Leveraging AMP-AD brain transcriptome modules as endophenotypes for cross-validation of human targets and AD models

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Open Science: AMP-AD Knowledge Portal (www.synapse.org/ampad)

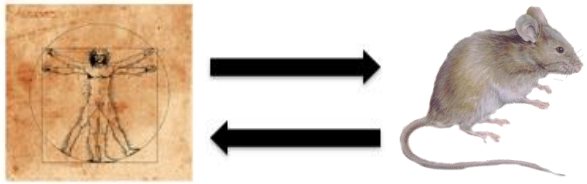
Challenges

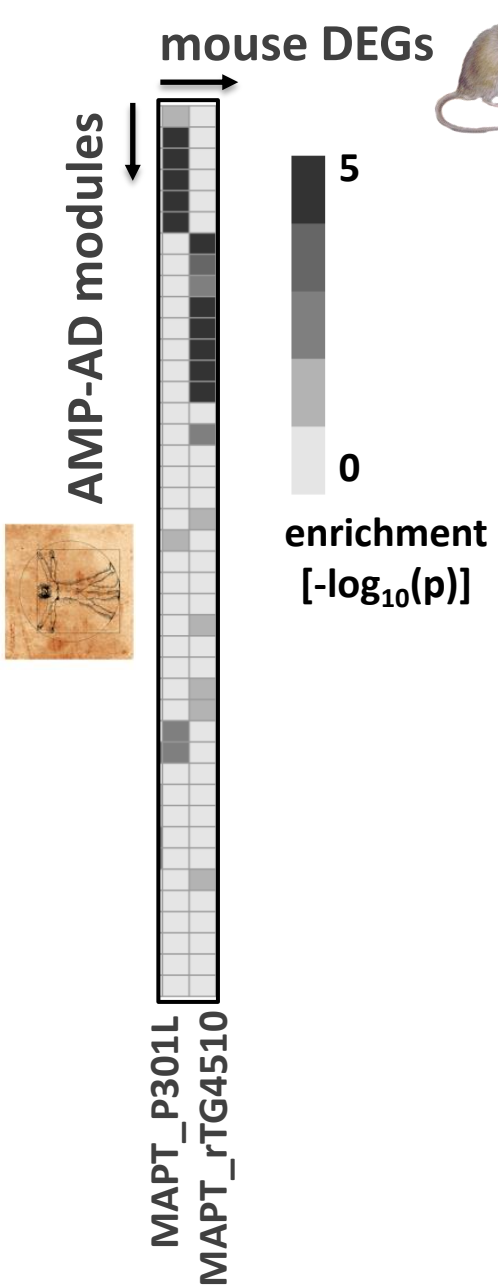
Human brain expression data is powerful for target nomination, but presents follow-up challenges for enabling precision medicine:

- Differentiating *specific* AD triggers (Aß vs. Tau)
- Dissecting *dynamic* age-dependent expression changes
- Selection of the *optimal* experimental model for follow-up studies
- Defining cross-species conservation at the *network* level
- Confirming which targets associated with AD traits are truly *causal*

Solution

Pinpoint correspondence between gene expression changes *associated* with AD in human brains and those *caused* by controlled experimental manipulations in animal models.

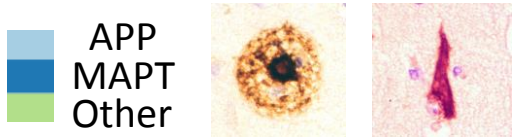


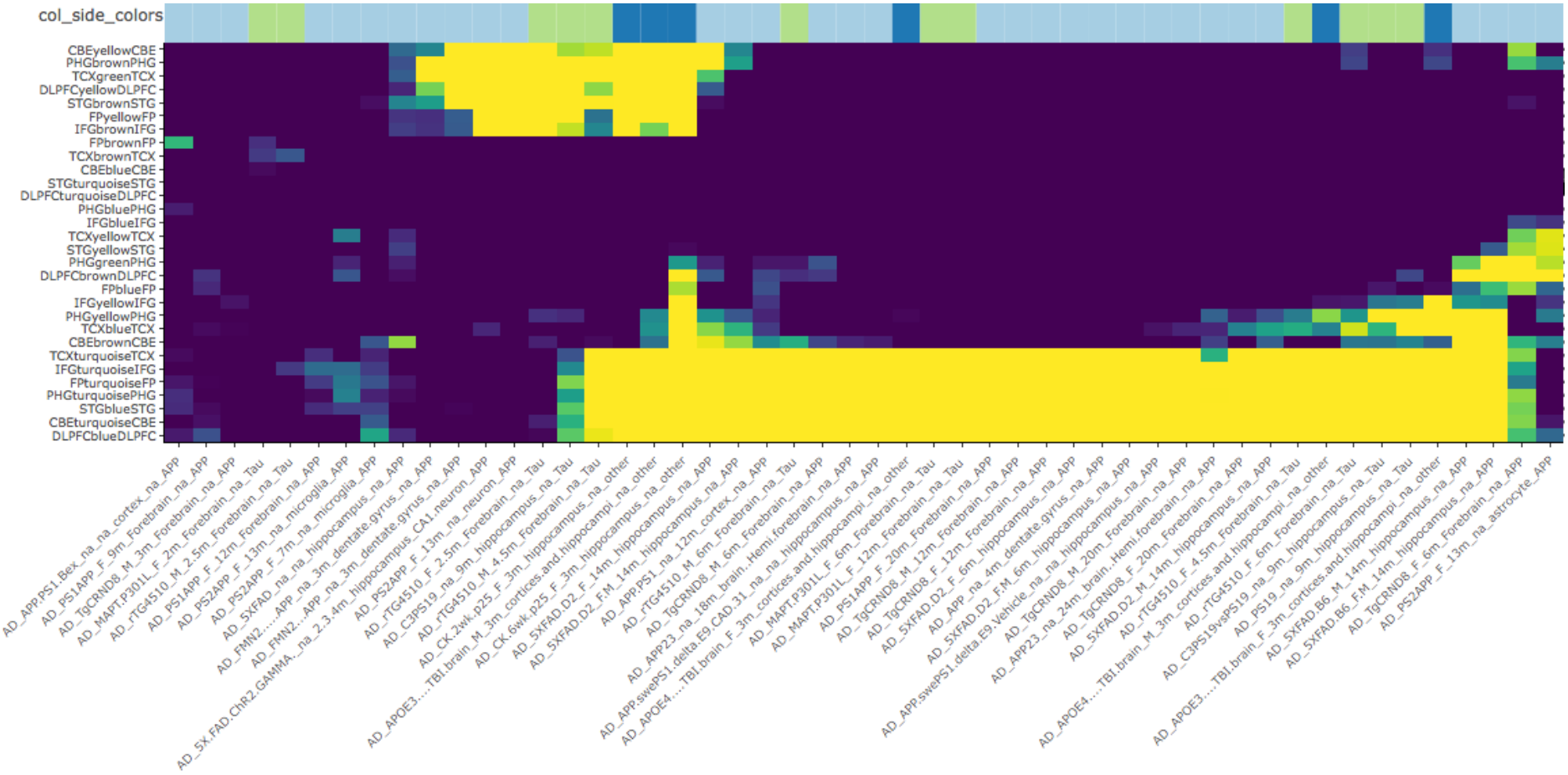


Module Activation in Mouse Models

- Rows: Human AMP-AD co-expression Modules
  - 30 “consensus” gene sets associated with AD
  - Derived from >2220 human brains (7 regions)
  - mean module size=2088 / range=504-4667
- Columns: Differentially expressed gene (DEGs) from mouse brain RNAseq datasests
  - AD and many other relevant experimental models
  - **95** distinct studies (AMP-AD and public databases)
  - **2672** samples with RNAseq data
  - **371** DEGs -> **252** remain after filters
- All RNA-seq data was re-processed using a single bioinformatic pipeline.
- Overlap based on hypergeometric overlap test.

AD Mouse Models



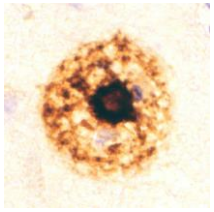


~50 APP and MAPT transgenic DEGs

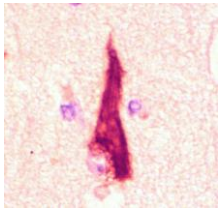
AD Mouse Models

ALZFORUM
NETWORKING FOR A CURE

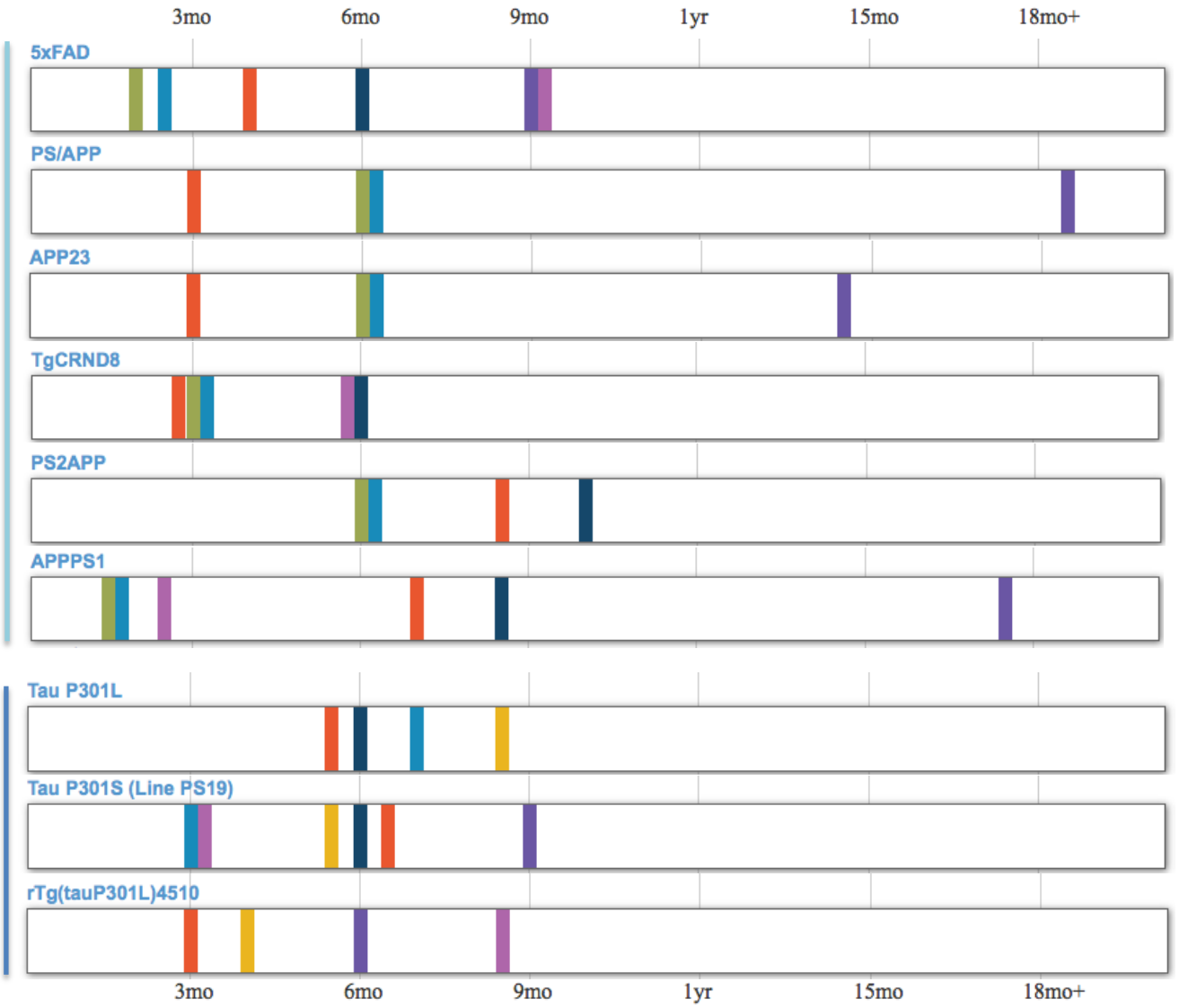
- Plaques
- Tangles
- Neuronal Loss
- Gliosis
- Changes in LTP/LTD
- Cognitive Impairment
- Synaptic Loss



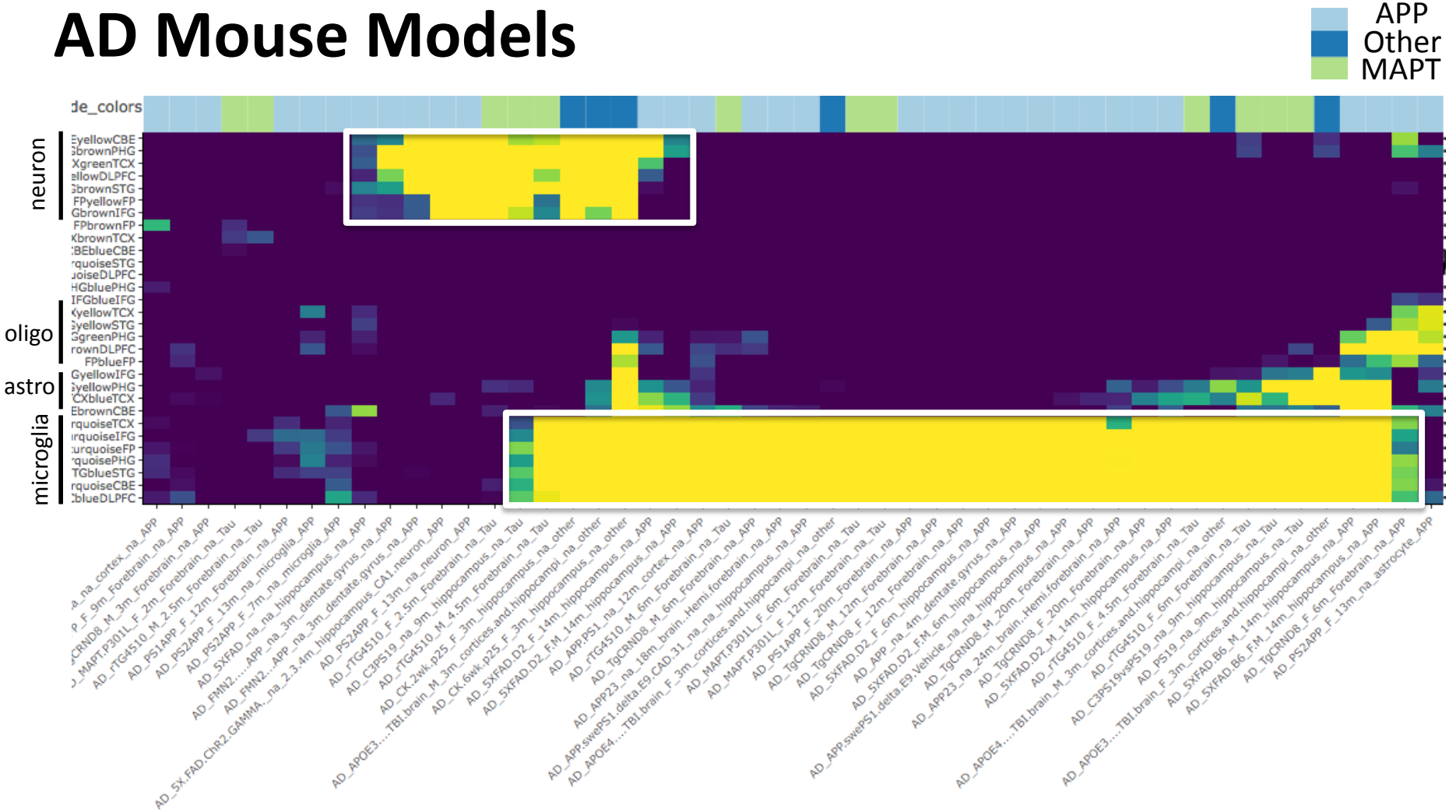
APP



MAPT

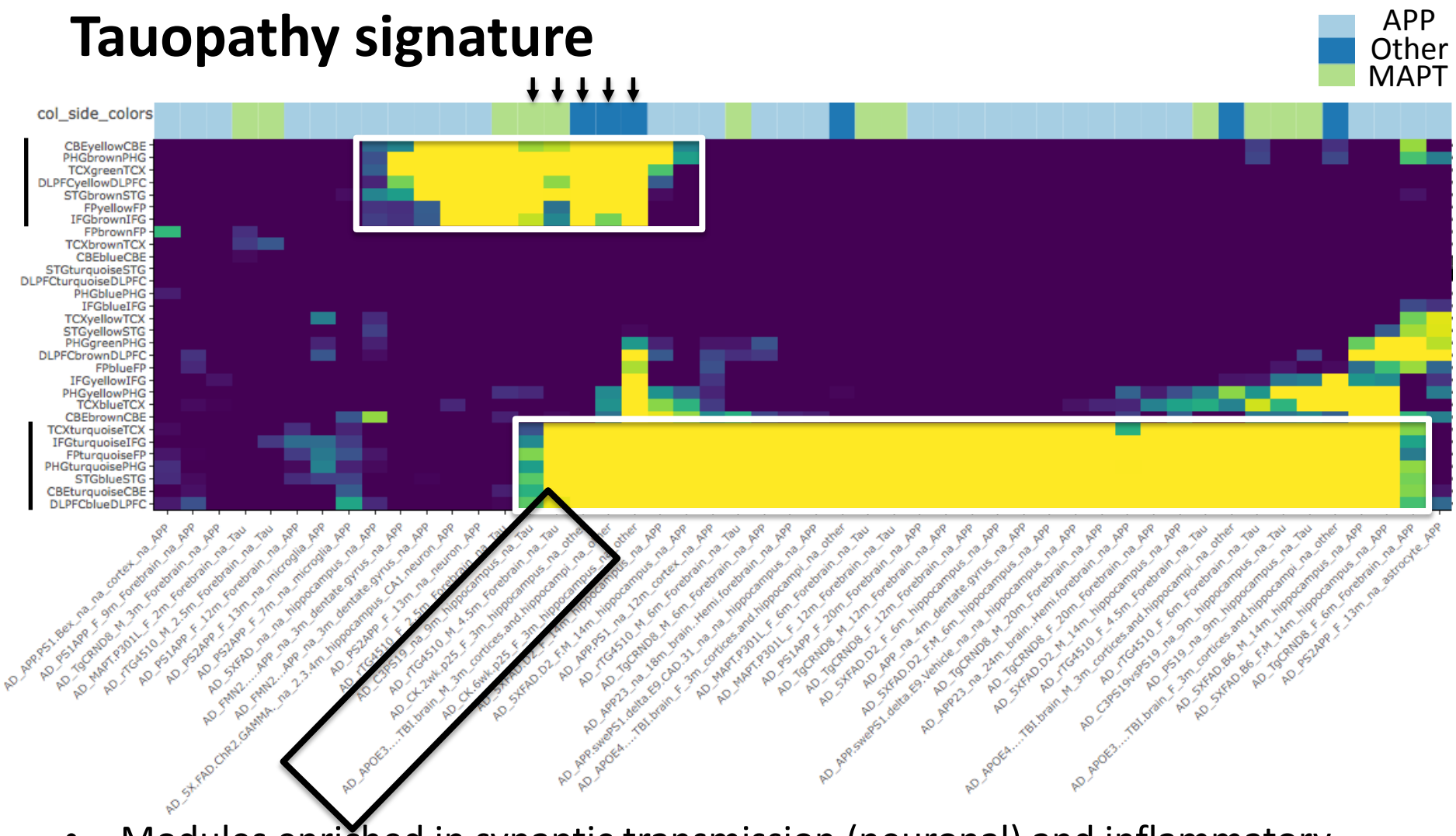


AD Mouse Models



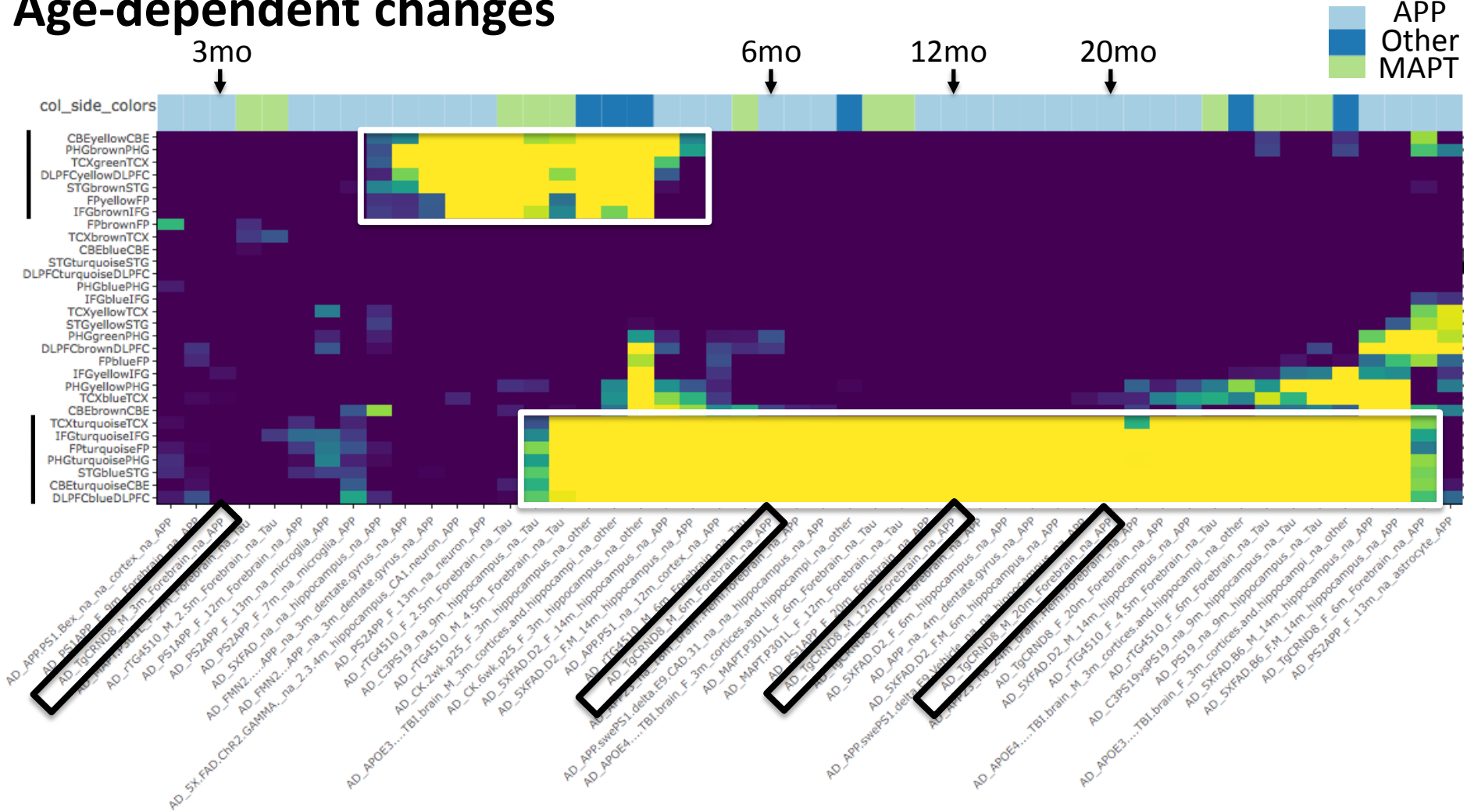
- Modules enriched in synaptic transmission (neuronal) and inflammatory response (microglial) are activated by many AD models

Tauopathy signature



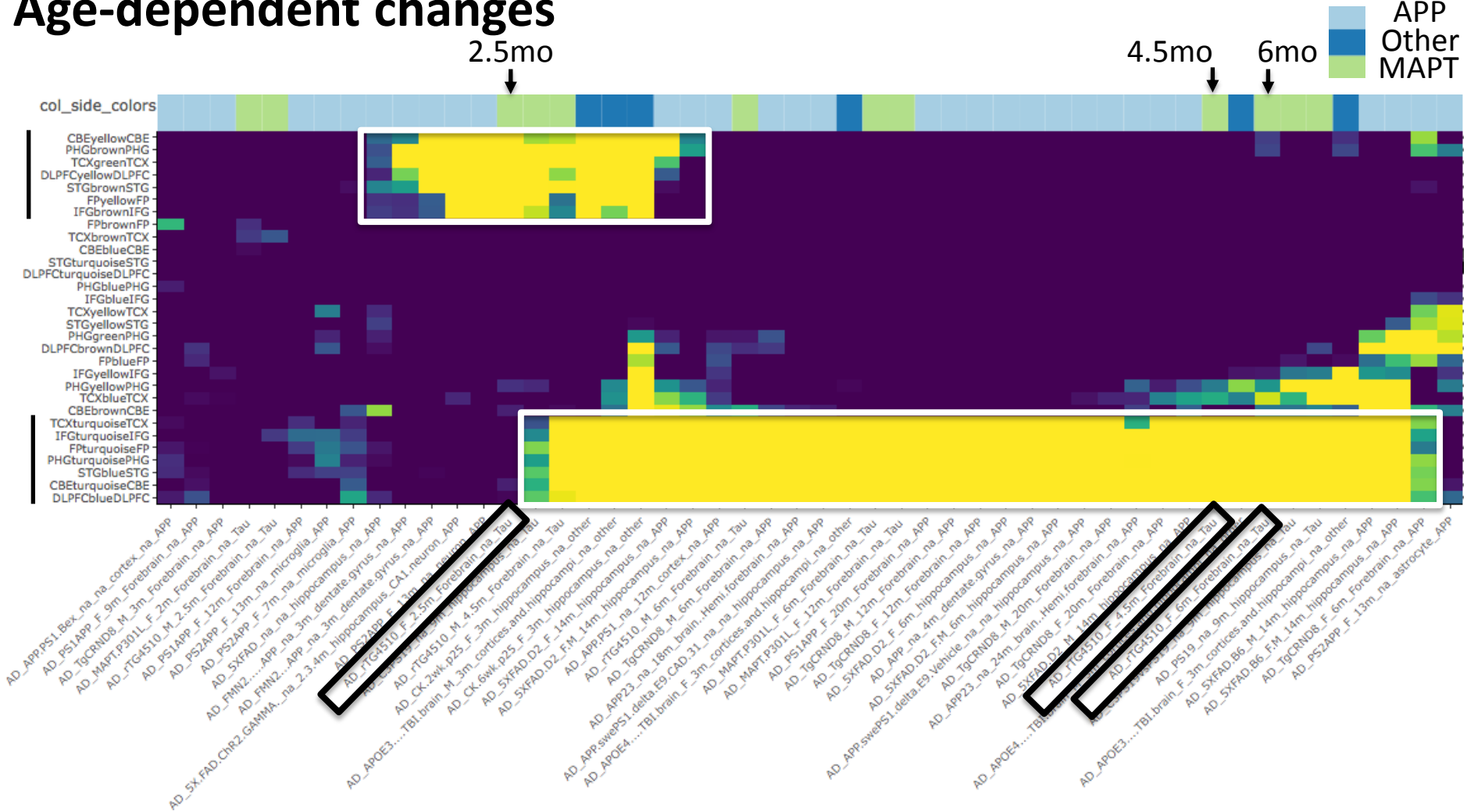
- Modules enriched in synaptic transmission (neuronal) and inflammatory response (microglial) are activated by many AD models
- These clusters are usually mutually exclusive, though many MAPT transgenics or other models with tangles (CK-P25) activate both.

Age-dependent changes

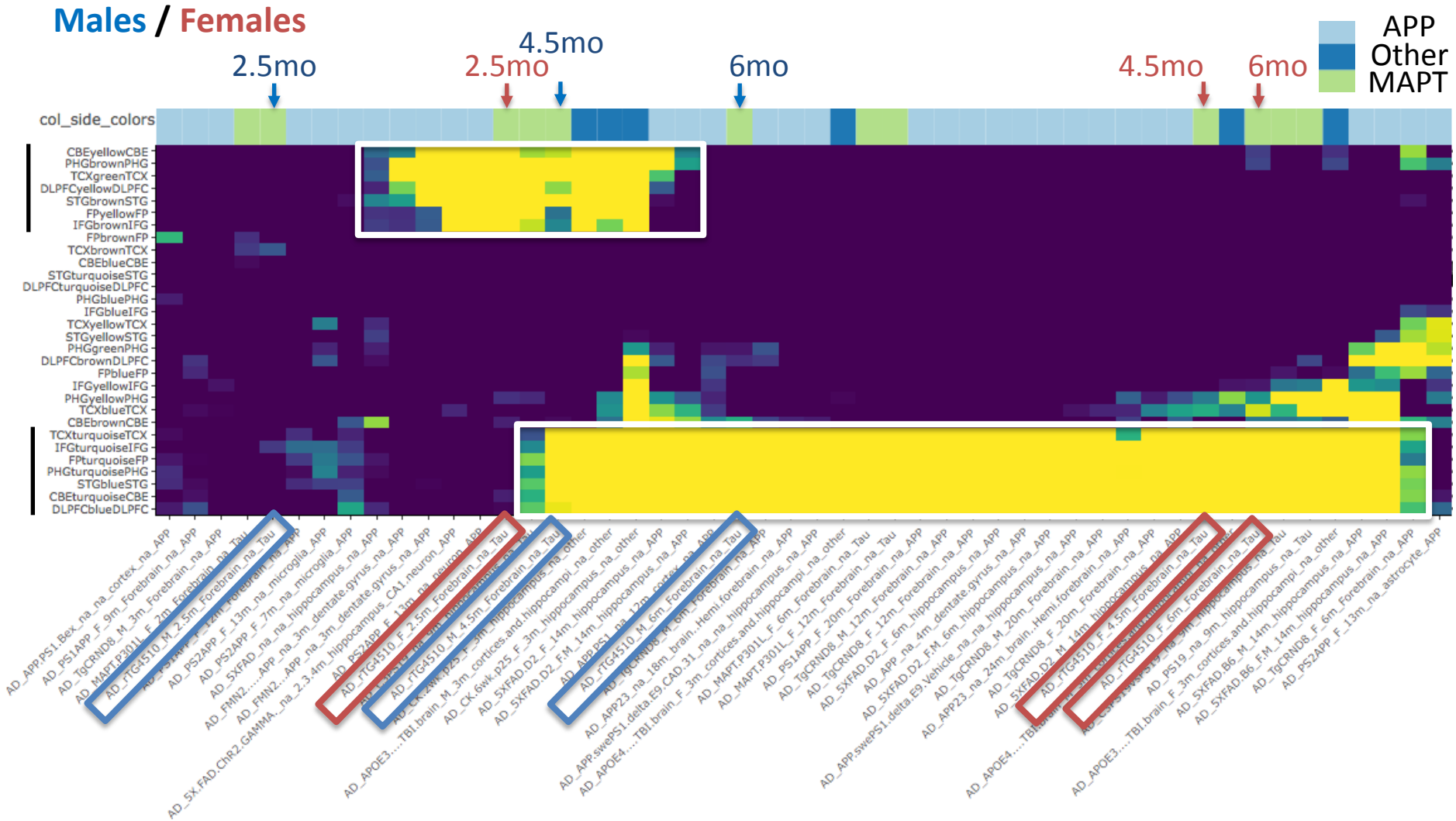


- Modules enriched in synaptic transmission (neuronal) and inflammatory response (microglial) are activated by many AD models
- In the **TgCRND8-APP** mice, sustained inflammatory signals appear at 6 months, when synaptic changes and neuronal loss are established

Age-dependent changes



- Modules enriched in synaptic transmission (neuronal) and inflammatory response (microglial) are activated by many AD models
- Sequential module activation in **rTG4510-MAPT** mice, which show neuronal loss and cognitive impairment between 4.5 and 6mo.



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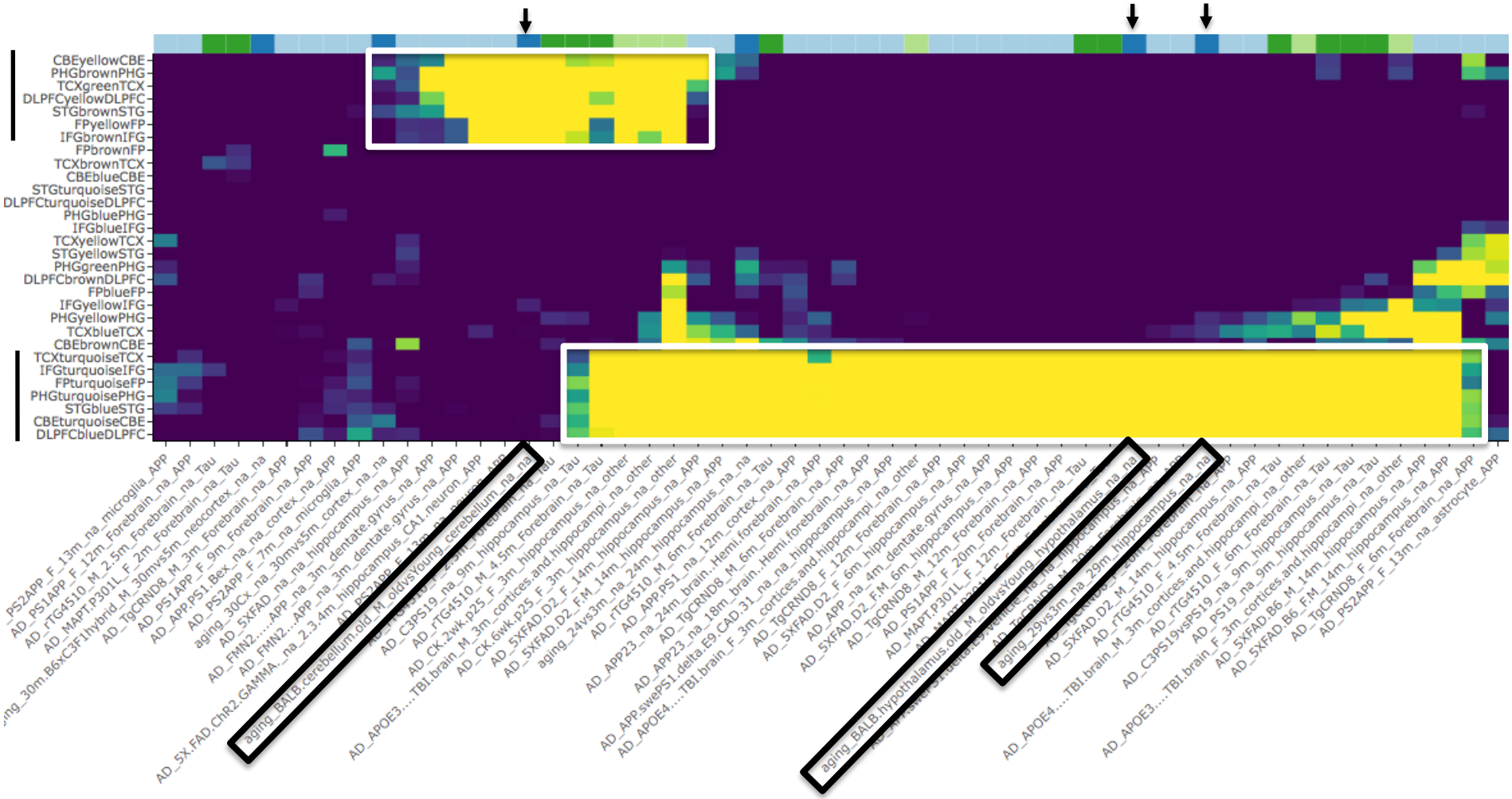
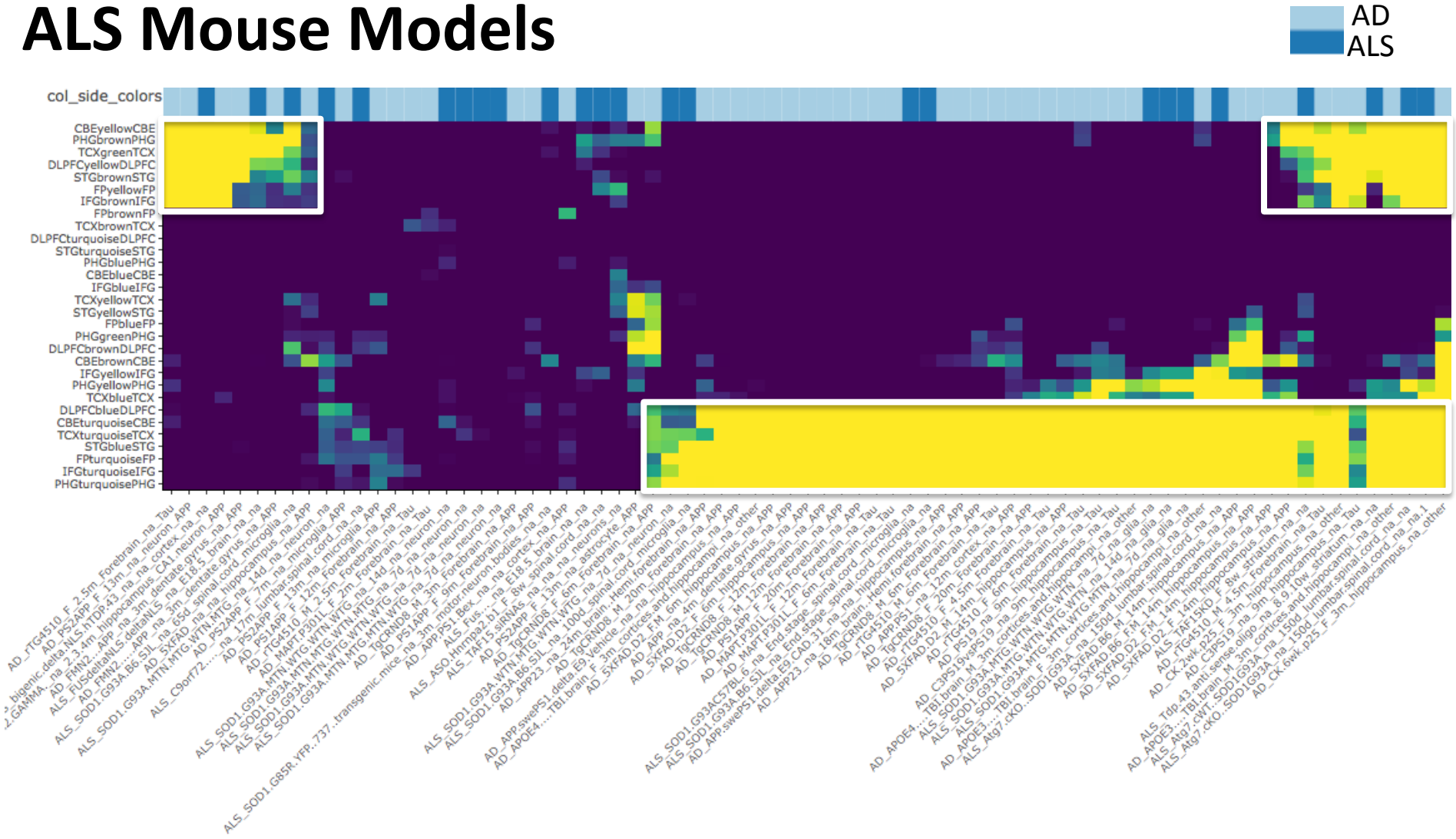
- Sequential module activation in **rTG4510-MAPT** mice, which show neuronal loss and cognitive impairment between 4.5 and 6mo.
- Gender x genotype interactions

Predominant AD signatures from mouse AD models are also seen in ”pure” aging



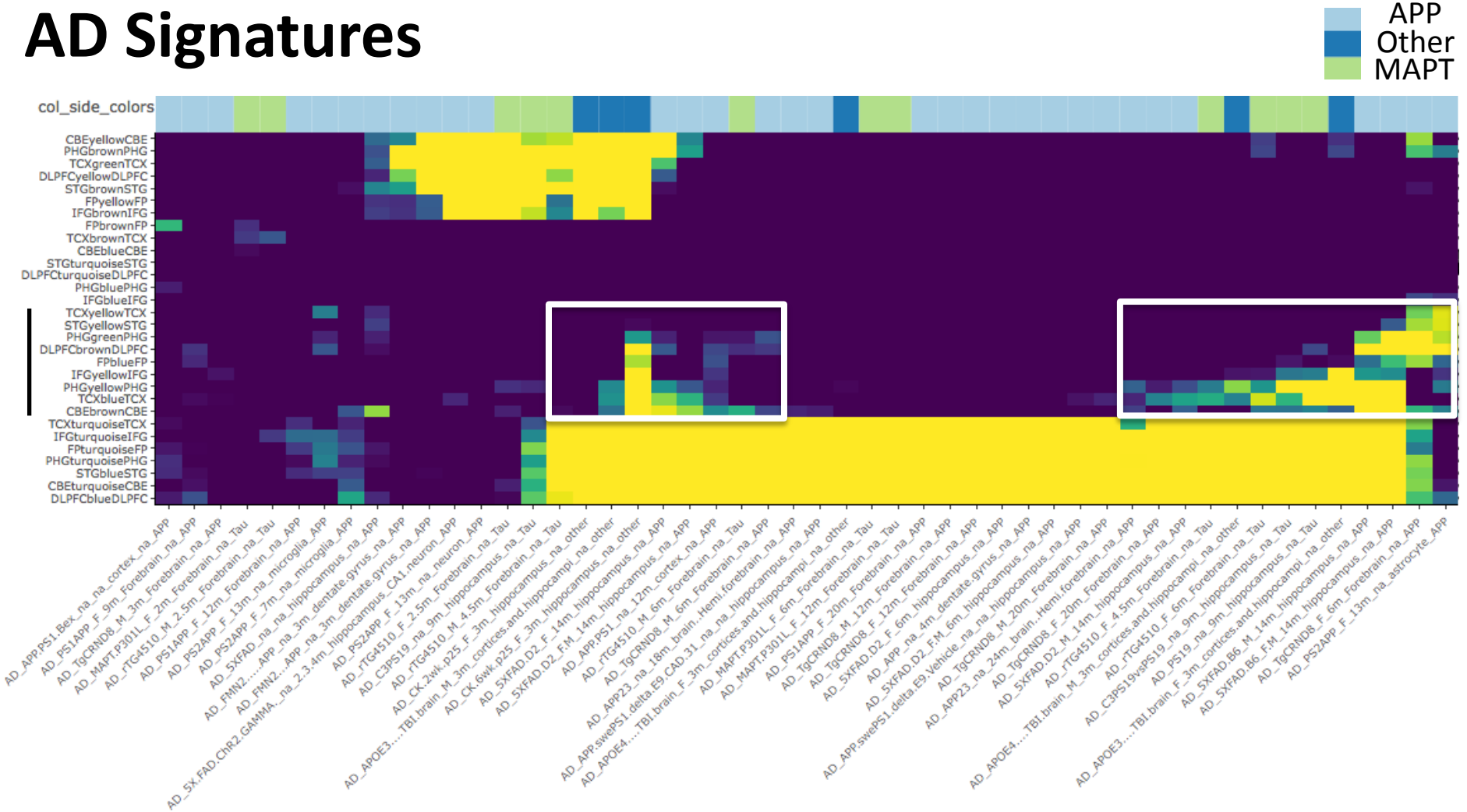
- These signatures are unlikely to be specific for AD pathologic triggers or pathophysiology. Consistent with findings from Hargis and Blalock (2016).

ALS Mouse Models



- These “aging” transcriptional signatures are activated in other mouse disease models, which co-cluster with AD patterns.
- Similar results in HD, SCA, and other models.

AD Signatures



- Several modules may be more specific for AD pathobiology, and may therefore inform AD-specific biomarkers for precision medicine approaches.

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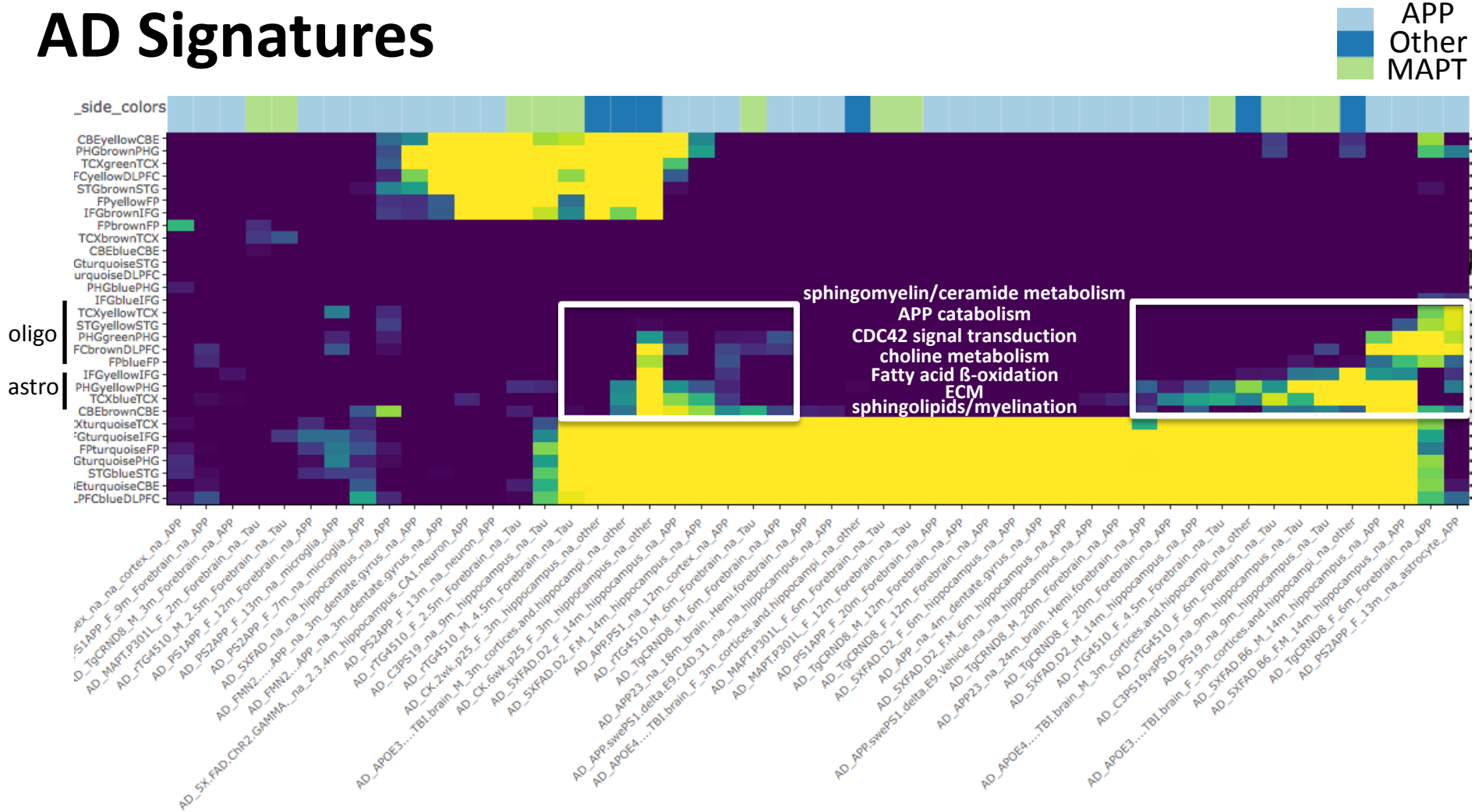

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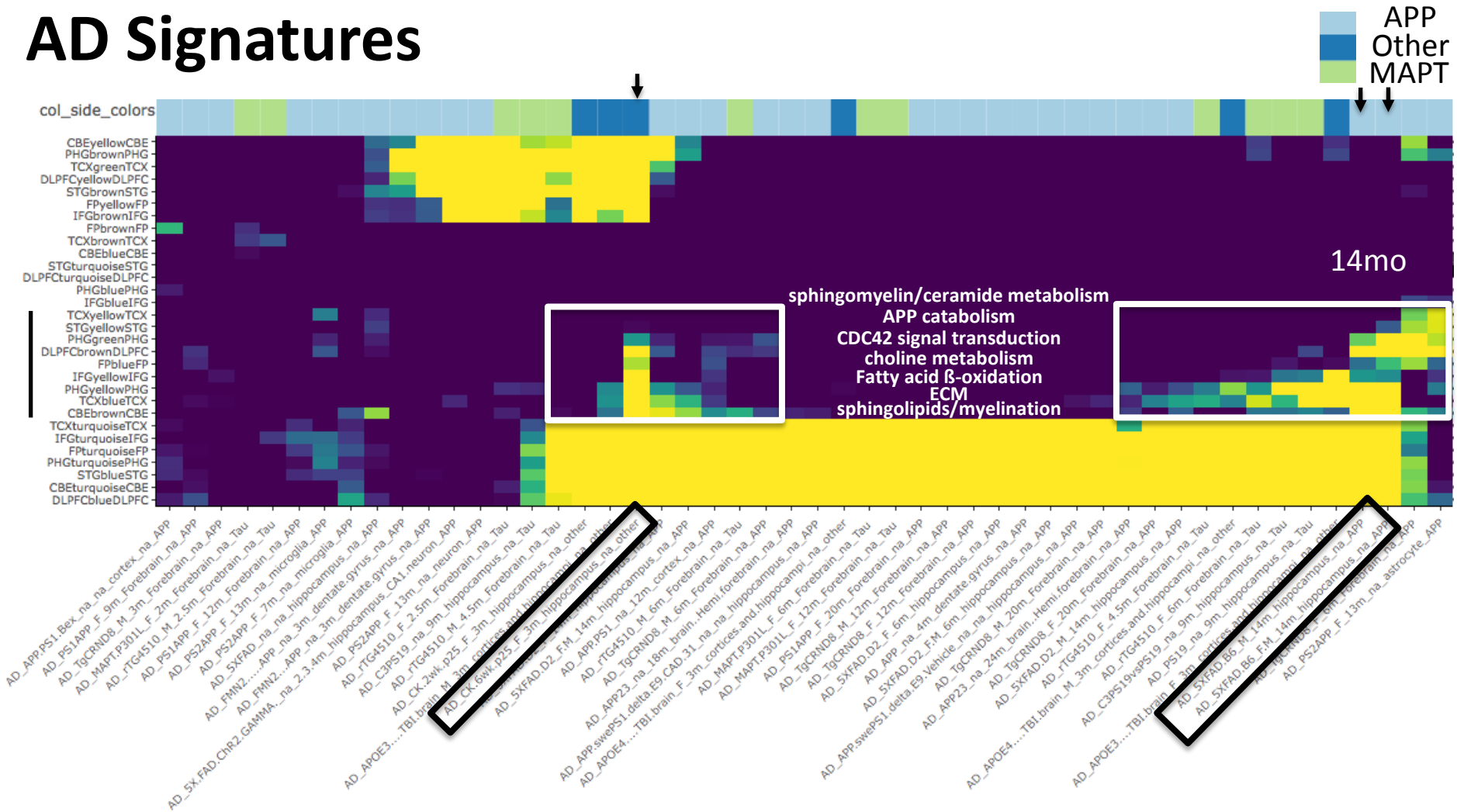
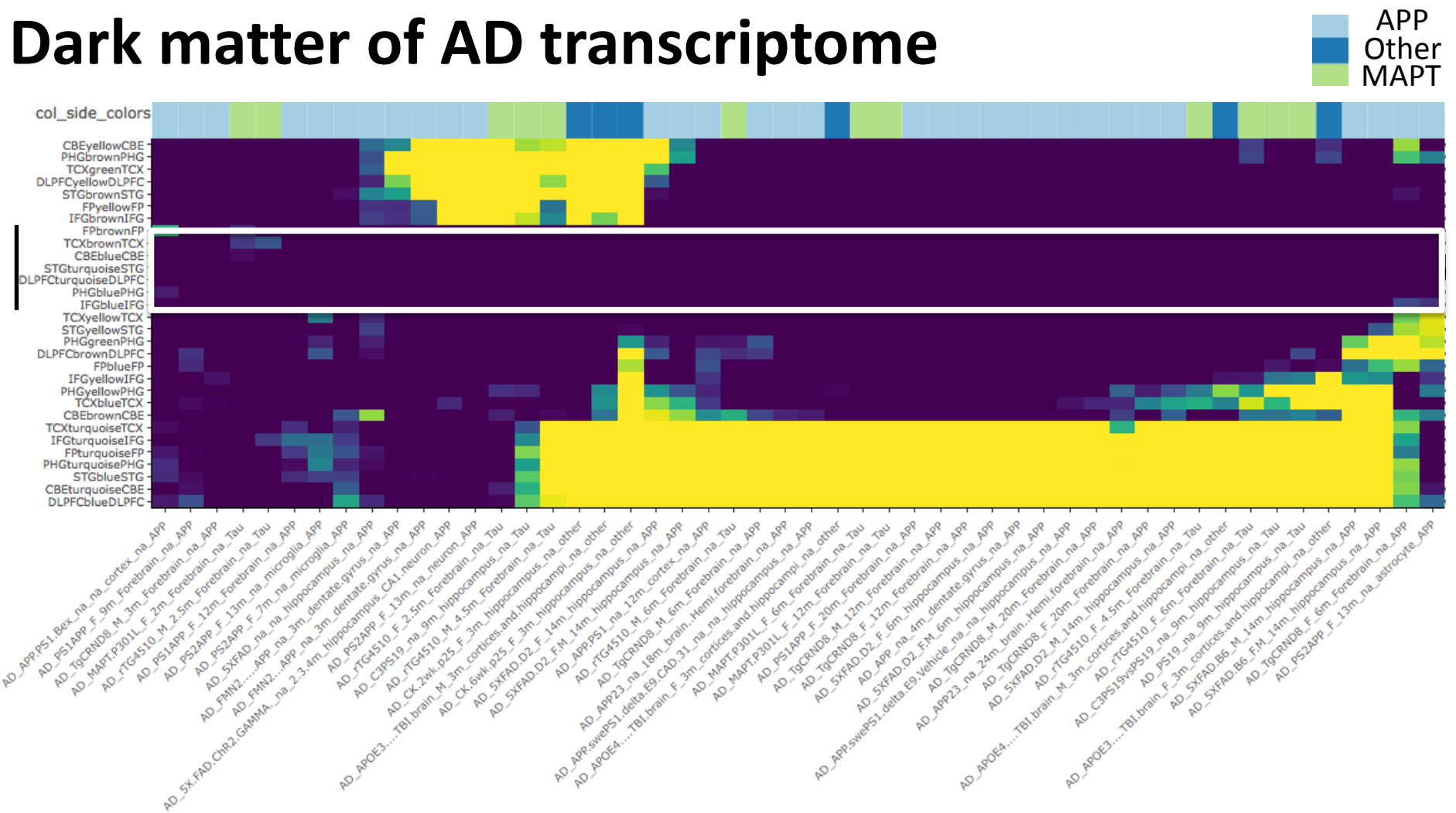


- Several modules may be more specific for AD pathobiology, and may therefore inform AD-specific biomarkers for precision medicine approaches.
- CDK-P25 and aged 5xFAD models activate these modules strongly

Dark matter of AD transcriptome



- Several modules are poorly activated in all available AD models

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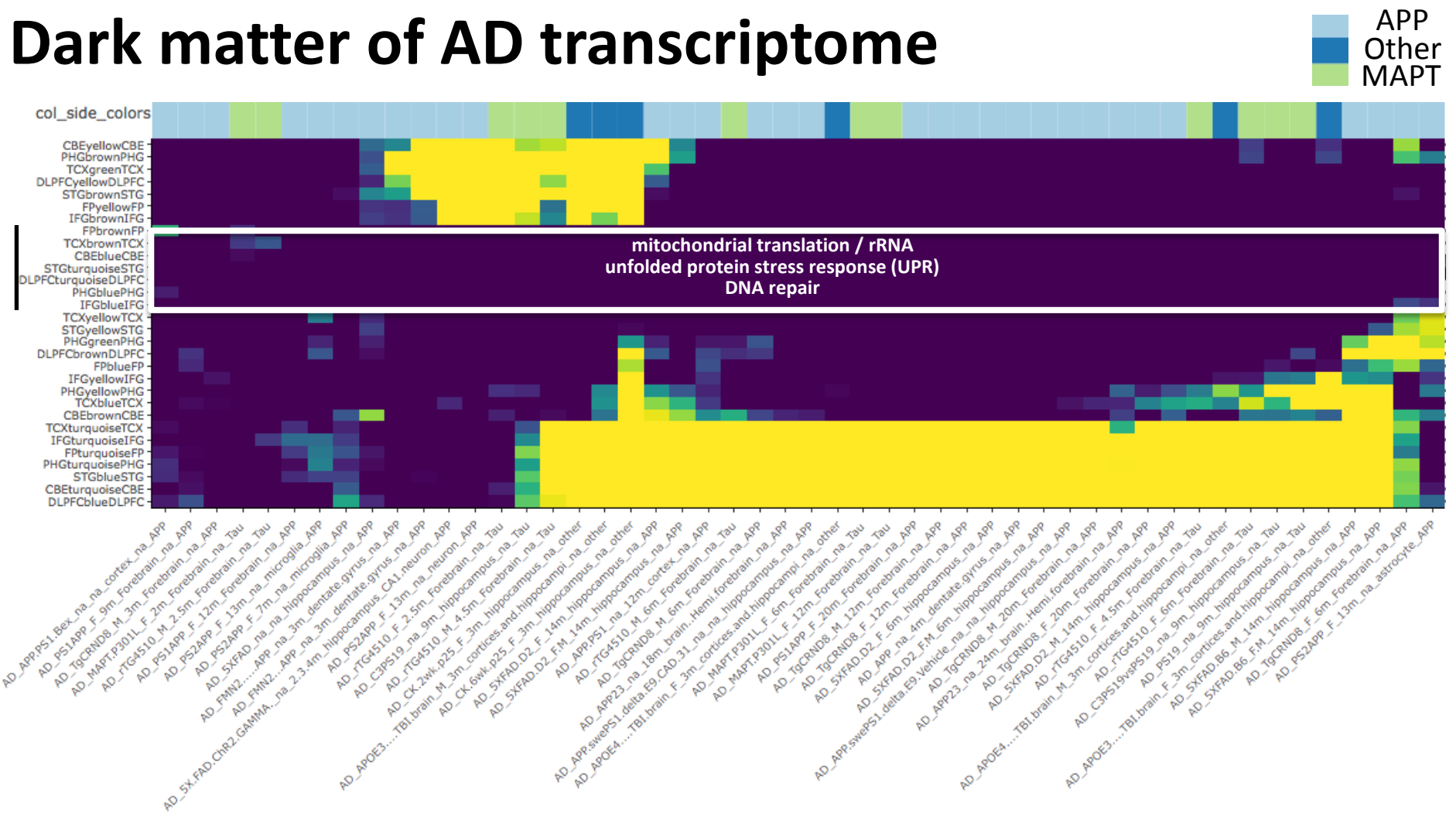

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- May highlight disease biology poorly recapitulated in existing models

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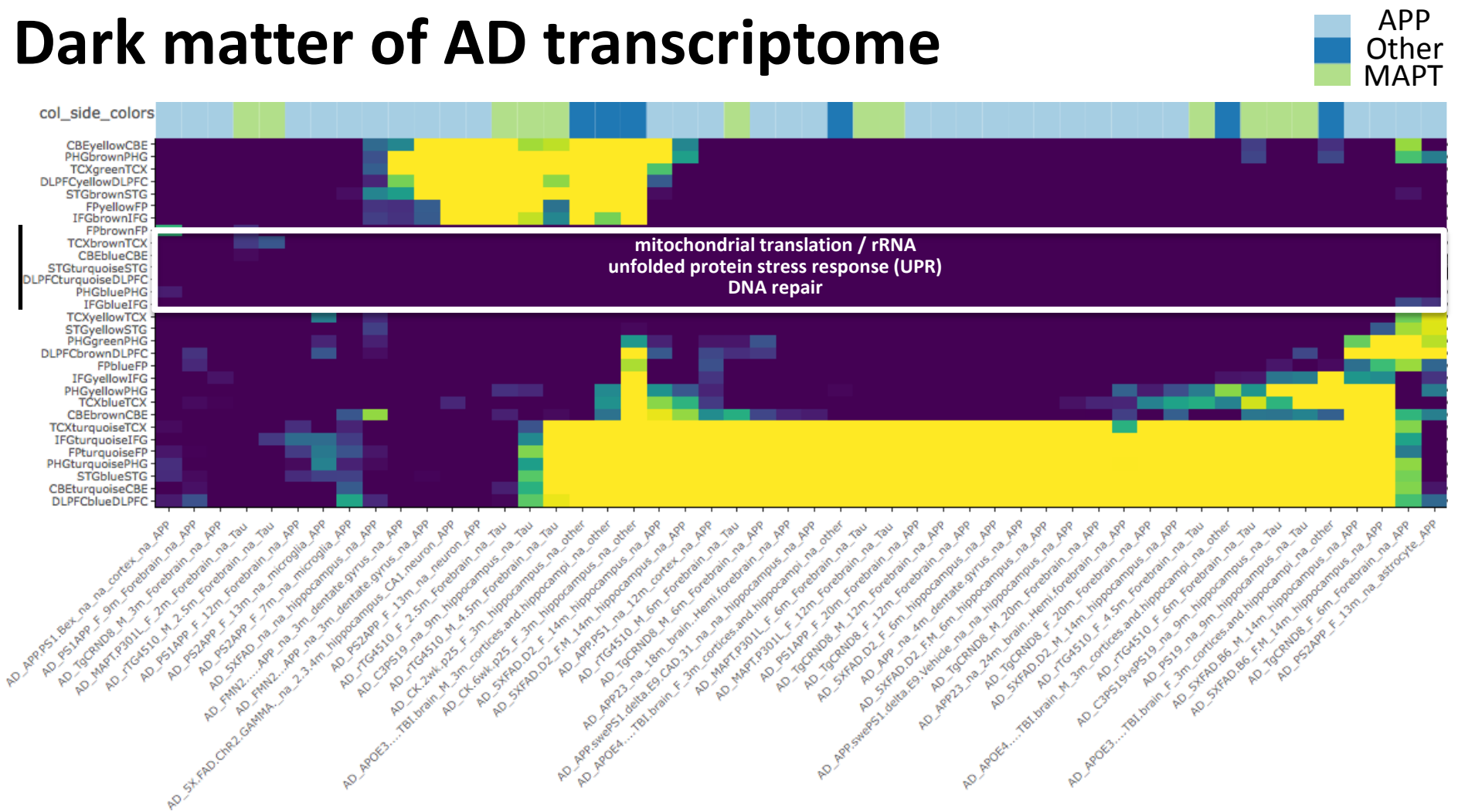

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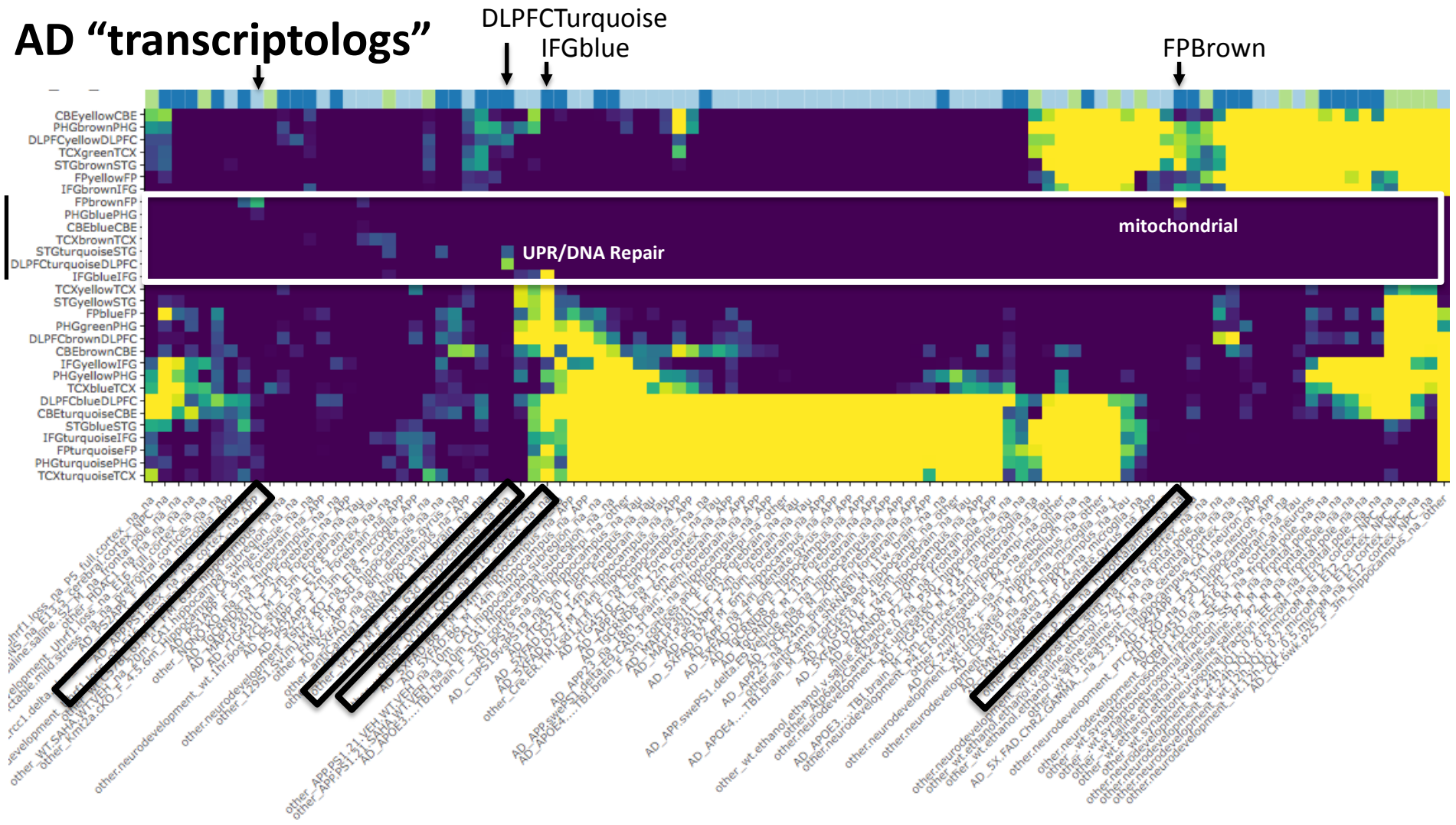
- Other mice activating these modules may identify non-obvious AD models

AD “transcriptologs”



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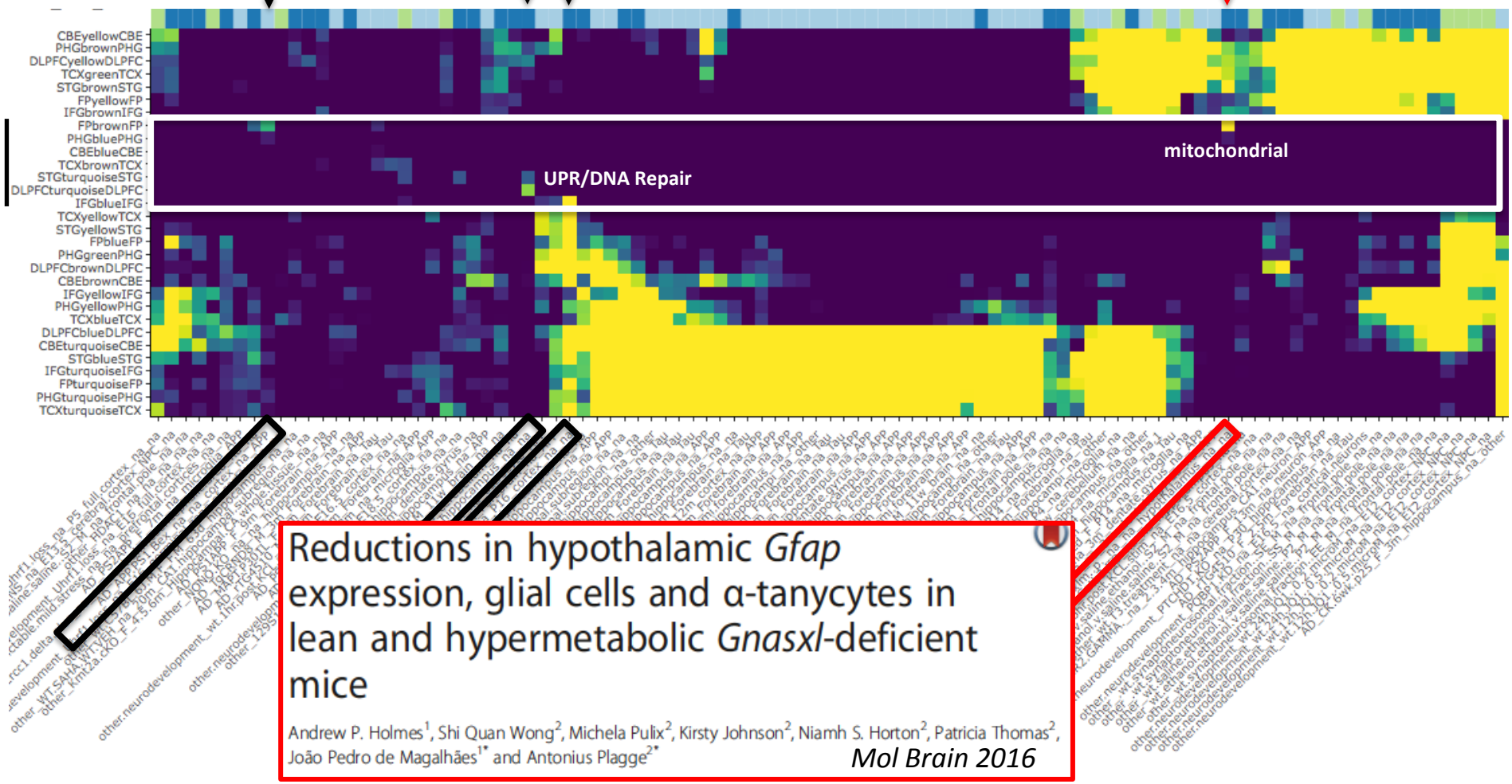

Reductions in hypothalamic *Gfap* expression, glial cells and α-tanycytes in lean and hypermetabolic *Gnasxl*-deficient mice

Andrew P. Holmes[1], Shi Quan Wong[2], Michela Pulix[2], Kirsty Johnson[2], Niamh S. Horton[2], Patricia Thomas[2], João Pedro de Magalhães[1*] and Antonius Plagge[2*]

Mol Brain 2016

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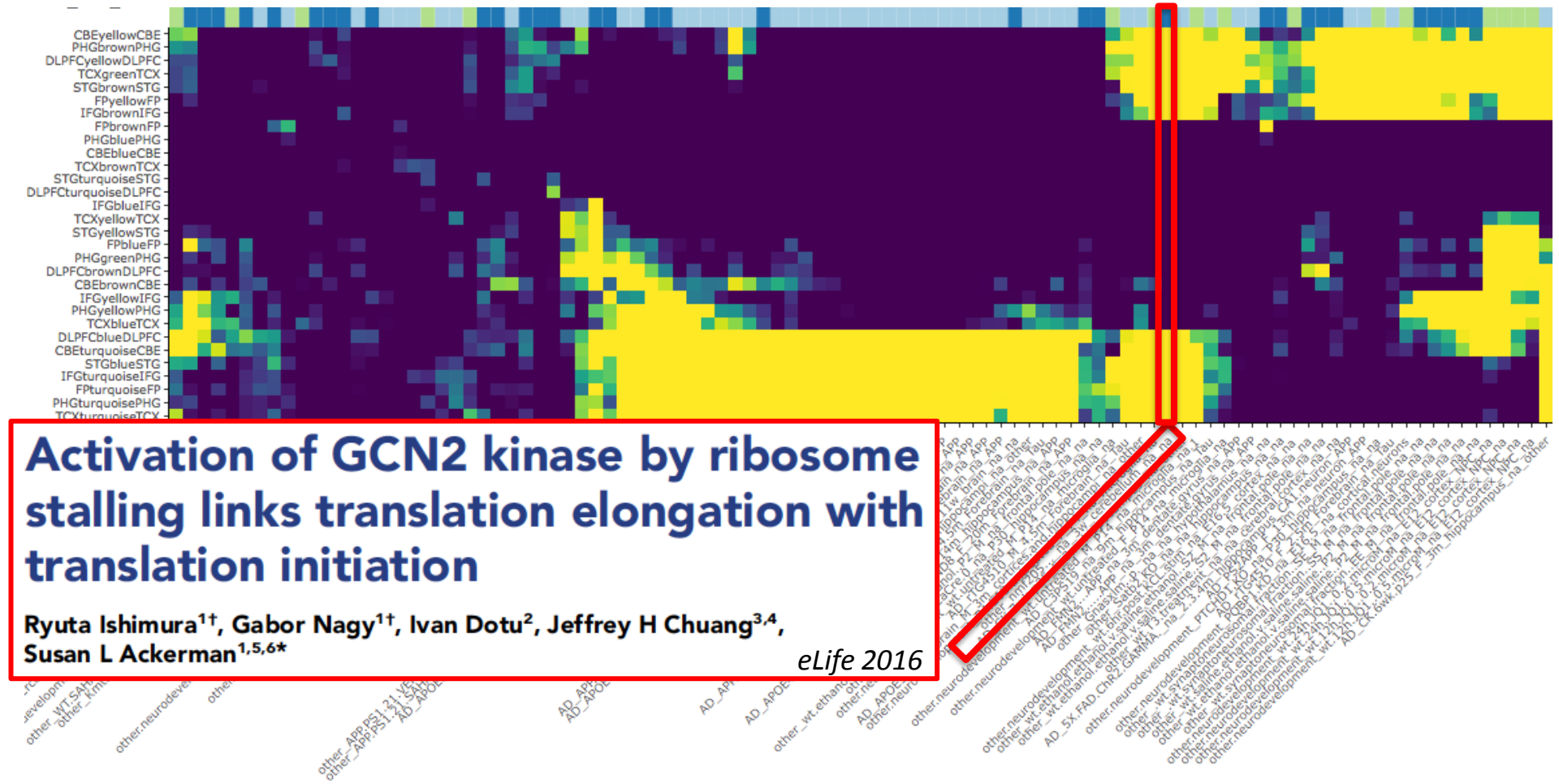

Activation of GCN2 kinase by ribosome stalling links translation elongation with translation initiation

Ryuta Ishimura[1†], Gabor Nagy[1†], Ivan Dotu[2], Jeffrey H Chuang[3,4], Susan L Ackerman[1,5,6*]

eLife 2016

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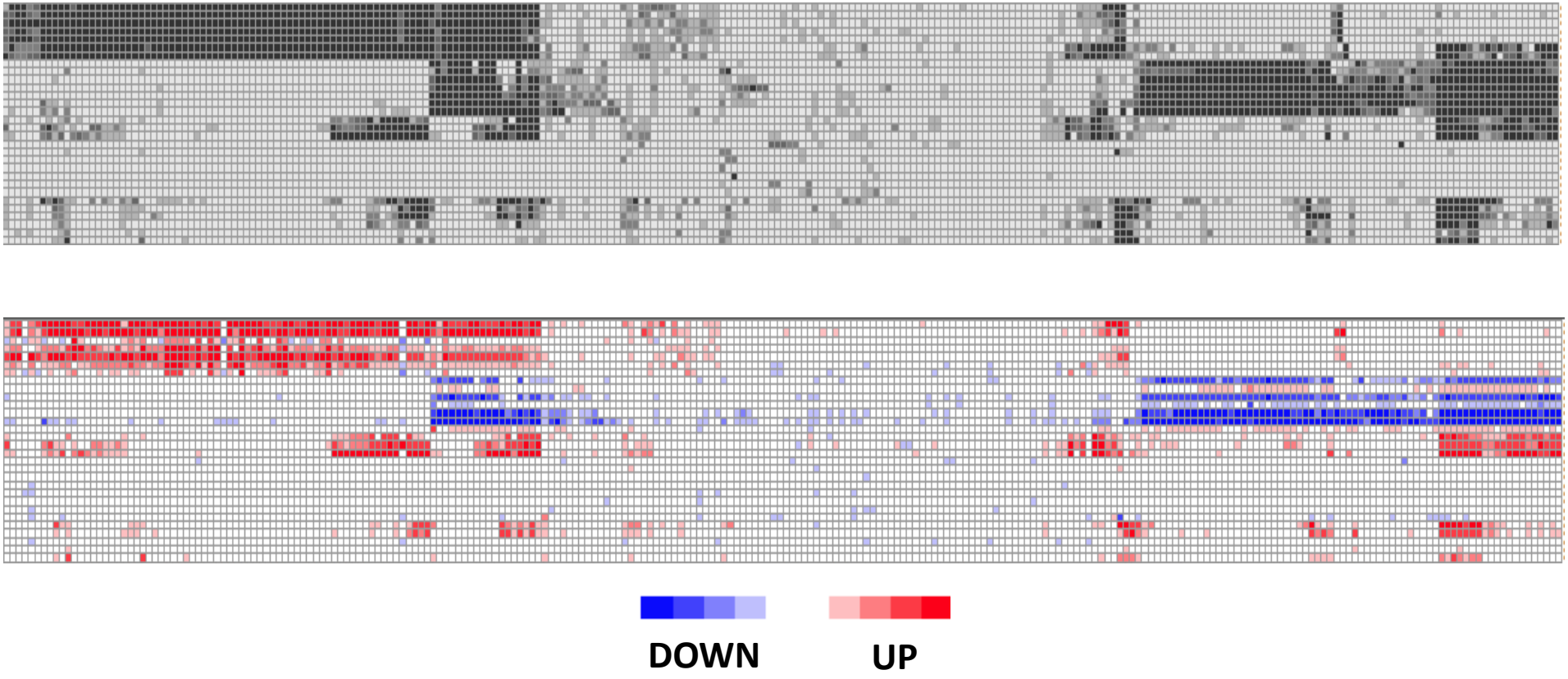
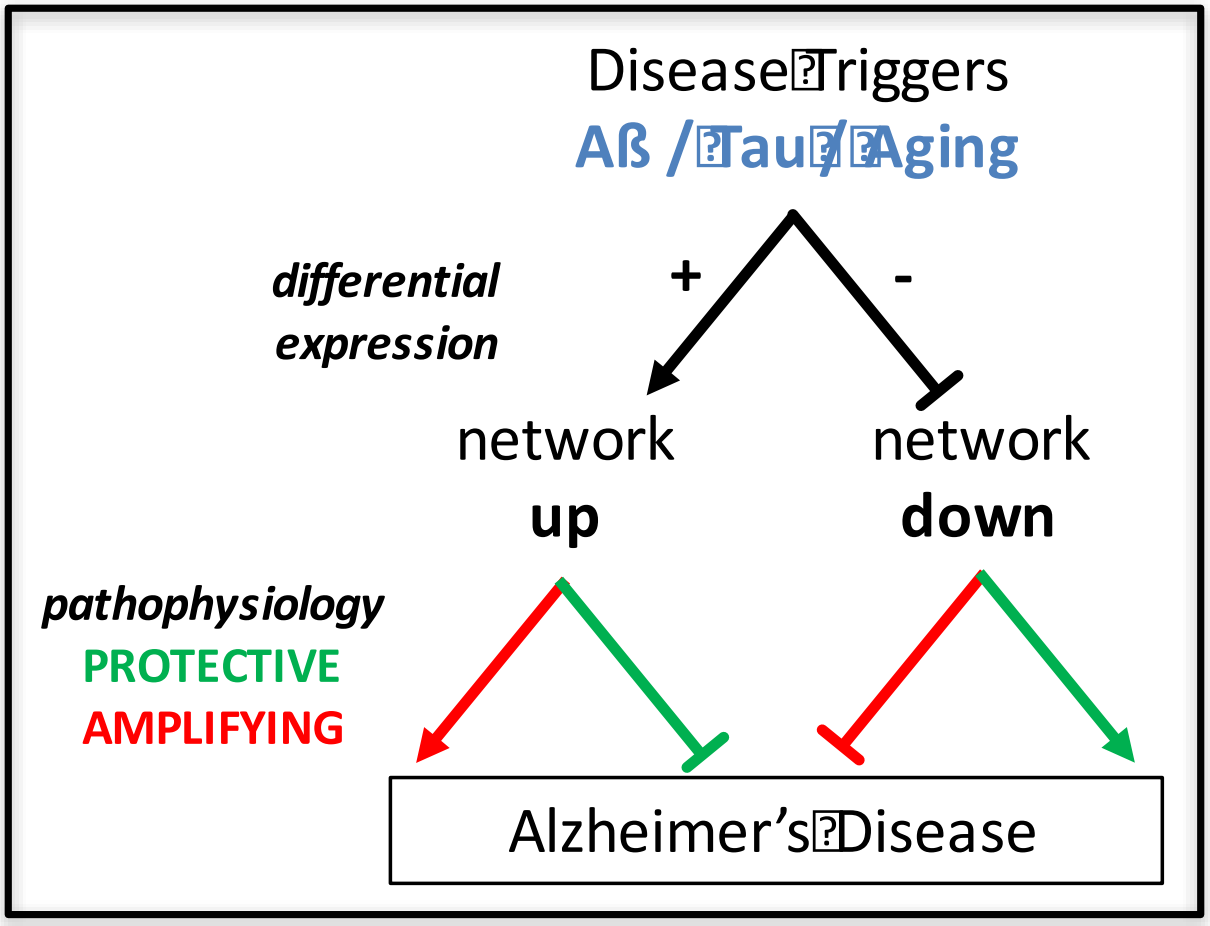
Concordant changes in human and mouse brains



Human-mouse overlaps being made available on AMP-AD Knowledge Portal

Pinpointing *Causal* Network Drivers



FIAMP-AD

Pinpointing *Causal* Network Drivers

Triggers:

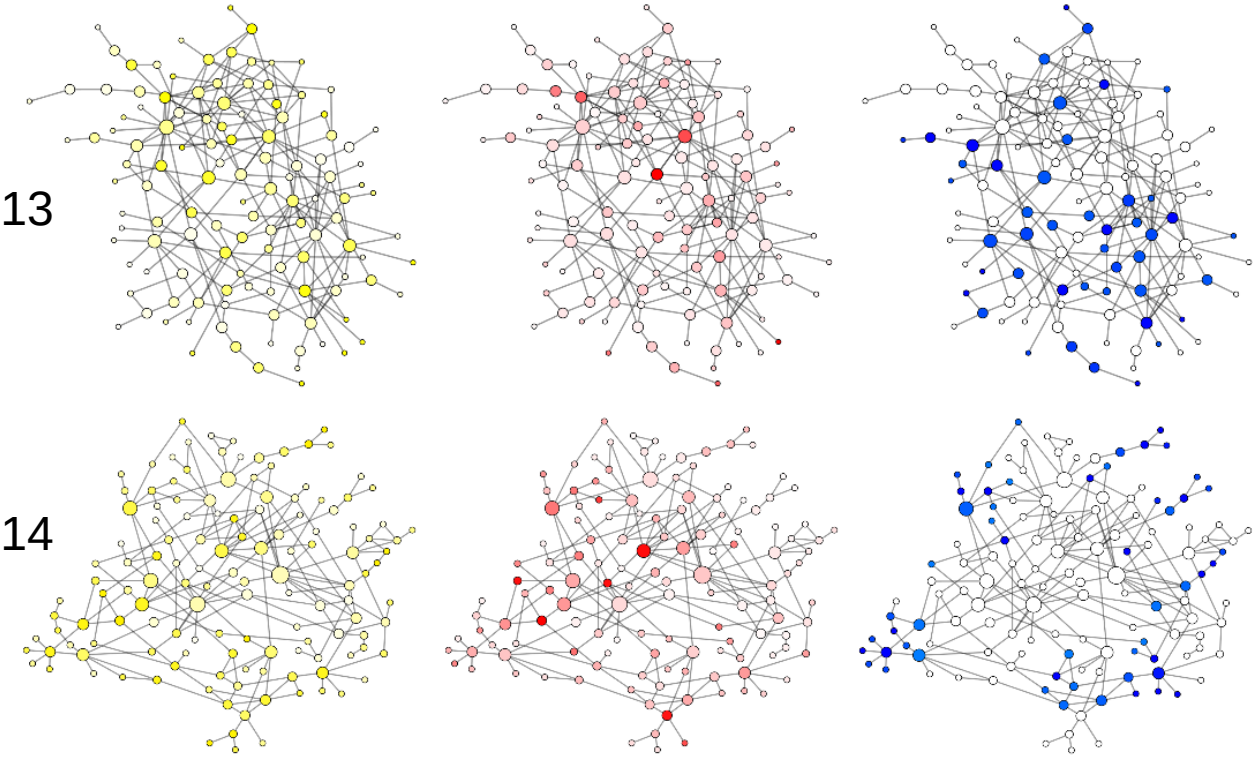
Tau

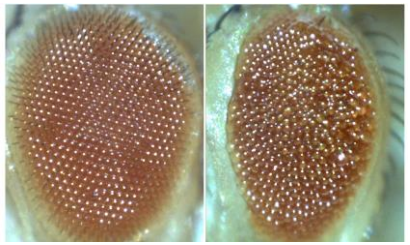
Age

Modifiers of Degeneration

Mod13

Mod14

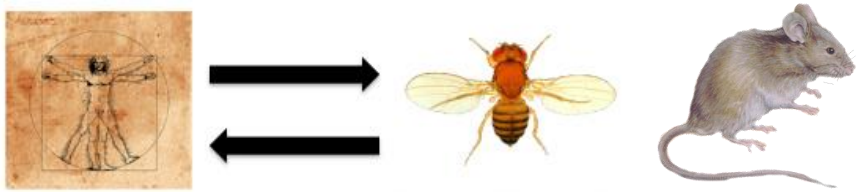




Enhancer/suppressor screens of druggable genes

RNA-seq in 1-, 10-, 20-day fly brains

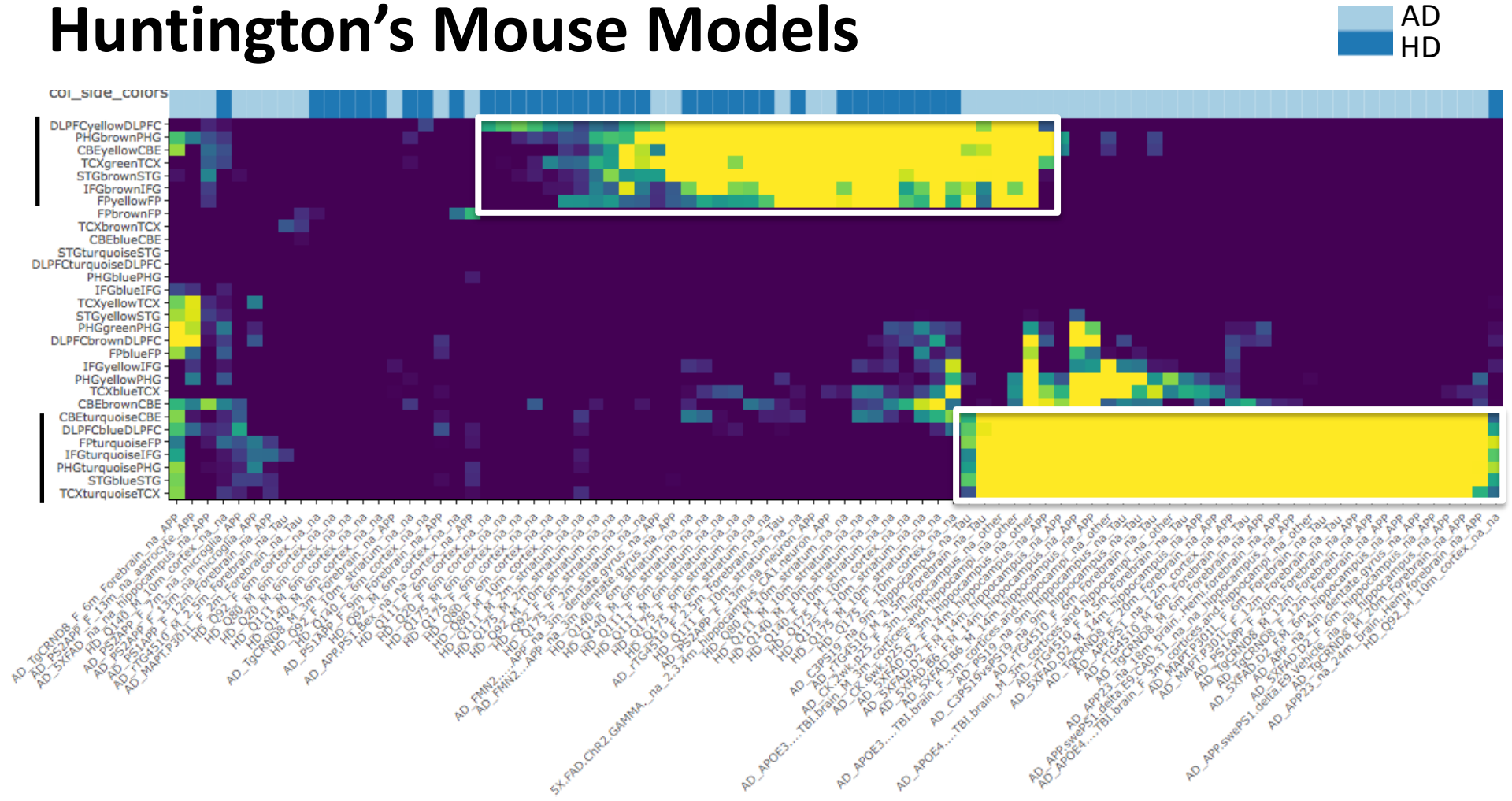
Conclusions



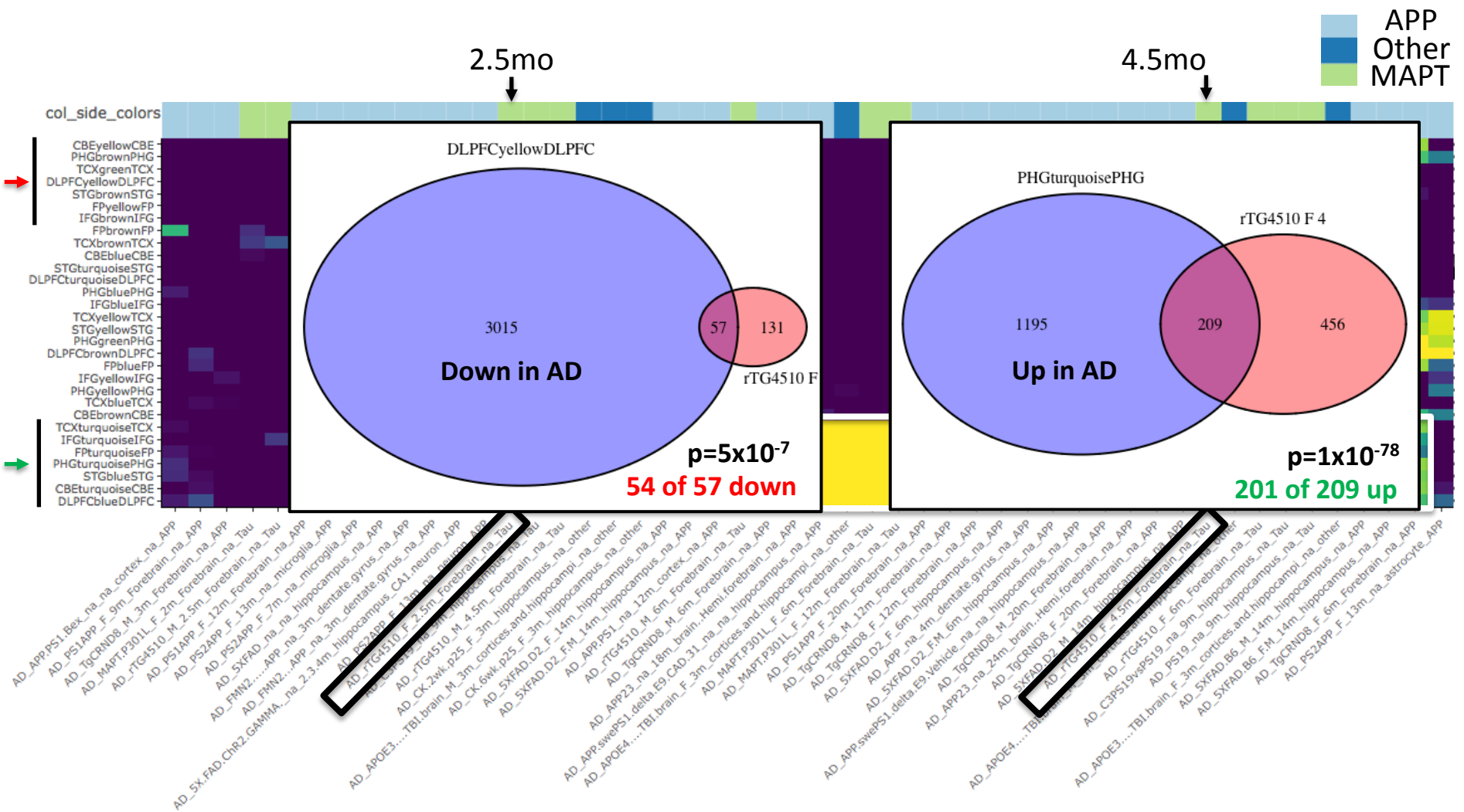
- Existing AD mouse models may predominantly activate brain responses that are non-specific, overlapping with aging and other disease models.
- Certain expression signatures may differentiate Tau vs. APP responses
- The cross-species approach highlights dynamic age- and sex-dependent brain expression changes that are potential markers for AD progression.
- Using transcriptomic signatures as endophenotypes, we can identify many non-obvious AD models, including some that activate modules not seen in existing MAPT/APP models.
- *Drosophila* models may accelerate network fine-mapping to pinpoint causal drivers.

Extra Slides

Huntington's Mouse Models



- These "aging" transcriptional signatures are activated in other mouse disease models, which co-cluster with AD patterns.
- HD models activate neuronal, but not microglial modules.



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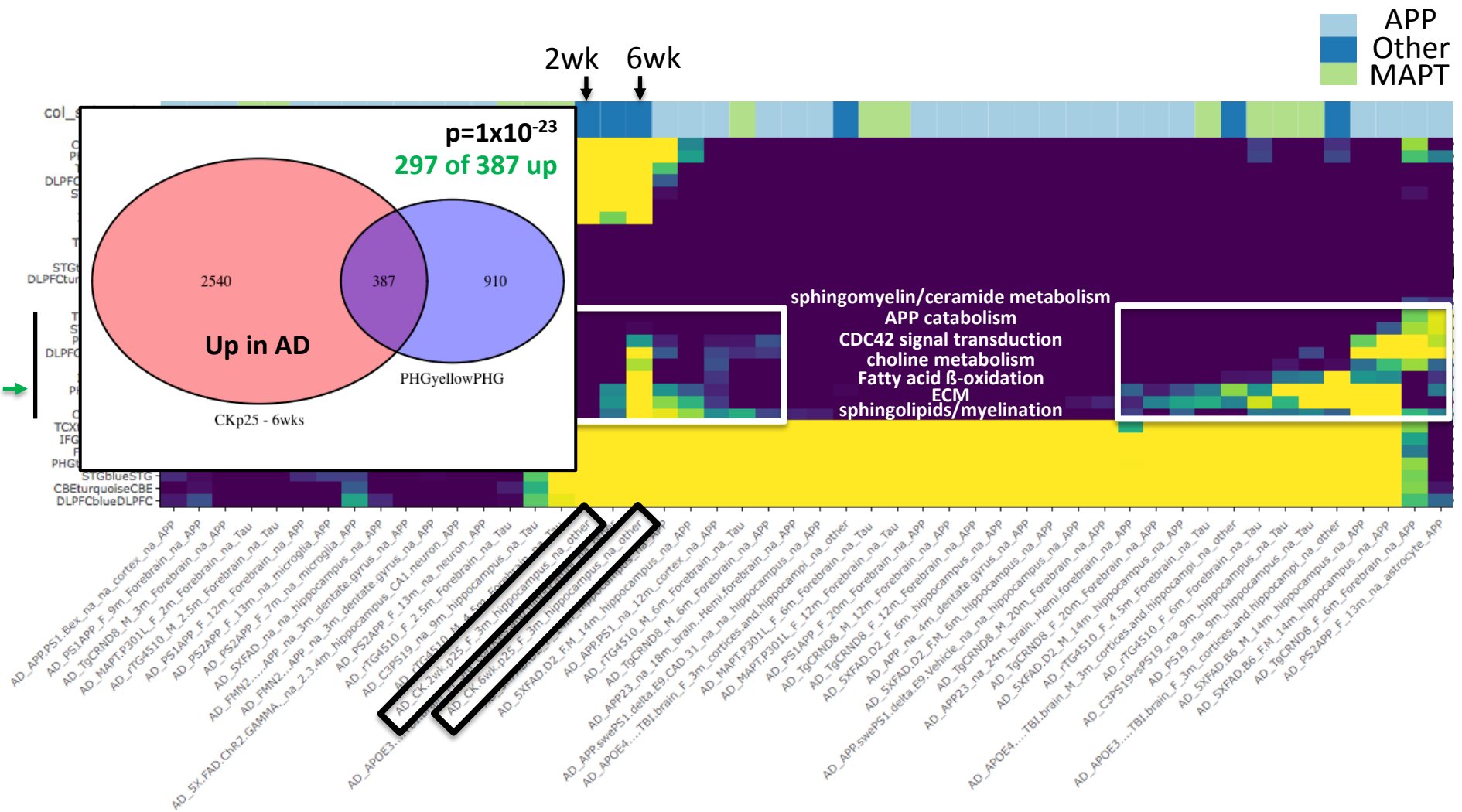
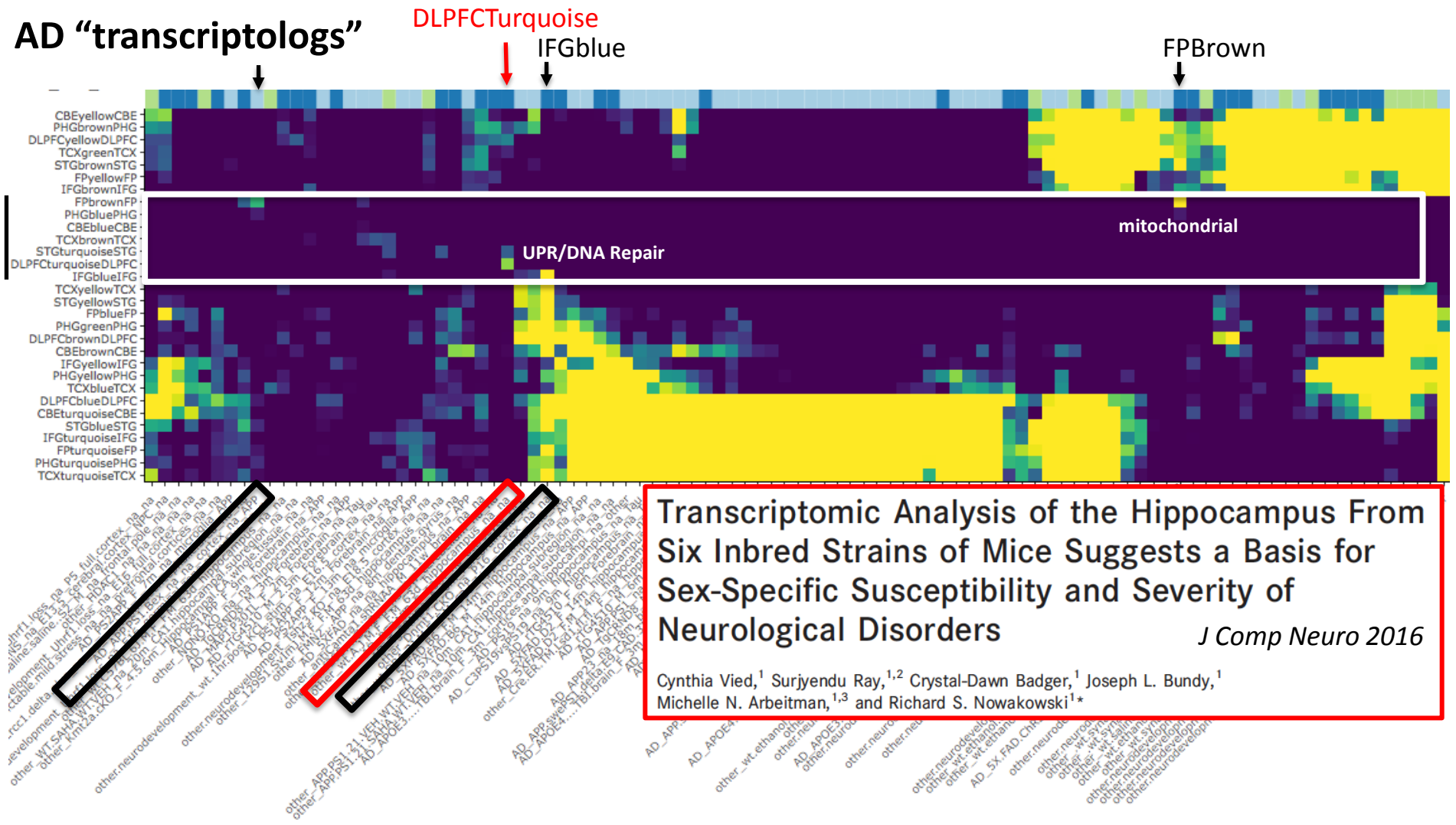


- Several weakly or variably activated modules may be more specific for AD pathobiology.
- CDK-P25 models strongly activate this group, with rapid time course between 2 and 6wks.

AD “transcriptologs”



Transcriptomic Analysis of the Hippocampus From Six Inbred Strains of Mice Suggests a Basis for Sex-Specific Susceptibility and Severity of Neurological Disorders

J Comp Neuro 2016

Cynthia Vied,[1] Surjyendu Ray,[1,2] Crystal-Dawn Badger,[1] Joseph L. Bundy,[1] Michelle N. Arbeitman,[1,3] and Richard S. Nowakowski[1]*

- Several modules are poorly activated in all available AD models
- These modules identify key disease biology not recapitulated in models
- Other mice activating these modules may identify non-obvious AD models
- Non-obvious models for study of AD dark matter

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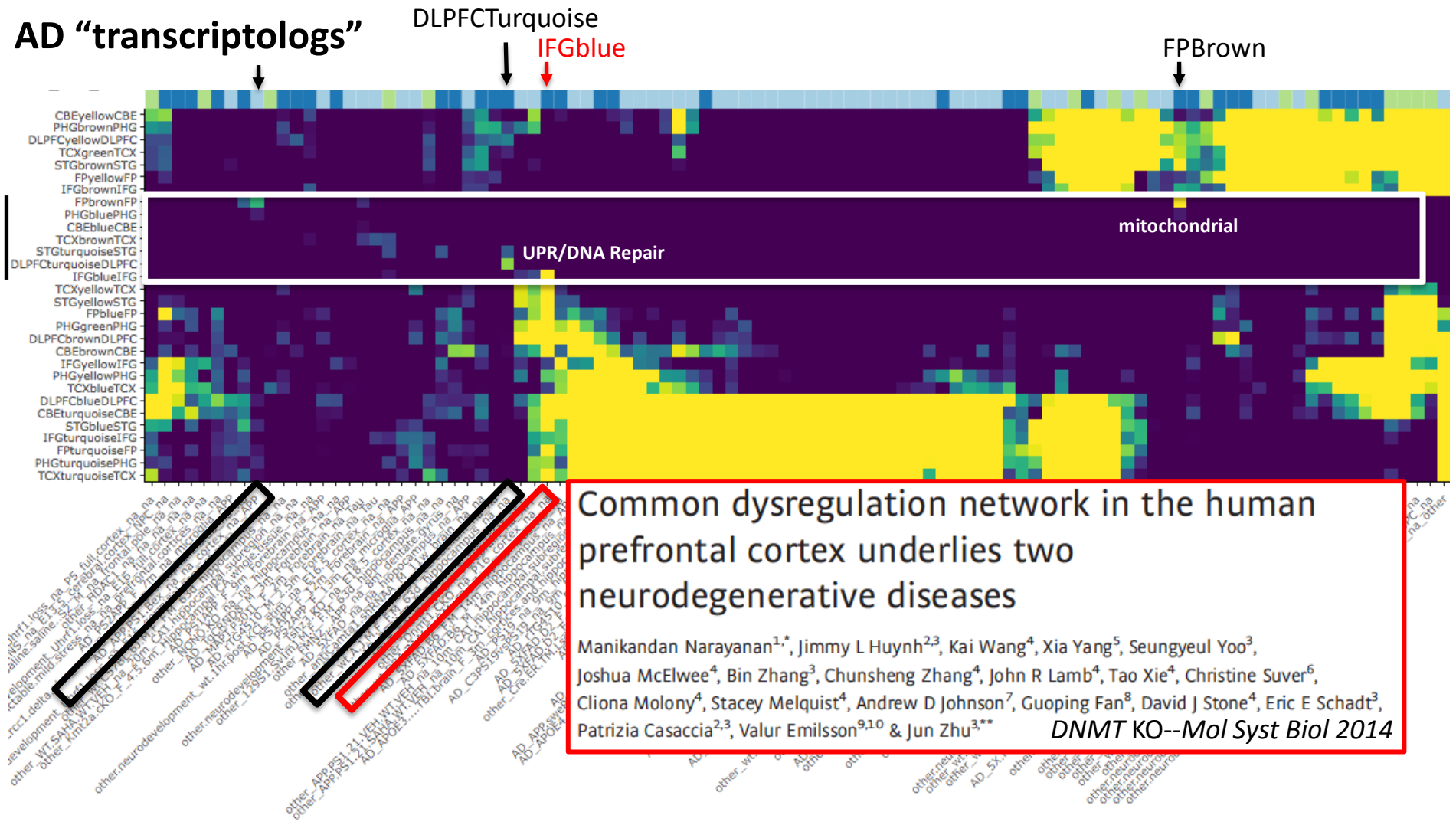

Common dysregulation network in the human prefrontal cortex underlies two neurodegenerative diseases

Manikandan Narayanan[1,*], Jimmy L Huynh[2,3], Kai Wang[4], Xia Yang[5], Seungyeul Yoo[3], Joshua McElwee[4], Bin Zhang[3], Chunsheng Zhang[4], John R Lamb[4], Tao Xie[4], Christine Suver[6], Cliona Molony[4], Stacey Melquist[4], Andrew D Johnson[7], Guoping Fan[8], David J Stone[4], Eric E Schadt[3], Patrizia Casaccia[2,3], Valur Emilsson[9,10] & Jun Zhu[3,**]

DNMT KO--*Mol Syst Biol 2014*

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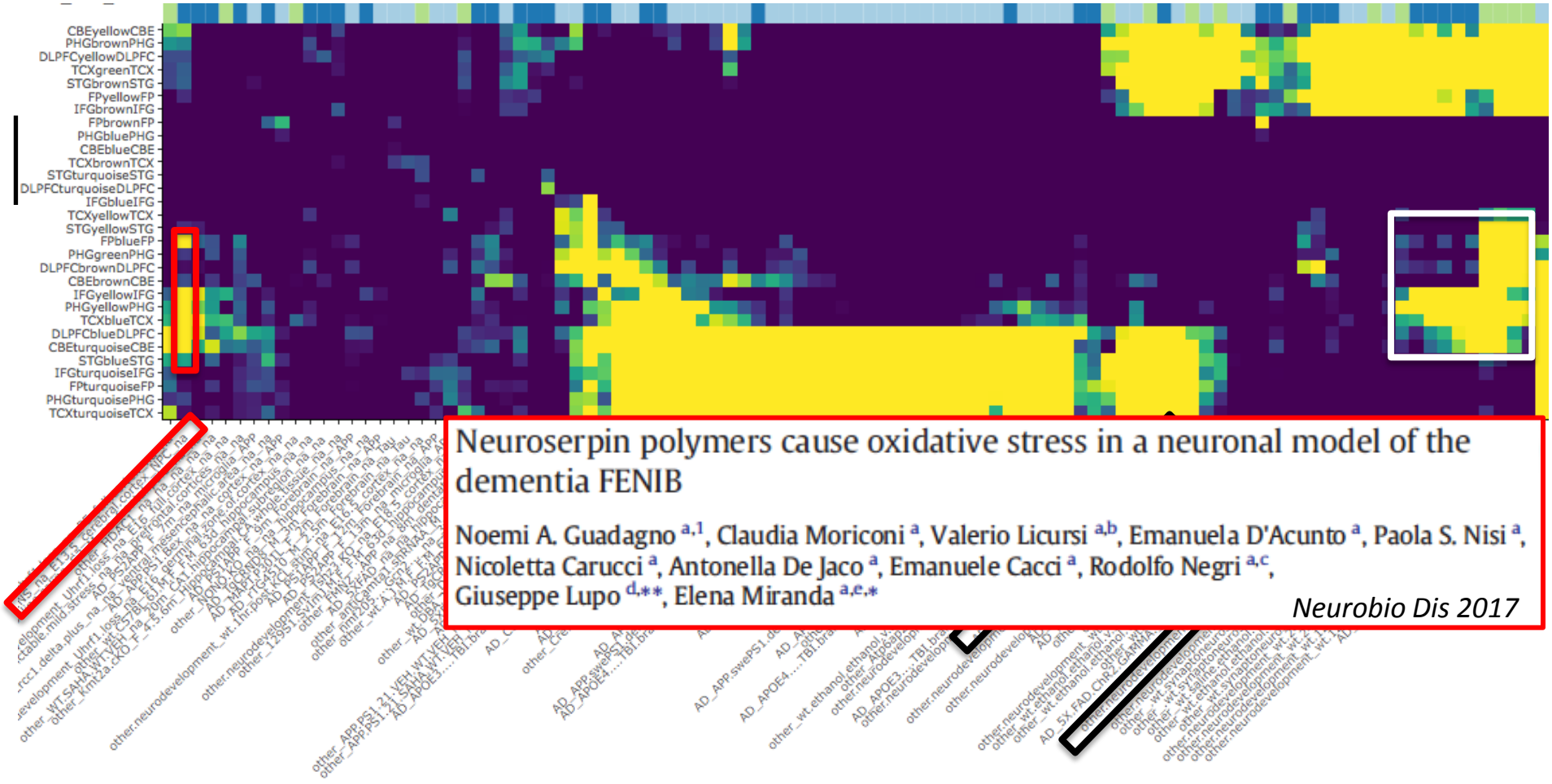

Neuroserpin polymers cause oxidative stress in a neuronal model of the dementia FENIB

Noemi A. Guadagno [a,1], Claudia Moriconi [a], Valerio Licursi [a,b], Emanuela D'Acunto [a], Paola S. Nisi [a], Nicoletta Carucci [a], Antonella De Jaco [a], Emanuele Cacci [a], Rodolfo Negri [a,c], Giuseppe Lupo [d,**], Elena Miranda [a,e,*]

Neurobio Dis 2017

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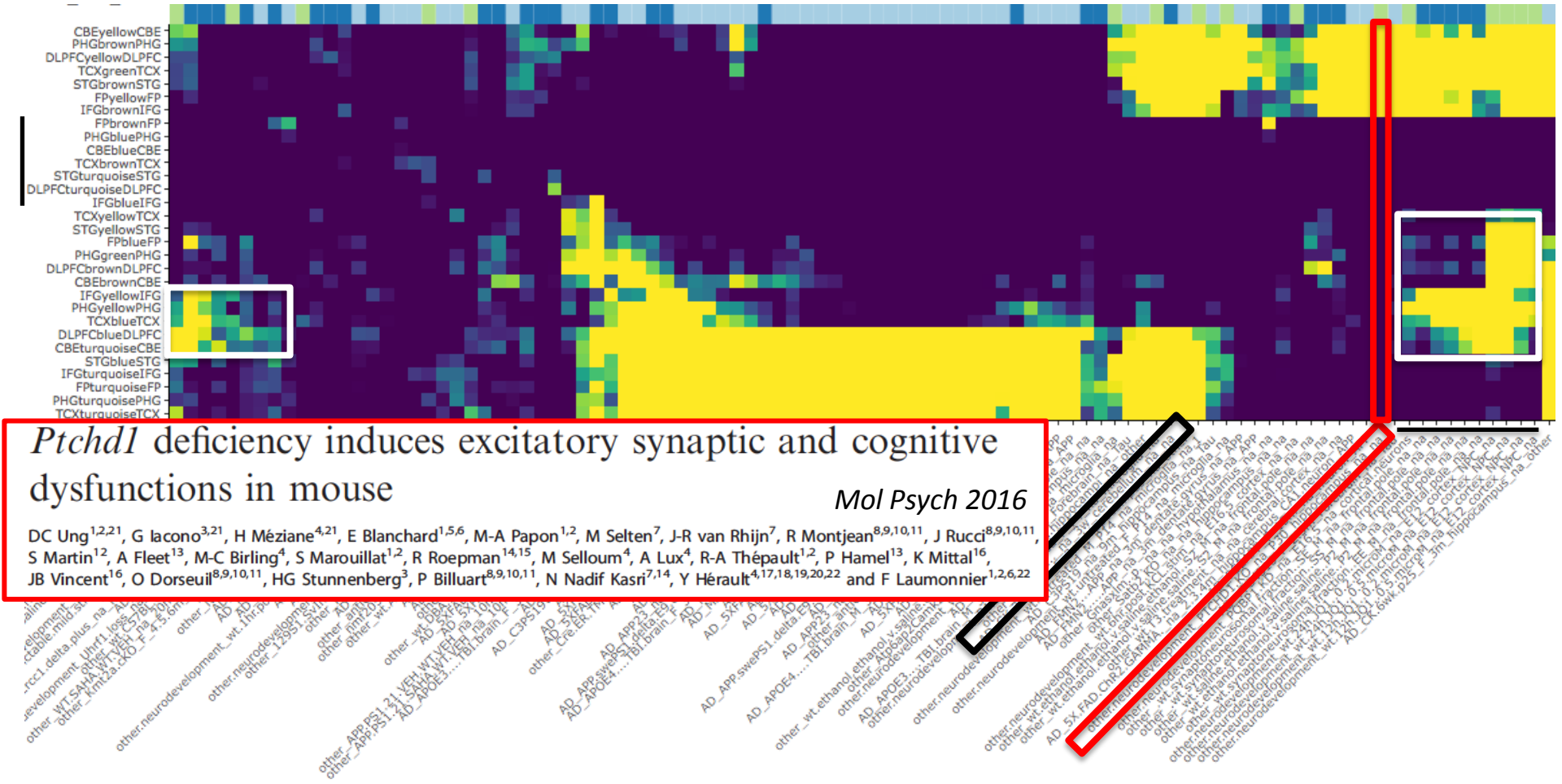

Ptchd1 deficiency induces excitatory synaptic and cognitive dysfunctions in mouse

Mol Psych 2016

DC Ung[1,2,21], G Iacono[3,21], H Méziane[4,21], E Blanchard[1,5,6], M-A Papon[1,2], M Selten[7], J-R van Rhijn[7], R Montjean[8,9,10,11], J Rucci[8,9,10,11], S Martin[12], A Fleet[13], M-C Birling[4], S Marouillat[1,2], R Roepman[14,15], M Selloum[4], A Lux[4], R-A Thépault[1,2], P Hamel[13], K Mittal[16], JB Vincent[16], O Dorseuil[8,9,10,11], HG Stunnenberg[3], P Billuart[8,9,10,11], N Nadif Kasri[7,14], Y Hérault[4,17,18,19,20,22] and F Laumonnier[1,2,6,22]

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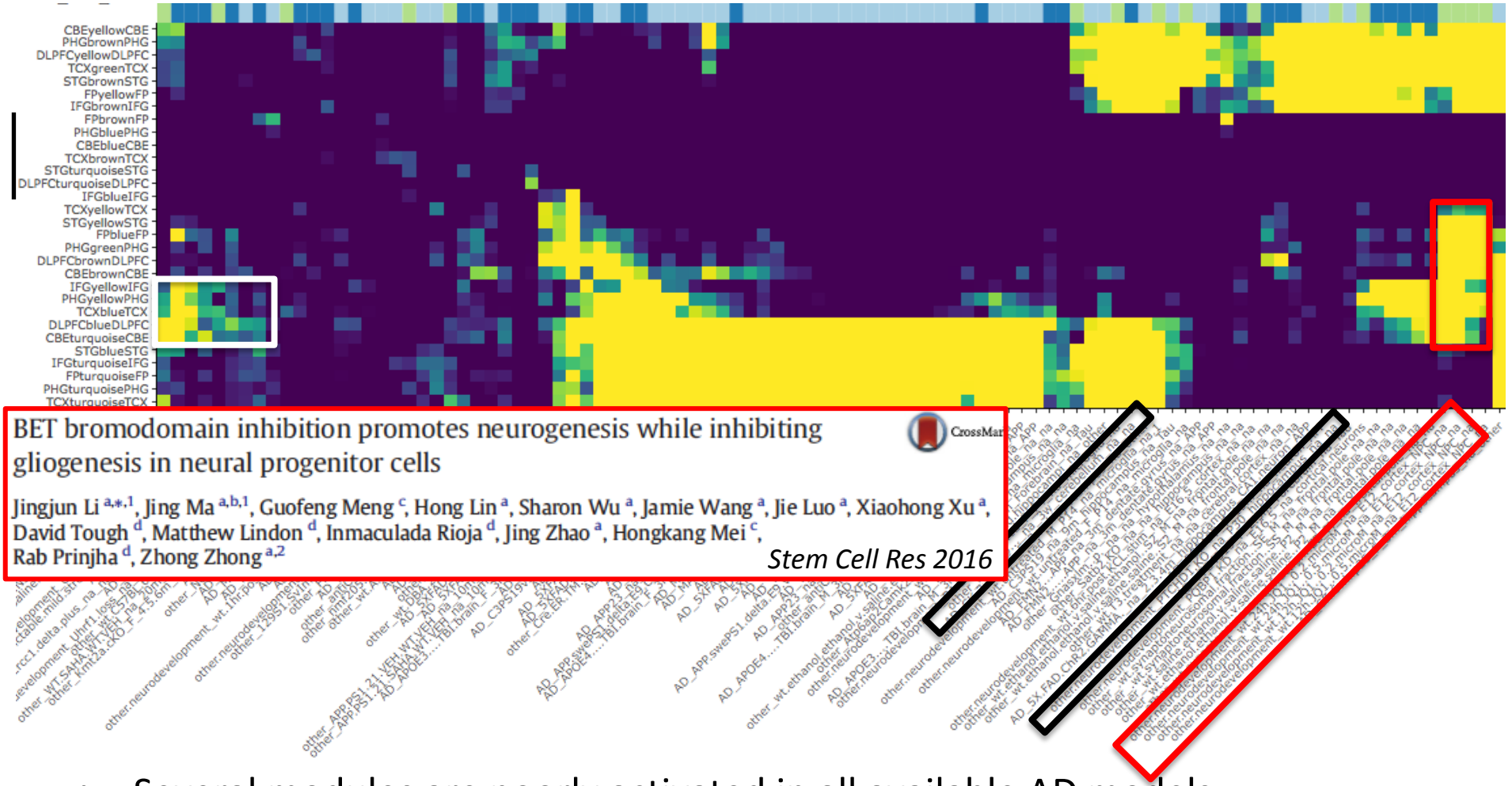
AD “transcriptologs”



BET bromodomain inhibition promotes neurogenesis while inhibiting gliogenesis in neural progenitor cells

Jingjun Li [a,*,1], Jing Ma [a,b,1], Guofeng Meng [c], Hong Lin [a], Sharon Wu [a], Jamie Wang [a], Jie Luo [a], Xiaohong Xu [a], David Tough [d], Matthew Lindon [d], Inmaculada Rioja [d], Jing Zhao [a], Hongkang Mei [c], Rab Prinjha [d], Zhong Zhong [a,2]

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- Several modules are poorly activated in all available AD models
- These modules identify key disease biology not recapitulated in models
- Other mice activating these modules may identify non-obvious AD models
- Non-obvious models for study of AD dark matter
- Other non-obvious models activate patterns similar to AD or with selectivity.