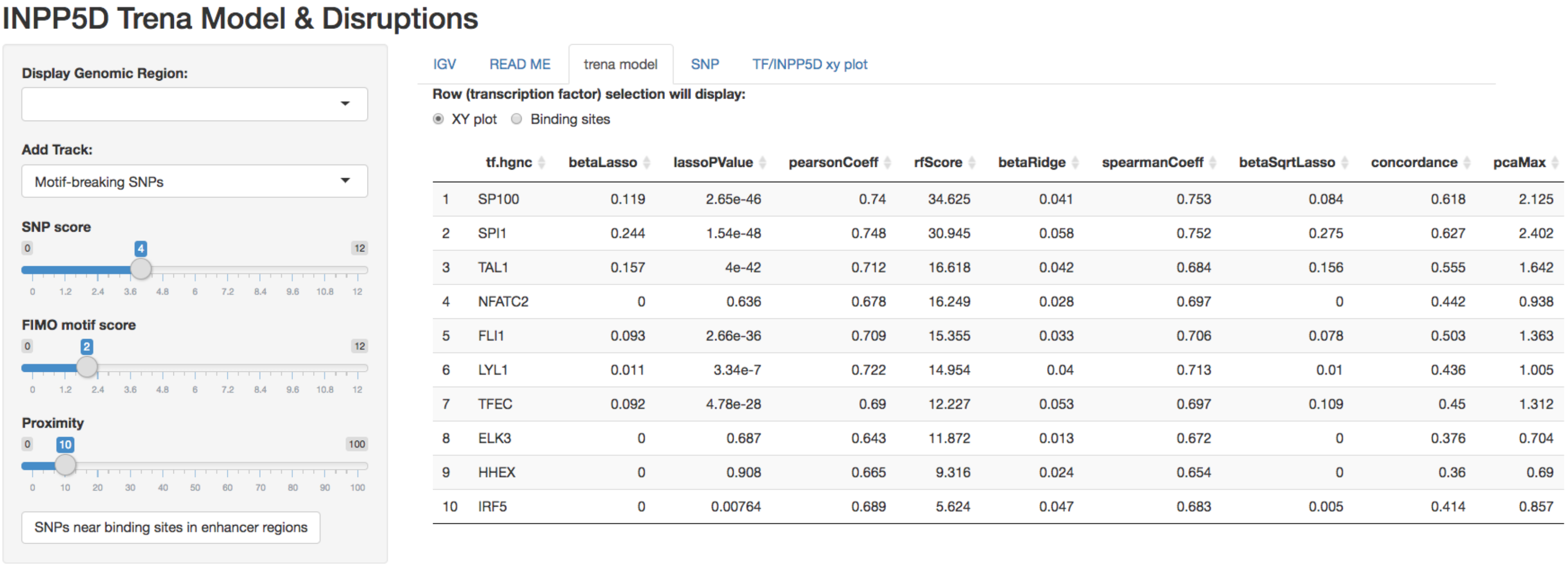
Synapse

- Models for each dataset and brain region
  - ROSMAP syn7984387
  - Mayo/UF/ISB temporal cortex syn8259337
  - Mayo/UF/ISB cerebellum syn8259326
  - MSSM frontal pole syn8281269
  - MSSM STG syn8281290
  - MSSM IFG syn8281276
  - MSSM PHG syn8281283
- Models are specific to brain region, but not cell type as RNA-seq data contains multiple cell types
  - If a gene is expressed in a single cell type, the TFs tend to be in same cell type
- **Models are mechanistic and directional**

TReNA applications

- Take advantage of the mechanistic and directional TReNA results
- Genome-scale model can be used to interpret data from other approaches
  - Functional annotation of variants (INPP5D)
  - Provide biological context (VGF)
  - TF drivers of co-expressed or differentially expressed genes
  - Network changes from drugs

Visualization of INPP5D in TReNA



INPP5D Trena Model & Disruptions

Display Genomic Region:

Add Track: Motif-breaking SNPs

SNP score 4

FIMO motif score 2

Proximity 10

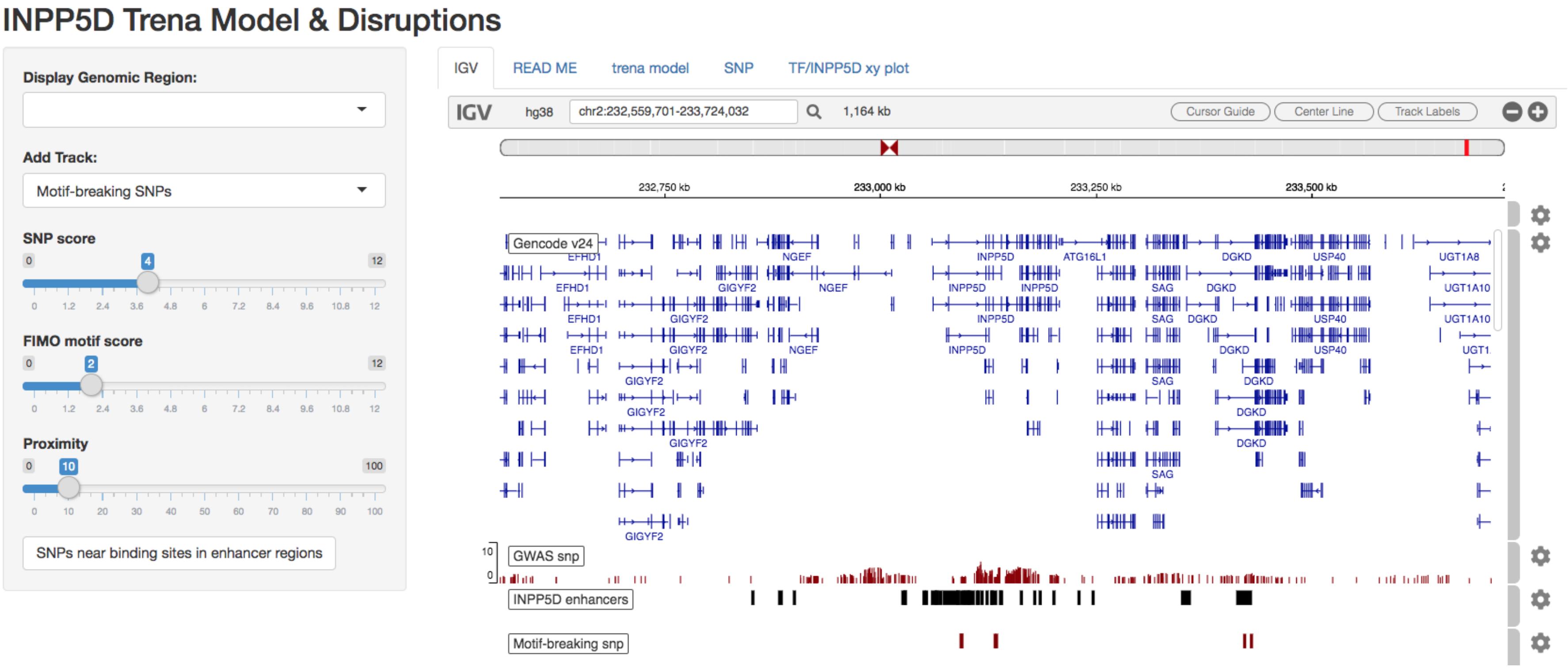
SNPs near binding sites in enhancer regions

Row (transcription factor) selection will display:

● XY plot ○ Binding sites

	tf.hgnc	betaLasso	lassoPValue	pearsonCoeff	rfScore	betaRidge	spearmanCoeff	betaSqrtLasso	concordance	pcaMax
1	SP100	0.119	2.65e-46	0.74	34.625	0.041	0.753	0.084	0.618	2.125
2	SPI1	0.244	1.54e-48	0.748	30.945	0.058	0.752	0.275	0.627	2.402
3	TAL1	0.157	4e-42	0.712	16.618	0.042	0.684	0.156	0.555	1.642
4	NFATC2	0	0.636	0.678	16.249	0.028	0.697	0	0.442	0.938
5	FLI1	0.093	2.66e-36	0.709	15.355	0.033	0.706	0.078	0.503	1.363
6	LYL1	0.011	3.34e-7	0.722	14.954	0.04	0.713	0.01	0.436	1.005
7	TFEC	0.092	4.78e-28	0.69	12.227	0.053	0.697	0.109	0.45	1.312
8	ELK3	0	0.687	0.643	11.872	0.013	0.672	0	0.376	0.704
9	HHEX	0	0.908	0.665	9.316	0.024	0.654	0	0.36	0.69
10	IRF5	0	0.00764	0.689	5.624	0.047	0.683	0.005	0.414	0.857

Visualization of INPP5D in TReNA



INPP5D Trena Model & Disruptions

Display Genomic Region:

Add Track: Motif-breaking SNPs

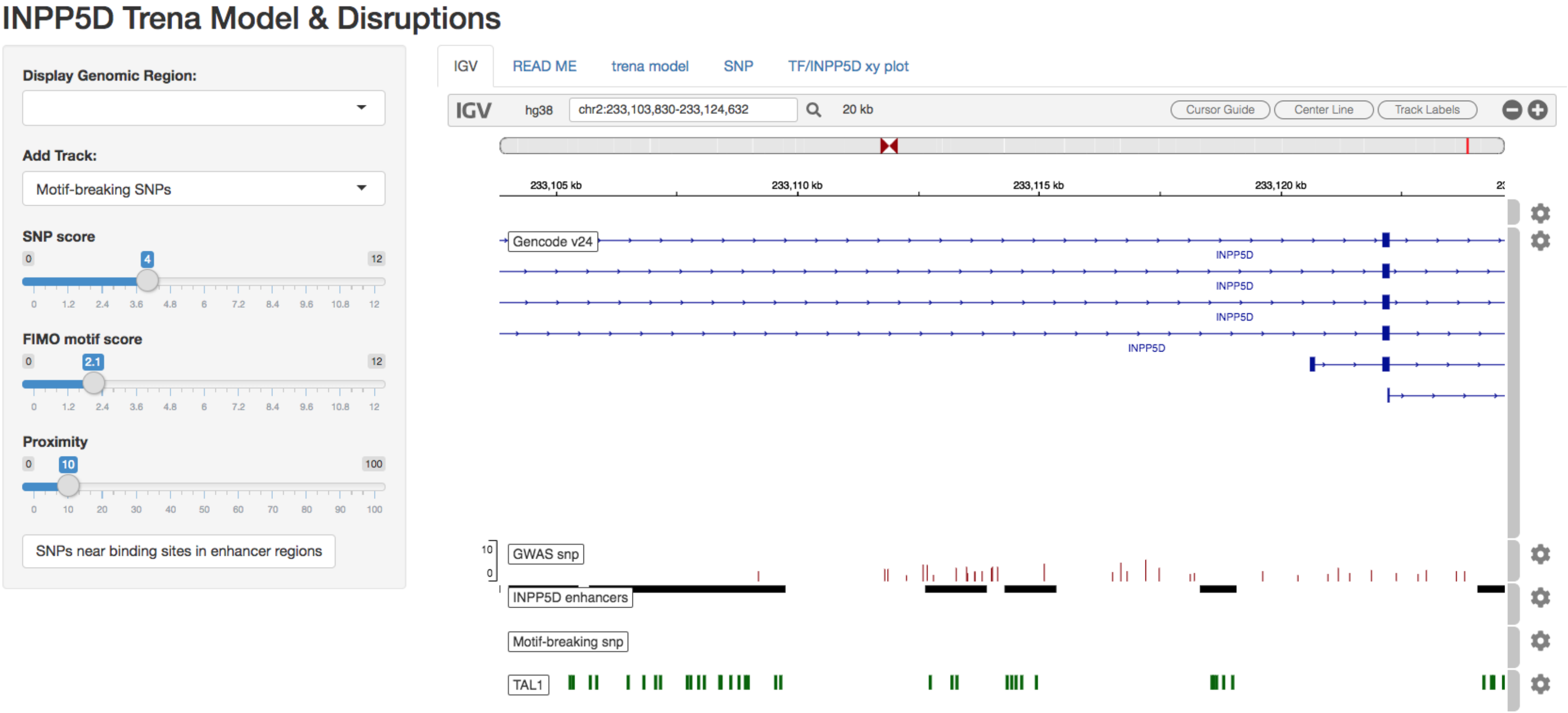
SNP score: 4

FIMO motif score: 2

Proximity: 10

IGV hg38 chr2:232,559,701-233,724,032 1,164 kb

Visualization of INPP5D in TReNA



INPP5D Trena Model & Disruptions

Display Genomic Region:

Add Track: Motif-breaking SNPs

SNP score: 4 (0–12)

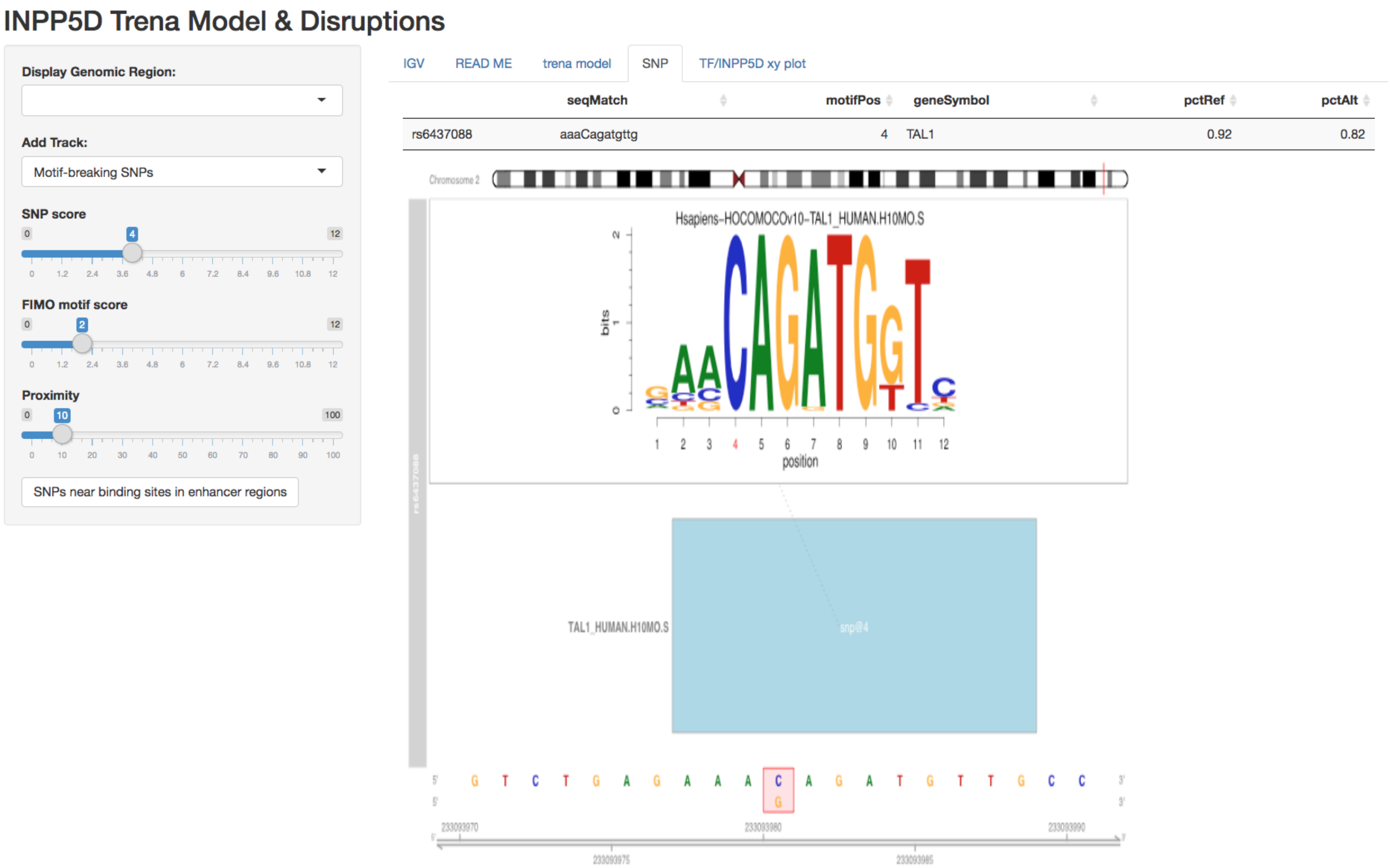
FIMO motif score: 2.1 (0–12)

Proximity: 10 (0–100)

SNPs near binding sites in enhancer regions

IGV hg38 chr2:233,103,830-233,124,632 20 kb

Visualization of INPP5D in TReNA



INPP5D Trena Model & Disruptions

Display Genomic Region:

Add Track: Motif-breaking SNPs

SNP score: 4 (0 – 12)

FIMO motif score: 2 (0 – 12)

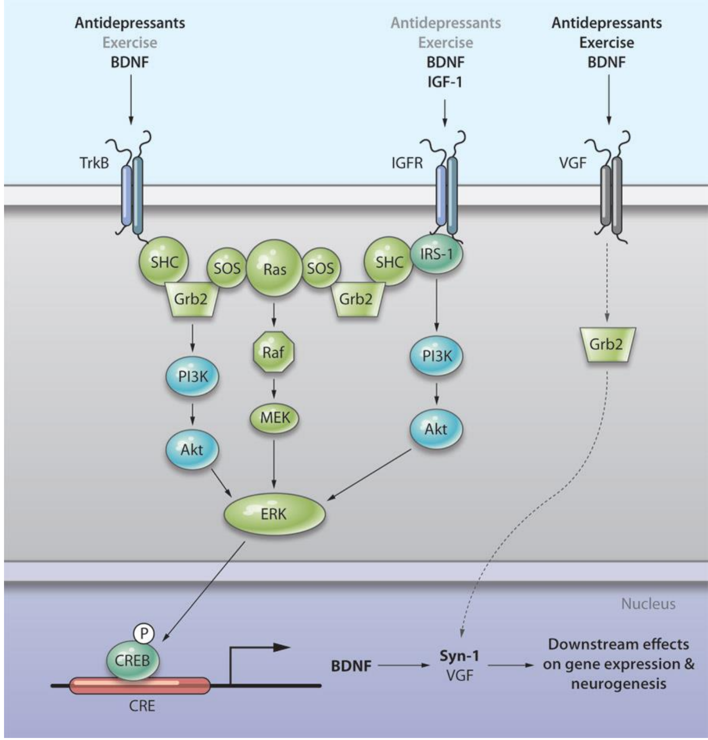
Proximity: 10 (0 – 100)

SNPs near binding sites in enhancer regions

	seqMatch	motifPos	geneSymbol	pctRef	pctAlt
rs6437088	aaaCagatgttg	4	TAL1	0.92	0.82

Agora nominee: VGF

- Nominated by multiple groups in AMP-AD
- Expressed in the adult brain in areas associated with higher cognitive functions, such as the hippocampus, the neocortex and the entorhinal cortex
- Regulates neural activity and survival
- Involved in energy balance
- TLPQ-62 regulates memory formation and depression
- TLPQ-21 (subset of TLPQ-62) binds to C3aR1 and has anti-obesity functions
- Downregulated in CSF 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.

Regulators of VGF are effectors TGF-beta pathway

🟩 Enhancer (GeneHancer

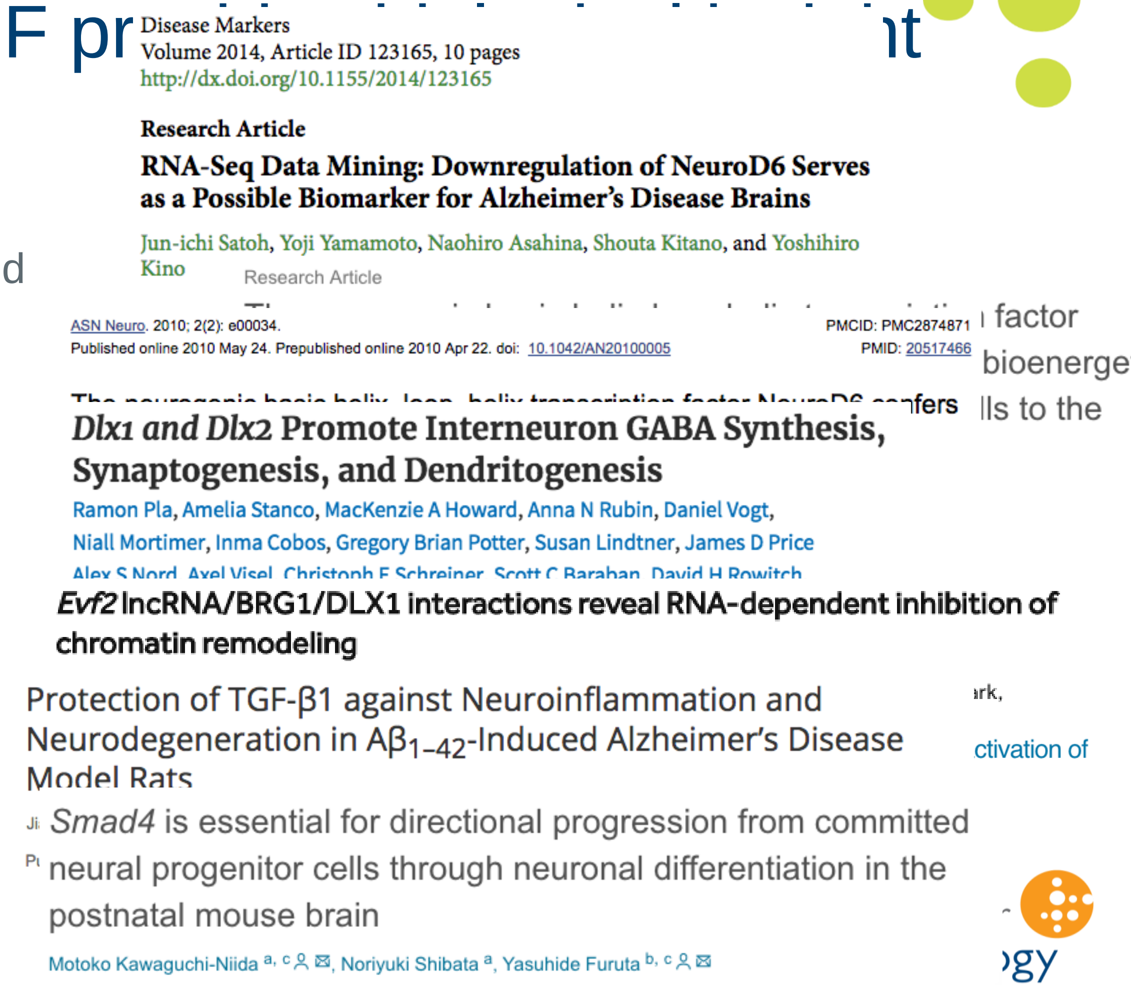
🟥 Footprints

▪ Open chromatin (DHS)

TReNA model of VGF pr nt

- NEURODG6
  - Developmental gene involved differentiation, antioxidant response and mitochondrial function

- DLX1 & SMAD4
  - Known effectors of TGF-β signaling



Disease Markers
Volume 2014, Article ID 123165, 10 pages
http://dx.doi.org/10.1155/2014/123165

Research Article

RNA-Seq Data Mining: Downregulation of NeuroD6 Serves as a Possible Biomarker for Alzheimer's Disease Brains

Jun-ichi Satoh, Yoji Yamamoto, Naohiro Asahina, Shouta Kitano, and Yoshihiro Kino

Research Article

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bioenerge
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ASN Neuro. 2010; 2(2): e00034.
Published online 2010 May 24. Prepublished online 2010 Apr 22. doi: 10.1042/AN20100005
PMCID: PMC2874871
PMID: 20517466

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Dlx1 and _Dlx2_ Promote Interneuron GABA Synthesis, Synaptogenesis, and Dendritogenesis

Ramon Pla, Amelia Stanco, MacKenzie A Howard, Anna N Rubin, Daniel Vogt,
Niall Mortimer, Inma Cobos, Gregory Brian Potter, Susan Lindtner, James D Price
Alex S Nord, Axel Visel, Christoph E Schreiner, Scott C Baraban, David H Rowitch

Evf2 lncRNA/BRG1/DLX1 interactions reveal RNA-dependent inhibition of chromatin remodeling

Protection of TGF-β1 against Neuroinflammation and Neurodegeneration in Aβ$_{1-42}$-Induced Alzheimer's Disease Model Rats

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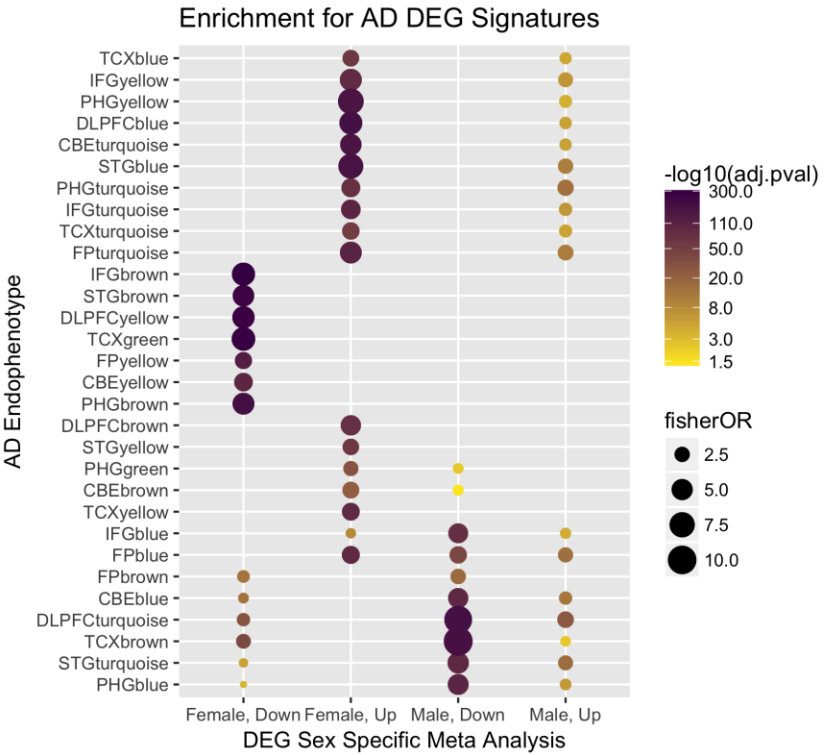
ctivation of

Smad4 is essential for directional progression from committed neural progenitor cells through neuronal differentiation in the postnatal mouse brain

Motoko Kawaguchi-Niida [a, c], Noriyuki Shibata [a], Yasuhide Furuta [b, c]

Transcriptional Regulation of Consensus Modules

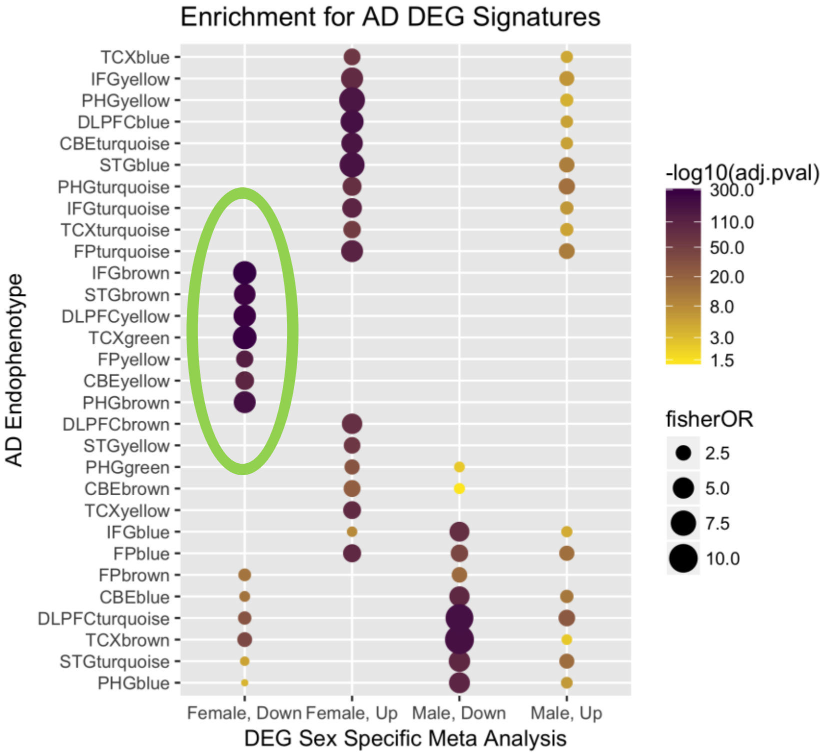


Consensus co-expression modules assessed using the 3 large RNA-seq brain transcriptomic data sets (several brain regions)

- Module prefix represents the dataset from which the base set of genes were evaluated
- Modules are not exclusive with many overlaps
- Expression levels were adjusted for other covariates
- Enrichments are for DEGs within co-expression modules, comparing AD to control

Ben Logsdon

Transcriptional Regulation of Consensus Modules

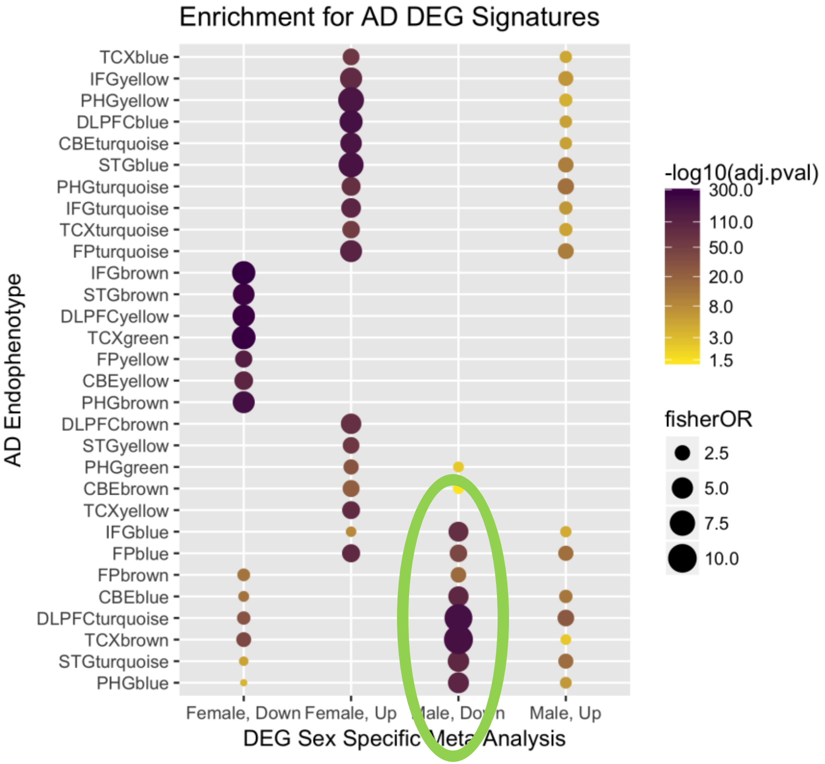


TCXgreen module contains 2,766 genes and 1,383 DEG

	Transcription Factor	frequency	avg.rank	sd.rank
1	MEF2D	108	2.12	1.33
2	TBR1	141	2.27	1.27
3	STAT4	298	2.50	1.38
4	PKNOX2	232	2.55	1.39
5	MXI1	99	2.60	1.37
6	SMARCA4	33	2.61	1.48
7	GABPA	265	2.62	1.42
8	MEF2C	246	2.63	1.32
9	SMAD5	232	2.68	1.41
10	NFIA	110	2.71	1.44

	gene	pearson.coeff	pcaMax	target.gene	Rank
1	MEF2C	0.66	14.00	TBC1D30	1
2	MEF2C	0.89	10.53	HECW1	2
3	MEF2C	0.81	9.85	STAT4	1
4	MEF2C	0.83	9.58	FAM19A1	1
5	MEF2C	0.78	9.38	SLC26A4	1
6	MEF2C	0.83	9.24	ADAM22	1
7	MEF2C	0.66	9.17	NUDCD3	1
8	MEF2C	0.83	8.82	PHF24	1
9	MEF2C	0.82	8.73	PPL	1

Transcriptional Regulation of Consensus Modules

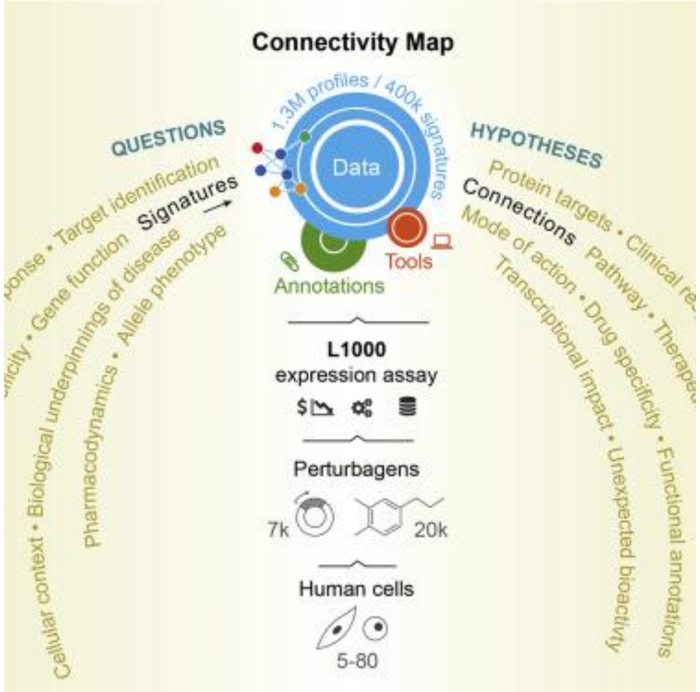


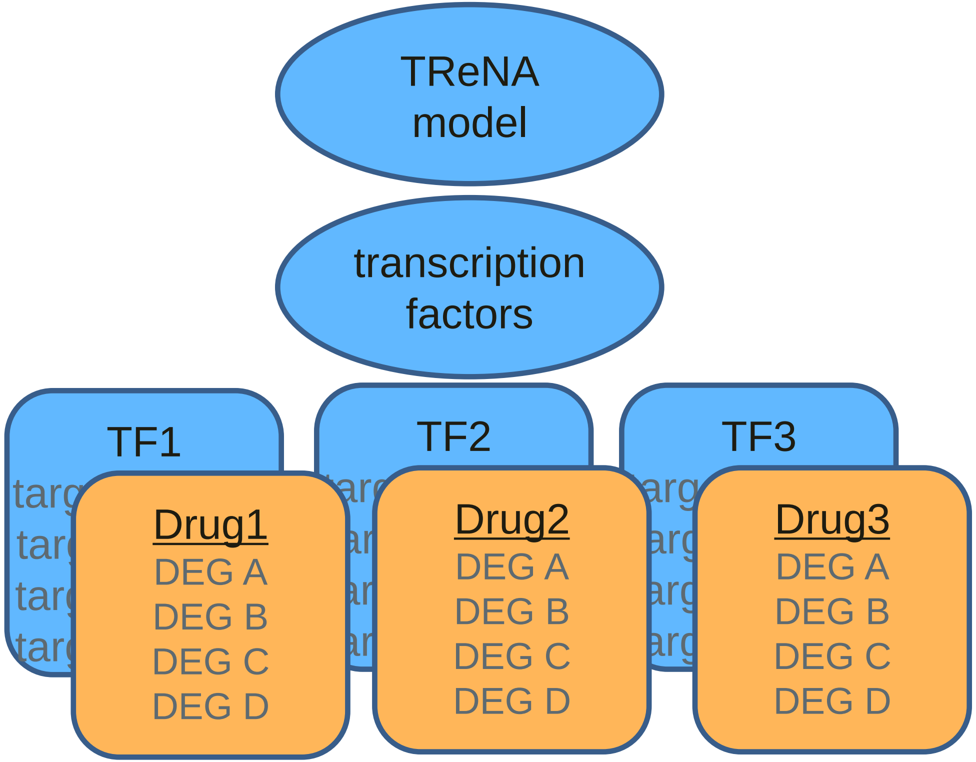
TCXbrown module contains 1,851 genes and 601 DEG

	Transcription Factor	frequency	avg.rank	sd.rank
1	TFCP2	43	1.88	0.96
2	RELA	25	2.32	1.18
3	NR2C1	82	2.43	1.43
4	THAP7	77	2.44	1.39
5	SREBF1	88	2.50	1.34
6	MAX	66	2.52	1.32
7	GABPB1	120	2.53	1.45
8	FOXN3	40	2.55	1.38
9	RCOR3	78	2.55	1.36
10	HLTF	34	2.56	1.31

	gene	pearson.coeff	pcaMax	target.gene	Rank
1	TFCP2	0.72	10.61	TRIM45	1
2	TFCP2	0.80	9.72	CIRBP	1
3	TFCP2	0.65	9.71	AIG1	1
4	TFCP2	0.53	9.23	GSTO2	1
5	TFCP2	0.71	9.13	VEZT	1
6	TFCP2	0.72	8.53	ARFGAP2	1
7	TFCP2	0.71	8.38	DUS4L	1
8	TFCP2	0.68	7.97	MED29	1
9	TFCP2	0.75	7.89	IBTK	1

Resolving Drug Expression Profiles with TReNA




TReNA model

transcription factors

TF1

TF2

TF3

Drug1
DEG A
DEG B
DEG C
DEG D

Drug2
DEG A
DEG B
DEG C
DEG D

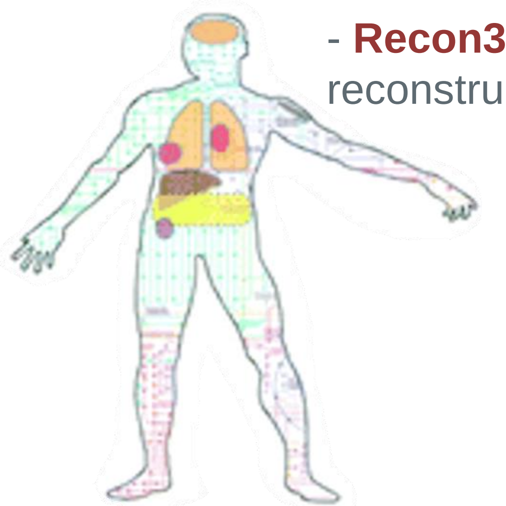
Drug3
DEG A
DEG B
DEG C
DEG D

Summary

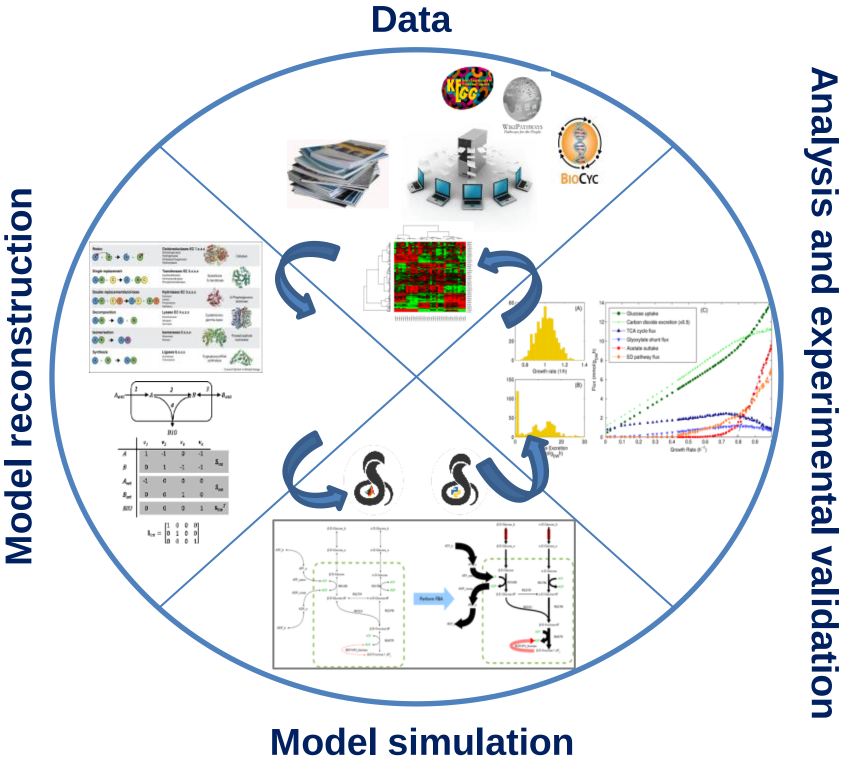
- Transcriptional regulatory networks produce mechanistic and directional gene models that can be useful for identifying key TFs for individual genes
- Models can be used to inform biological hypotheses
- Models can be integrated with genomic data, enabling functional annotation of variants
- Models can be used to identify key TF drivers of DEGs and co-expressed networks

Genome-scale metabolic models (GSMs)

- **Recon3** : most comprehensive and updated human metabolic reconstruction



Reactions	13,543
Genes	3,288 (unique)
Metabolites	4,140 (unique)
Compartments	9 (Cytoplasm, Extracellular, Golgi, Lysosome, Mitochondria, Nucleus, Endoplasmic reticulum, Peroxisome, unknown)
Subsystems	111



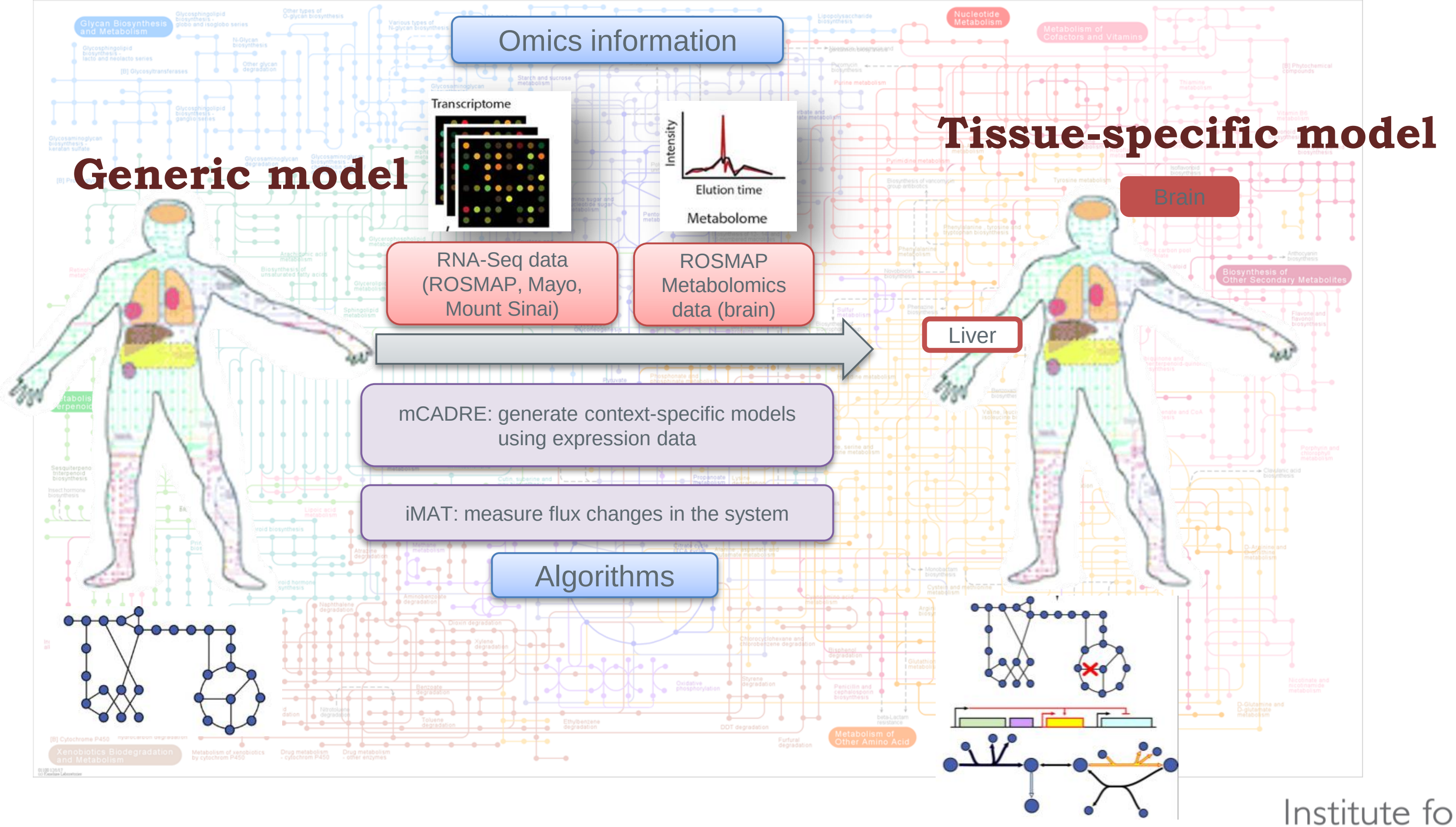
Data

Analysis and experimental validation

Model simulation

Model reconstruction

Priyanka Baloni



Generic model

Omics information

RNA-Seq data (ROSMAP, Mayo, Mount Sinai)

ROSMAP Metabolomics data (brain)

mCADRE: generate context-specific models using expression data

iMAT: measure flux changes in the system

Algorithms

Tissue-specific model

Brain

Liver

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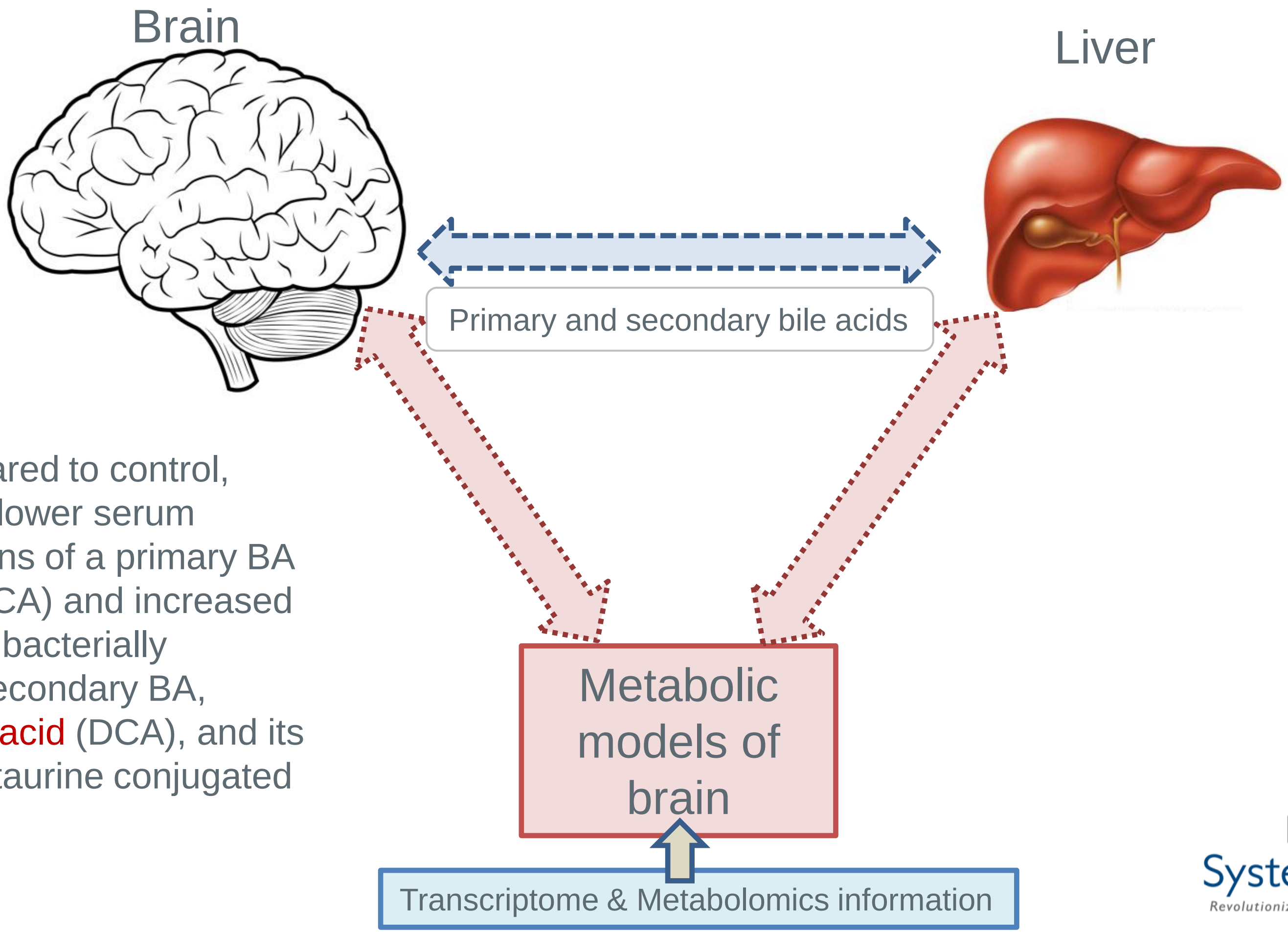
Role of Bile Acids in Alzheimer’s disease


Brain

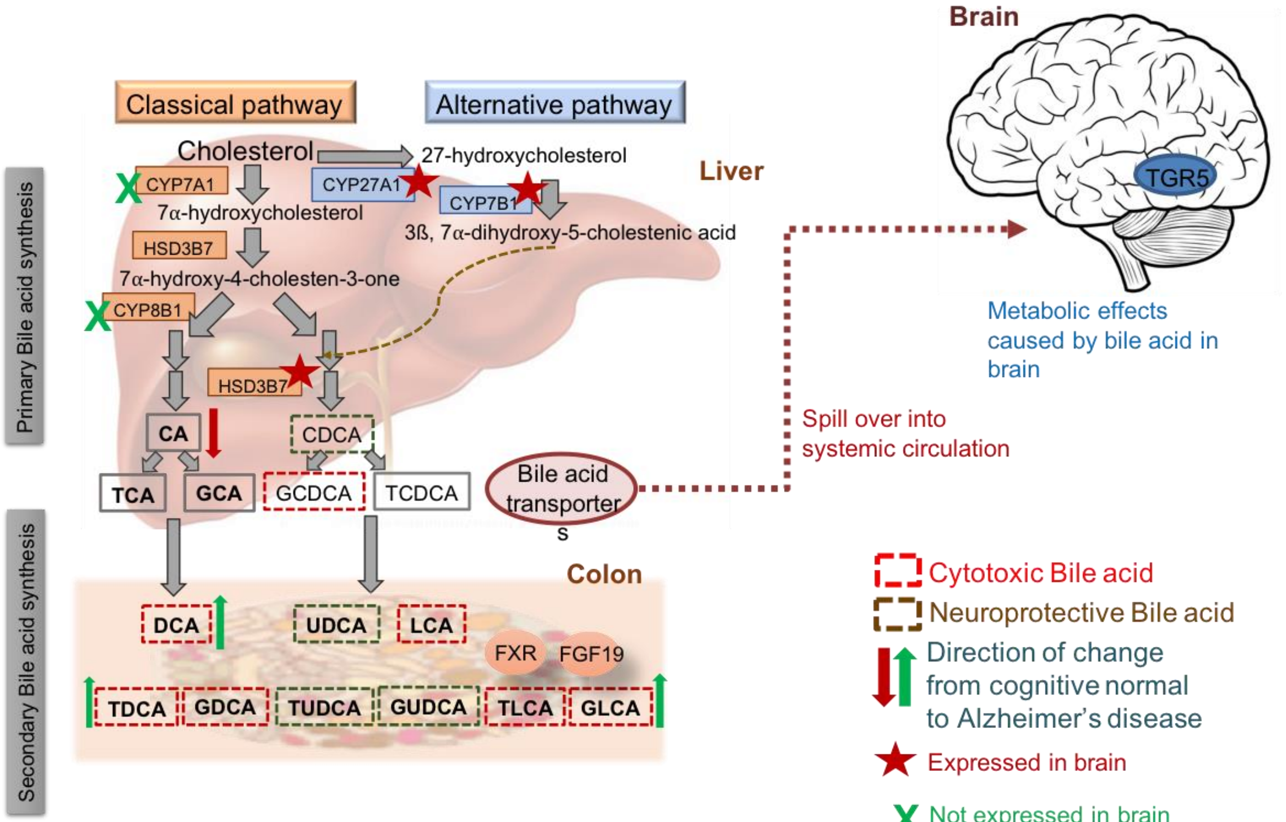
Liver

Primary and secondary bile acids

Metabolic models of brain

Transcriptome & Metabolomics information

In AD compared to control, significantly lower serum concentrations of a primary BA (cholic acid CA) and increased levels of the bacterially produced, secondary BA, deoxycholic acid (DCA), and its glycine and taurine conjugated forms



Metabolic effects caused by bile acid in brain

Spill over into systemic circulation

🟥 Cytotoxic Bile acid

🟫 Neuroprotective Bile acid

↓↑ Direction of change from cognitive normal to Alzheimer's disease

★ Expressed in brain

X Not expressed in brain

Mahmoudiandehkordi, Siamak, et al. *bioRxiv* (2018)

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Generating context-specific models of brain regions

- The most comprehensive human reconstruction, Recon3, was used as template for generating context-specific models

ROSMAP

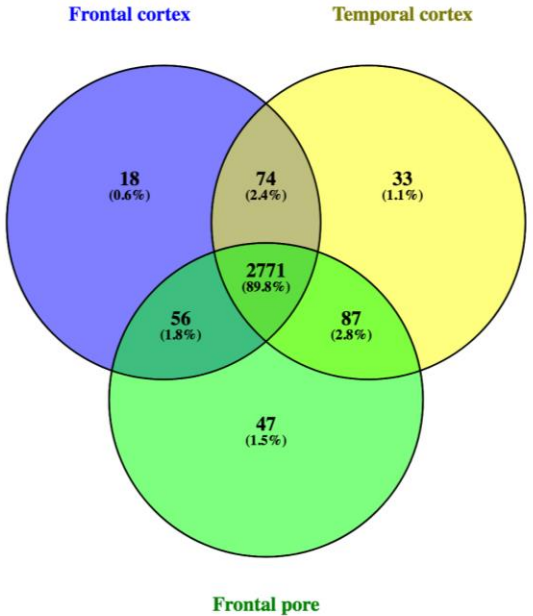
	Frontal cortex
Reactions	5786
Genes	3254
Metabolites	5685

Mayo

	Cerebellum	**Temporal cortex**
Reactions	5355	6011
Genes	3316	3304
Metabolites	5278	5843

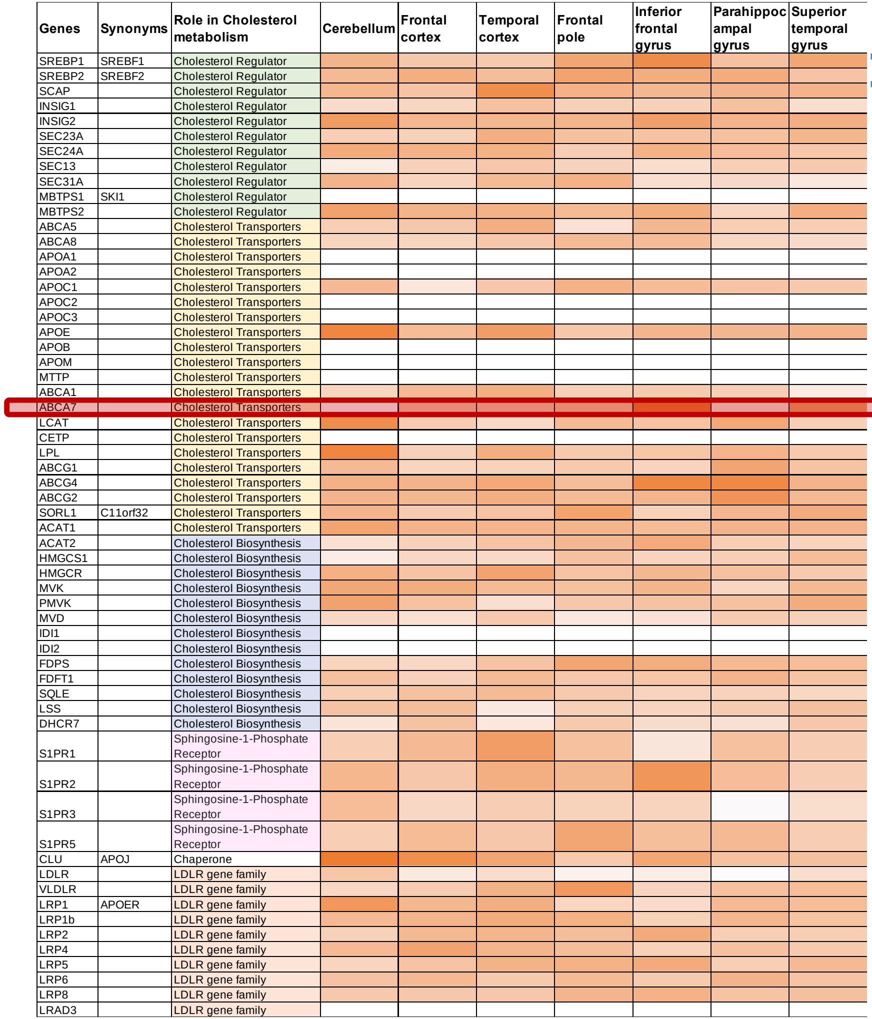
Mount Sinai

	FP	**IFG**	**PHG**	**STG**
Reactions	5565	5677	5152	5590
Genes	3297	3337	3270	3305
Metabolites	5707	5786	5408	5758



~ 90% similarity between brain models of FC, TC & FP

Cholesterol metabolism



Genes	Synonyms	Role in Cholesterol metabolism	Cerebellum	Frontal cortex	Temporal cortex	Frontal pole	Inferior frontal gyrus	Parahippocampal gyrus	Superior temporal gyrus
SREBP1	SREBF1	Cholesterol Regulator							
SREBP2	SREBF2	Cholesterol Regulator							
SCAP		Cholesterol Regulator							
INSIG1		Cholesterol Regulator							
INSIG2		Cholesterol Regulator							
SEC23A		Cholesterol Regulator							
SEC24A		Cholesterol Regulator							
SEC13		Cholesterol Regulator							
SEC31A		Cholesterol Regulator							
MBTPS1	SKI1	Cholesterol Regulator							
MBTPS2		Cholesterol Regulator							
ABCA5		Cholesterol Transporters							
ABCA8		Cholesterol Transporters							
APOA1		Cholesterol Transporters							
APOA2		Cholesterol Transporters							
APOC1		Cholesterol Transporters							
APOC2		Cholesterol Transporters							
APOC3		Cholesterol Transporters							
APOE		Cholesterol Transporters							
APOB		Cholesterol Transporters							
APOM		Cholesterol Transporters							
MTTP		Cholesterol Transporters							
ABCA1		Cholesterol Transporters							
ABCA7		Cholesterol Transporters							
LCAT		Cholesterol Transporters							
CETP		Cholesterol Transporters							
LPL		Cholesterol Transporters							
ABCG1		Cholesterol Transporters							
ABCG4		Cholesterol Transporters							
ABCG2		Cholesterol Transporters							
SORL1	C11orf32	Cholesterol Transporters							
ACAT1		Cholesterol Transporters							
ACAT2		Cholesterol Biosynthesis							
HMGCS1		Cholesterol Biosynthesis							
HMGCR		Cholesterol Biosynthesis							
MVK		Cholesterol Biosynthesis							
PMVK		Cholesterol Biosynthesis							
MVD		Cholesterol Biosynthesis							
IDI1		Cholesterol Biosynthesis							
IDI2		Cholesterol Biosynthesis							
FDPS		Cholesterol Biosynthesis							
FDFT1		Cholesterol Biosynthesis							
SQLE		Cholesterol Biosynthesis							
LSS		Cholesterol Biosynthesis							
DHCR7		Cholesterol Biosynthesis							
S1PR1		Sphingosine-1-Phosphate Receptor							
S1PR2		Sphingosine-1-Phosphate Receptor							
S1PR3		Sphingosine-1-Phosphate Receptor							
S1PR5		Sphingosine-1-Phosphate Receptor							
CLU	APOJ	Chaperone							
LDLR		LDLR gene family							
VLDLR		LDLR gene family							
LRP1	APOER	LDLR gene family							
LRP1b		LDLR gene family							
LRP2		LDLR gene family							
LRP4		LDLR gene family							
LRP5		LDLR gene family							
LRP6		LDLR gene family							
LRP8		LDLR gene family							
LRAD3		LDLR gene family							

TFs regulating sterol-regulated genes

Major apoprotein of the chylomicron

ATP-binding cassette (ABC) transporters and risk factor for late-onset AD

Peripheral cholesterol transport

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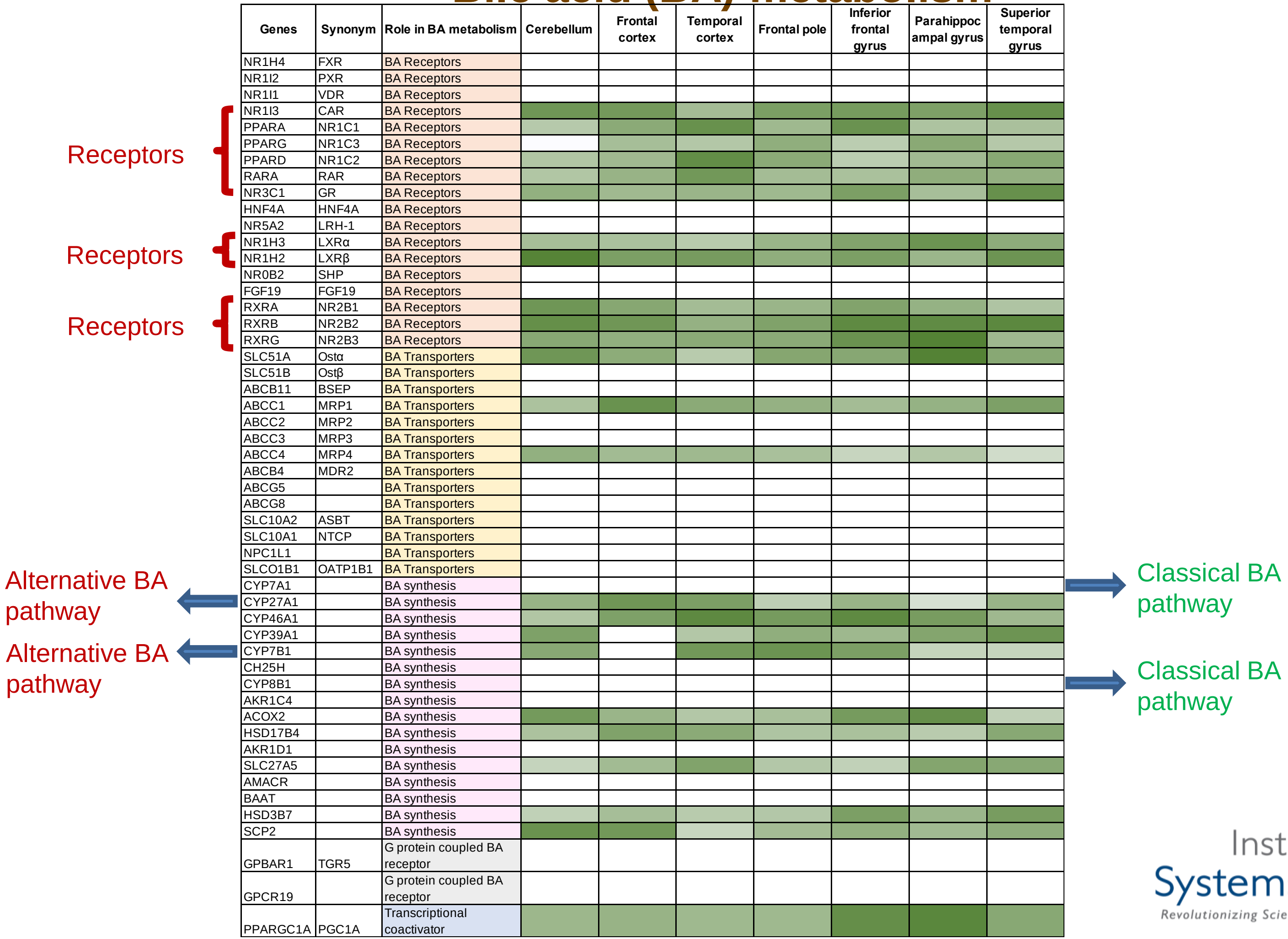
Bile acid (BA) metabolism



Receptors

Receptors

Receptors

Alternative BA pathway

Alternative BA pathway

Classical BA pathway

Classical BA pathway

Genes	Synonym	Role in BA metabolism	Cerebellum	Frontal cortex	Temporal cortex	Frontal pole	Inferior frontal gyrus	Parahippocampal gyrus	Superior temporal gyrus
NR1H4	FXR	BA Receptors							
NR1I2	PXR	BA Receptors							
NR1I1	VDR	BA Receptors							
NR1I3	CAR	BA Receptors	🟩	🟩	🟩	🟩	🟩	🟩	🟩
PPARA	NR1C1	BA Receptors	🟩	🟩	🟩	🟩	🟩	🟩	🟩
PPARG	NR1C3	BA Receptors		🟩	🟩	🟩	🟩	🟩	🟩
PPARD	NR1C2	BA Receptors	🟩	🟩	🟩	🟩	🟩	🟩	🟩
RARA	RAR	BA Receptors	🟩	🟩	🟩	🟩	🟩	🟩	🟩
NR3C1	GR	BA Receptors	🟩	🟩	🟩	🟩	🟩	🟩	🟩
HNF4A	HNF4A	BA Receptors							
NR5A2	LRH-1	BA Receptors							
NR1H3	LXRα	BA Receptors	🟩	🟩	🟩	🟩	🟩	🟩	🟩
NR1H2	LXRβ	BA Receptors	🟩	🟩	🟩	🟩	🟩	🟩	🟩
NR0B2	SHP	BA Receptors							
FGF19	FGF19	BA Receptors							
RXRA	NR2B1	BA Receptors	🟩	🟩	🟩	🟩	🟩	🟩	🟩
RXRB	NR2B2	BA Receptors	🟩	🟩	🟩	🟩	🟩	🟩	🟩
RXRG	NR2B3	BA Receptors	🟩	🟩	🟩	🟩	🟩	🟩	🟩
SLC51A	Ostα	BA Transporters	🟩	🟩	🟩	🟩	🟩	🟩	🟩
SLC51B	Ostβ	BA Transporters							
ABCB11	BSEP	BA Transporters							
ABCC1	MRP1	BA Transporters	🟩	🟩	🟩	🟩	🟩	🟩	🟩
ABCC2	MRP2	BA Transporters							
ABCC3	MRP3	BA Transporters							
ABCC4	MRP4	BA Transporters	🟩	🟩	🟩	🟩	🟩	🟩	🟩
ABCB4	MDR2	BA Transporters							
ABCG5		BA Transporters							
ABCG8		BA Transporters							
SLC10A2	ASBT	BA Transporters							
SLC10A1	NTCP	BA Transporters							
NPC1L1		BA Transporters							
SLCO1B1	OATP1B1	BA Transporters							
CYP7A1		BA synthesis							
CYP27A1		BA synthesis	🟩	🟩	🟩	🟩	🟩	🟩	🟩
CYP46A1		BA synthesis	🟩	🟩	🟩	🟩	🟩	🟩	🟩
CYP39A1		BA synthesis	🟩		🟩	🟩	🟩	🟩	🟩
CYP7B1		BA synthesis	🟩		🟩	🟩	🟩	🟩	🟩
CH25H		BA synthesis							
CYP8B1		BA synthesis							
AKR1C4		BA synthesis							
ACOX2		BA synthesis	🟩	🟩	🟩	🟩	🟩	🟩	🟩
HSD17B4		BA synthesis	🟩	🟩	🟩	🟩	🟩	🟩	🟩
AKR1D1		BA synthesis							
SLC27A5		BA synthesis	🟩	🟩	🟩	🟩	🟩	🟩	🟩
AMACR		BA synthesis							
BAAT		BA synthesis							
HSD3B7		BA synthesis	🟩	🟩	🟩	🟩	🟩	🟩	🟩
SCP2		BA synthesis	🟩	🟩	🟩	🟩	🟩	🟩	🟩
GPBAR1	TGR5	G protein coupled BA receptor							
GPCR19		G protein coupled BA receptor							
PPARGC1A	PGC1A	Transcriptional coactivator	🟩	🟩	🟩	🟩	🟩	🟩	🟩

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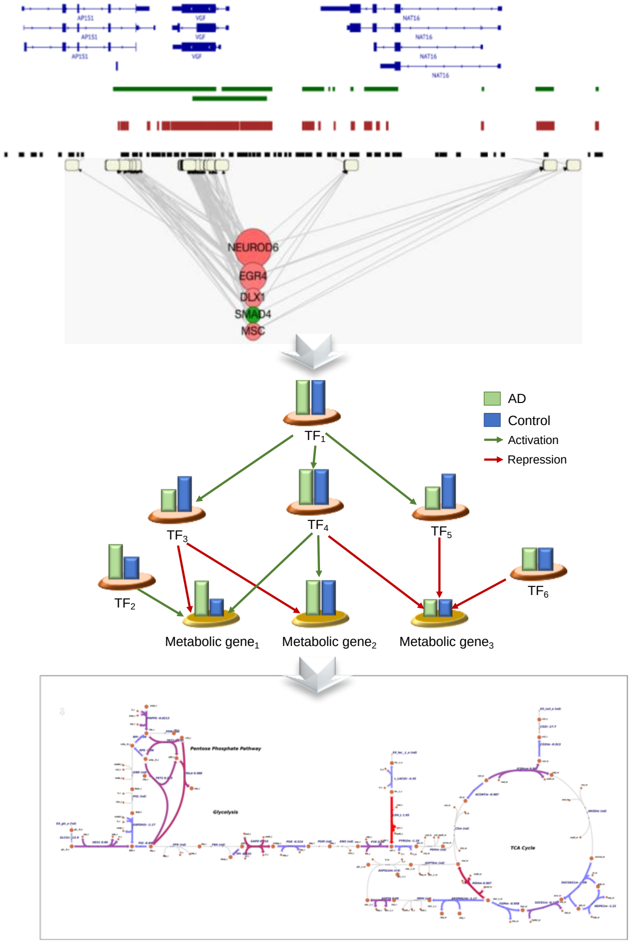
Transcriptional Regulation of metabolism



Transcriptional regulatory network
(SREBF1, SREBF2, PPARA, PPARG, LXRα/ß, RAR and RXR)

TF-metabolic gene interactions

Metabolites and genes involved in AD pathology

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What do we infer from metabolomics analysis of brain samples?

- Brains from 111 AD and control patients profiled using the p180 platform
- >60 bile acids (primary+secondary) identified in metabolomics study of brain samples[4] (targeted approach)
- Bile acids not produce in the brain may be coming from the periphery (gut) and are being characterized by the consortium
- Curation of our metabolic models will attempt to include this information

12-DHCA	12-dehydrocholic acid
3-DHCA	3-dehydrocholic acid
CDCA	Chenodeoxycholic acid
CA	Cholic acid
DCA	Deoxycholic acid
GCDCA	Glycochenodeoxycholate
GCA	Glycocholic acid
LCA	Lithocholic acid
GLCA	Glycolithocholate
UDCA	Ursodeoxycholic acid
GUDCA	Glycoursodeoxycholic acid
HCA	Hyocholic acid
LCA-3S	Lithocholic acid 3 sulfate
GDCA	Glycodeoxycholic acid
HDCA	Hyodeoxycholic acid
TCA	Taurocholic acid
TCDCA	Taurochenodeoxycholate
TDCA	Ttaurodeoxycholate
UCA	Ursocholic acid
alloLCA	Allolithocholic acid

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[4] AMP-AD Knowledge Portal. www.synapse.org/#!Synapse:syn2580853

Summary

- SREBP1 and SREBP2 are important cholesterol regulators and variants of SREBP2 are linked with AD

- Role of Cholesterol transporters such as ABCA1, ABCA5, **ABCA7**, **APOE**, LPL and LCAT in AD pathophysiology is being probed

- Classical pathway of bile acid synthesis is less active than alternative pathway
  - Expression of CYP27A1 and CYP7B1 and lack of expression of CYP7A1 and CYP8B1 indicates the role of alternative pathway in brain
  - 7α,12α-dihydroxycholesterol or 7α,12α-dihydroxycholest-4-en-3-one may cross the BBB from the circulation and enter the “classical pathway” down-stream of CYP7A1 and CYP8B1, helping to produce cholic acid (CA).

- Bile acid receptors such as PPARA, PPARG, LXRα/ß, RAR and RXRs are expressed in brain but not yet par of our metabolic models (future work)

- Metabolic modeling of the transporters, receptors, synthesis enzymes and metabolites will help provide a mechanistic understanding of the relationship between cholesterol and bile acid metabolism to cognitive decline in AD

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