DNA methylation and chromatin accessibility in the normal human brain

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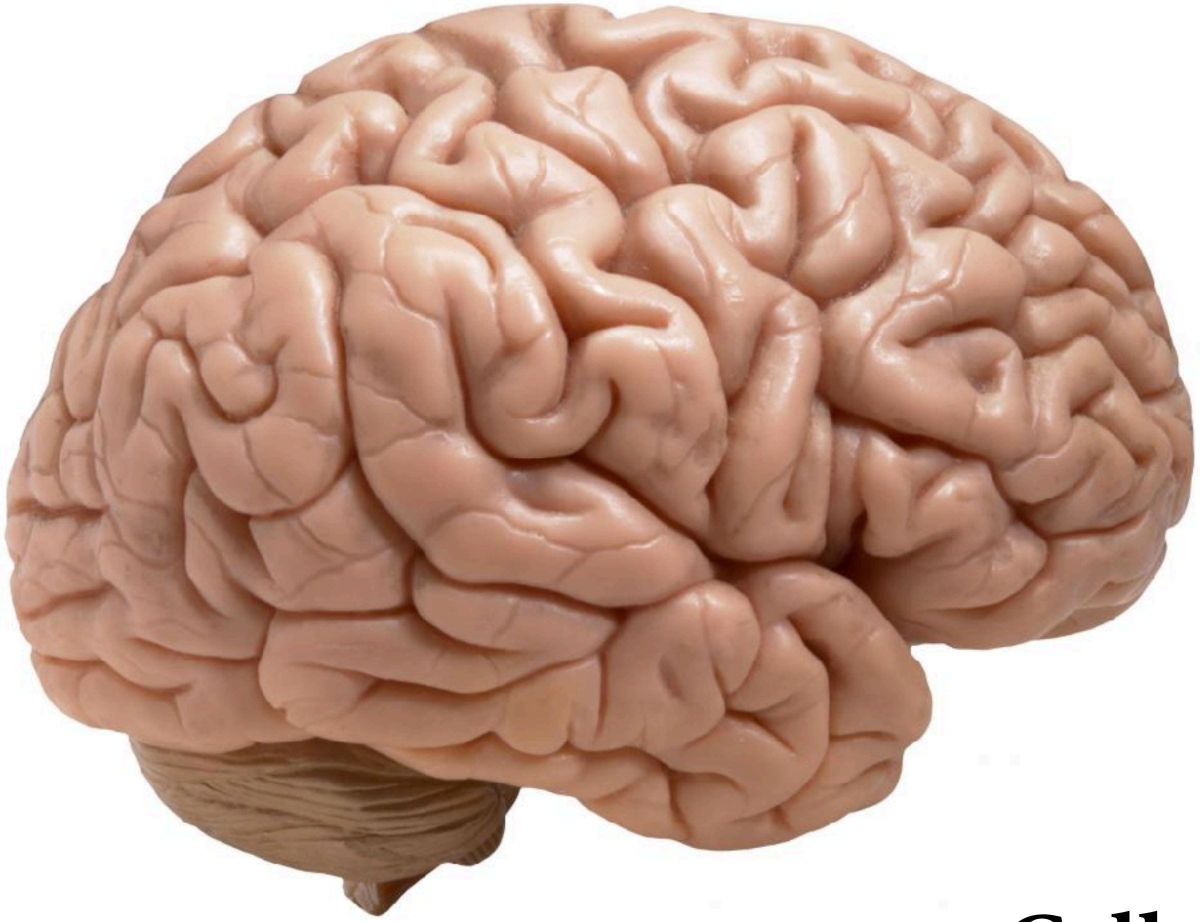
Design



Brain regions:
BA9 (part of frontal cortex)
BA24 (part of anterior cingulate)
HC (hippocampus)
NAcc (nucleus accumbens)

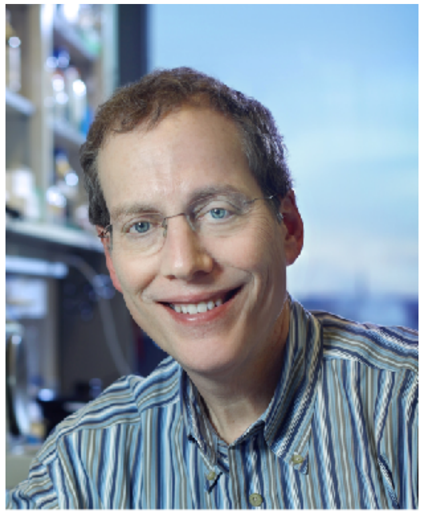
Cell types:
Bulk
Neurons (NeuN+)
Glia (NeuN-)

Assays: WGBS (everything), roughly 6 individuals
ATAC+RNA on 6 separate individuals

Acknowledgements

Lindsay Rizzardi

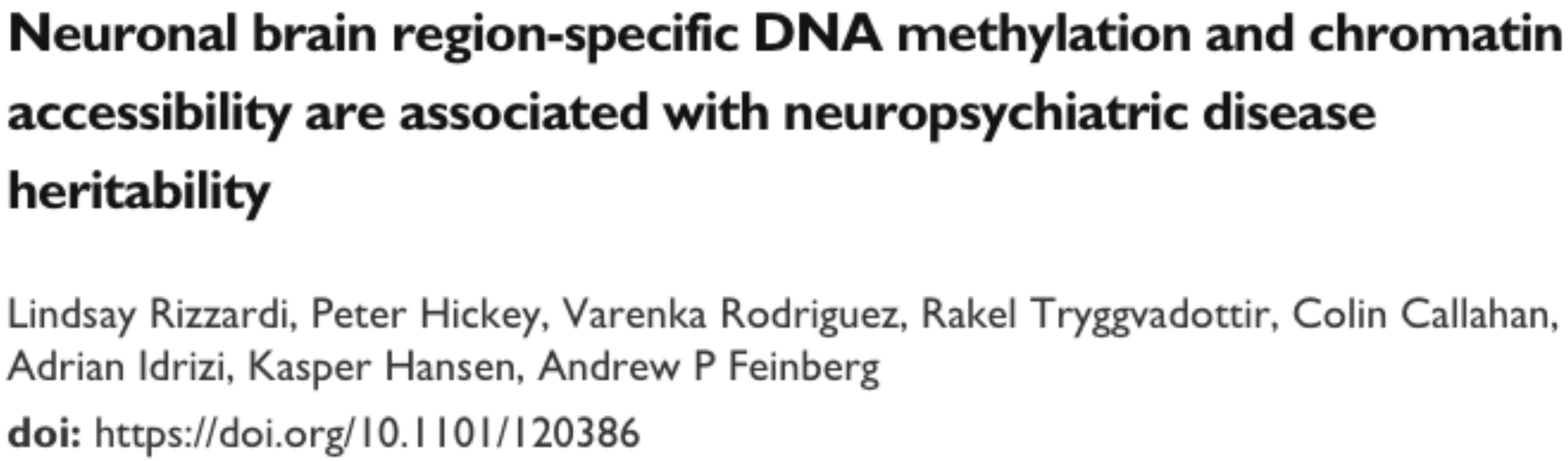
Pete Hickey



Andrew Feinberg

Jeff Leek

Preprint on bioRxiv:

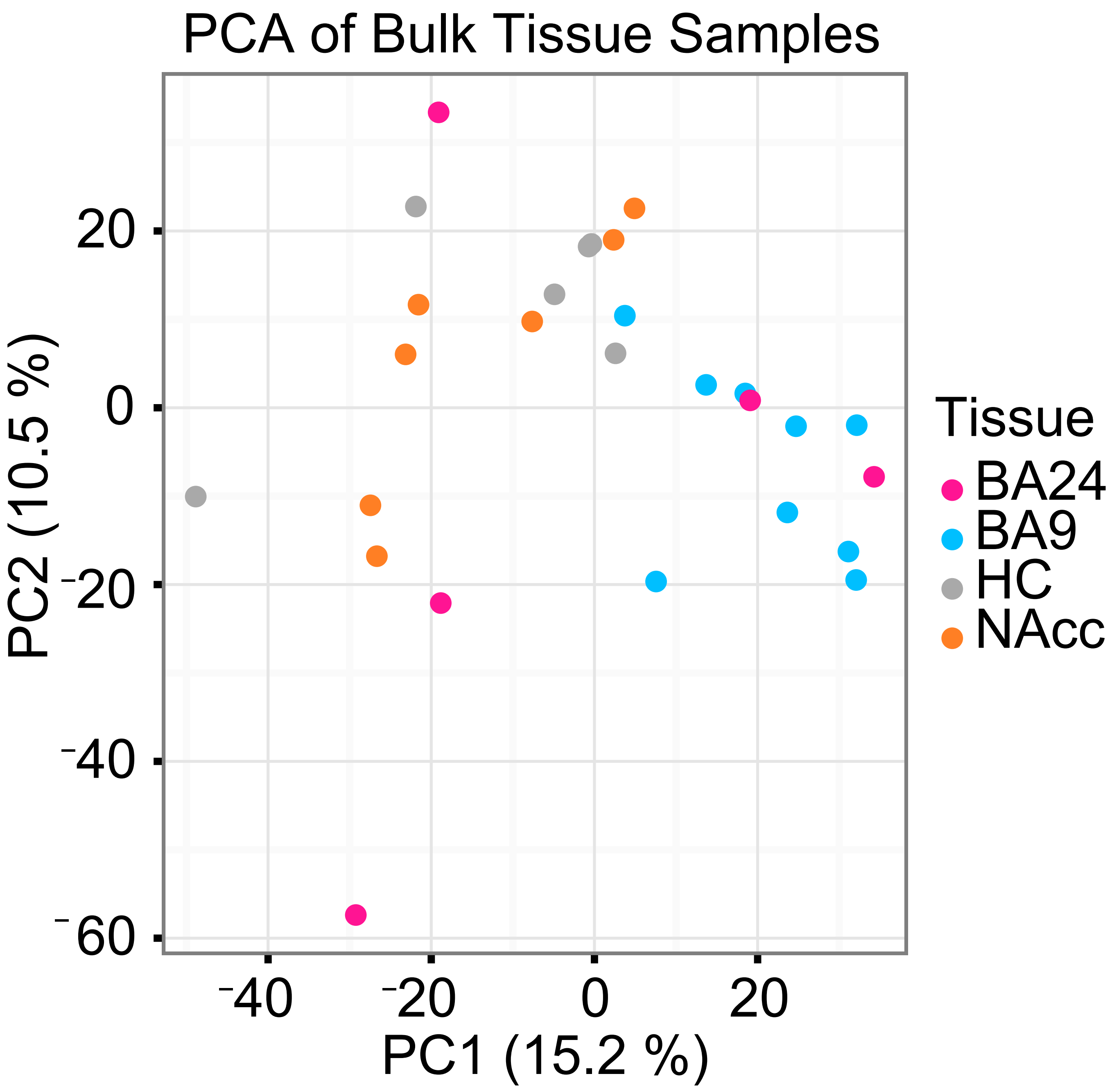


Neuronal brain region-specific DNA methylation and chromatin accessibility are associated with neuropsychiatric disease heritability

Lindsay Rizzardi, Peter Hickey, Varenka Rodriguez, Rakel Tryggvadottir, Colin Callahan, Adrian Idrizi, Kasper Hansen, Andrew P Feinberg

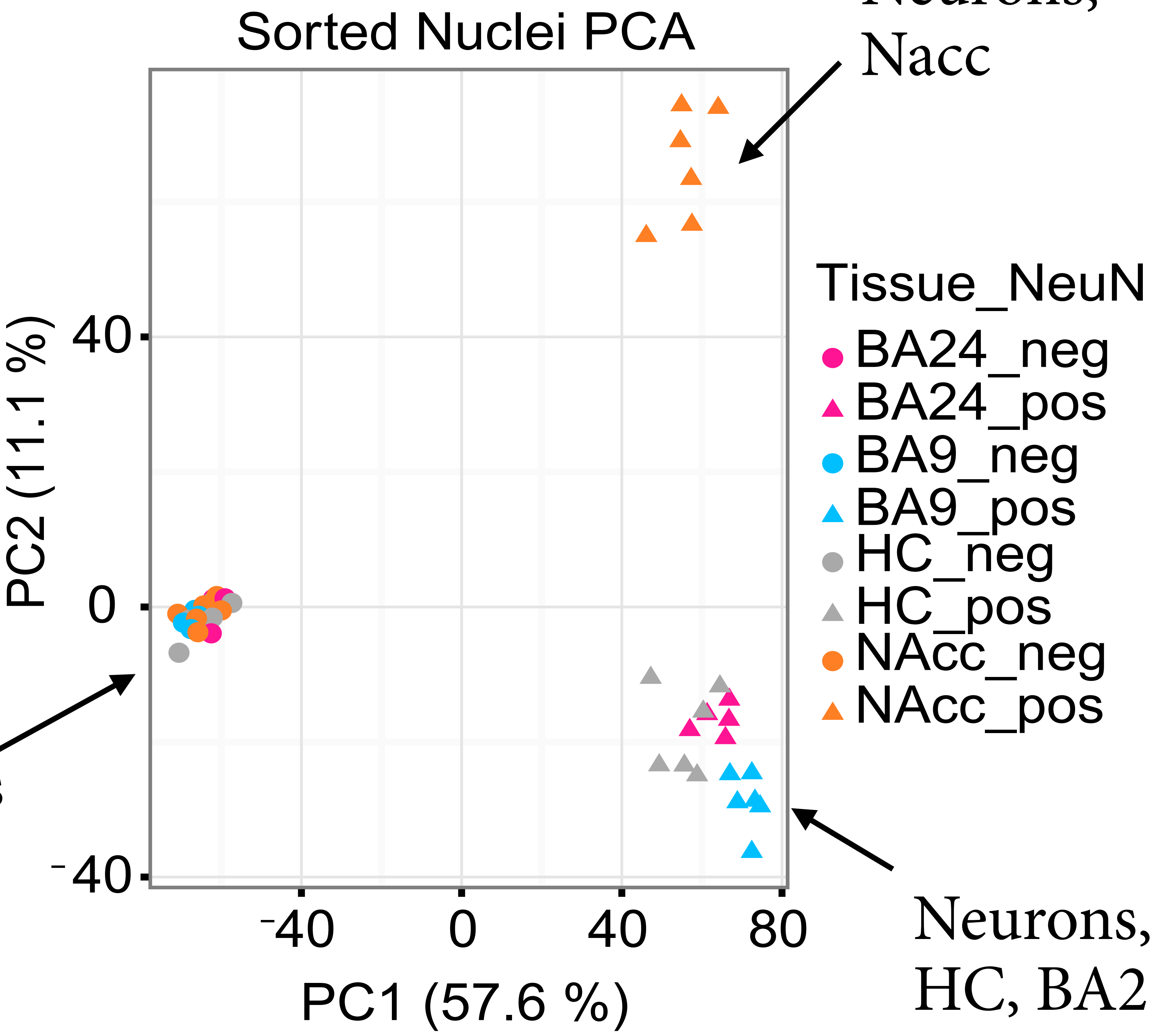
doi: https://doi.org/10.1101/120386

WGBS of bulk tissue (6 individuals)



(Bin genome in 1kb bins, discard bins with few CpGs, compute average methylation per bin)

WGBS of sorted tissue (6 individuals)

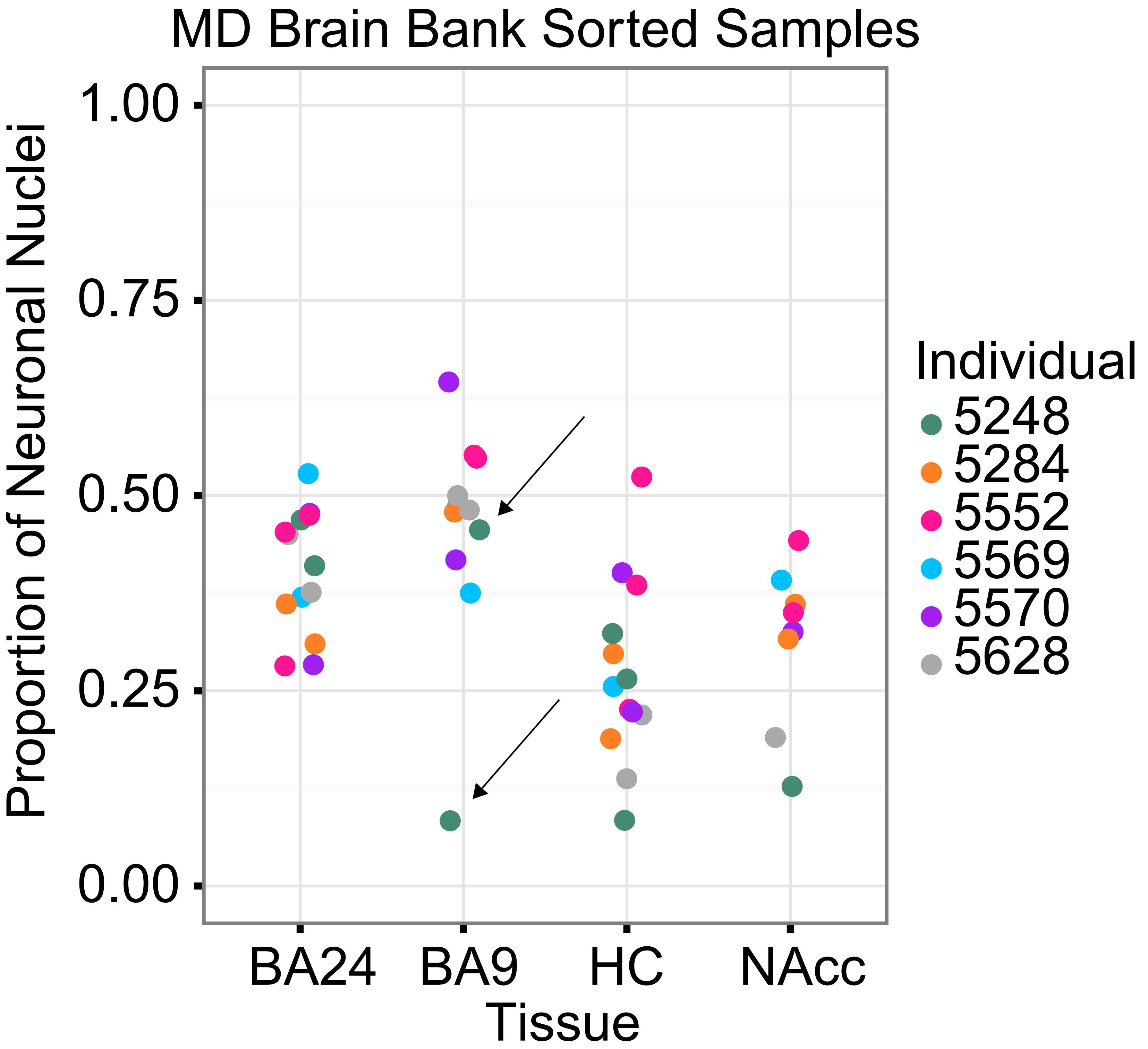


Neurons,
Nacc

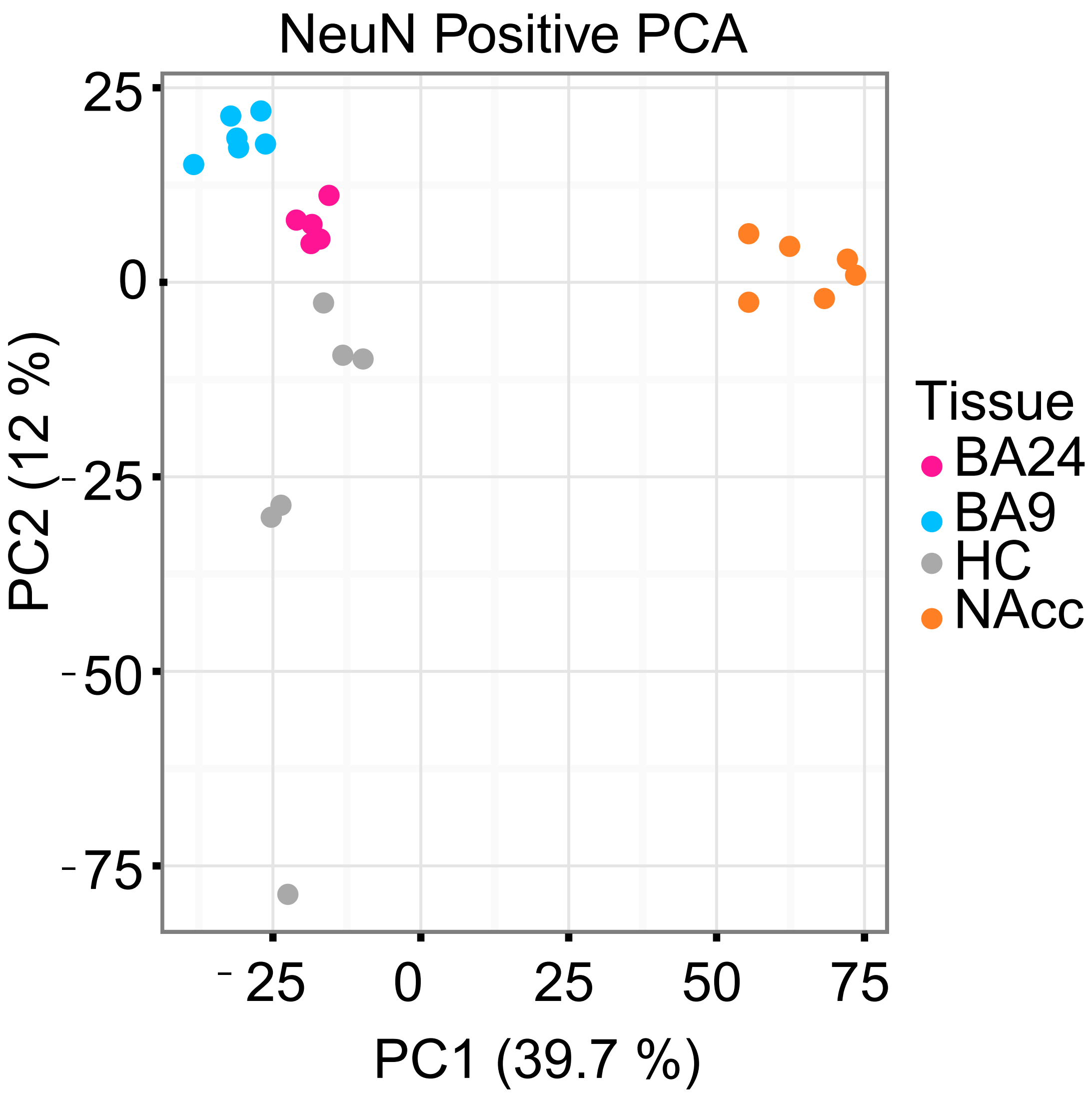
Glial, all regions

Neurons,
HC, BA24, BA9

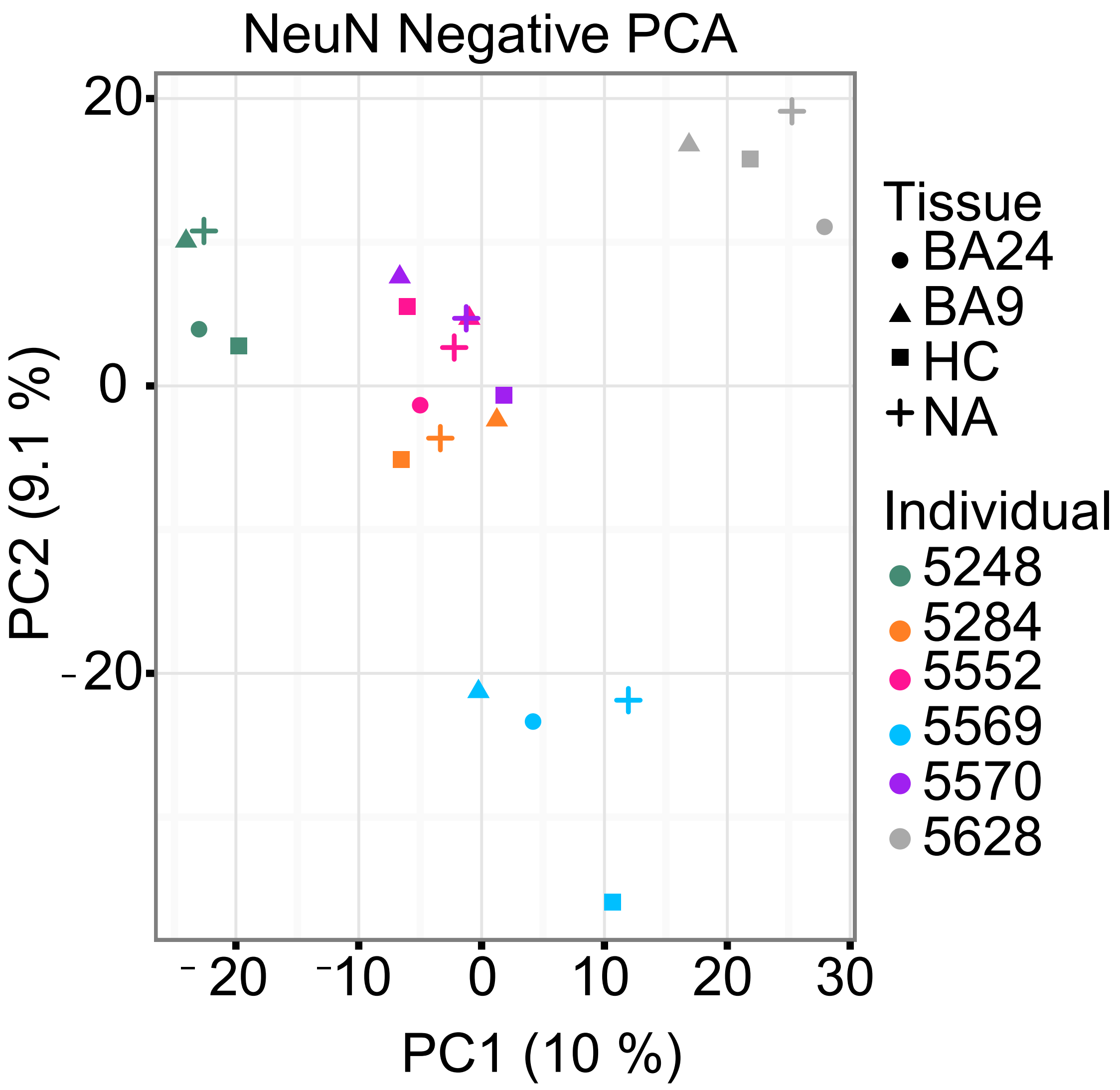
Substantial variation in proportion of neurons



Cell type specific analysis



Neurons:
Cluster by brain region



Glial:
Cluster by individual

Conclusions so far

Substantial cell type heterogeneity between samples

Flow sorting is critical

Glial is similar between brain regions

Neurons are different between brain regions

DMRs

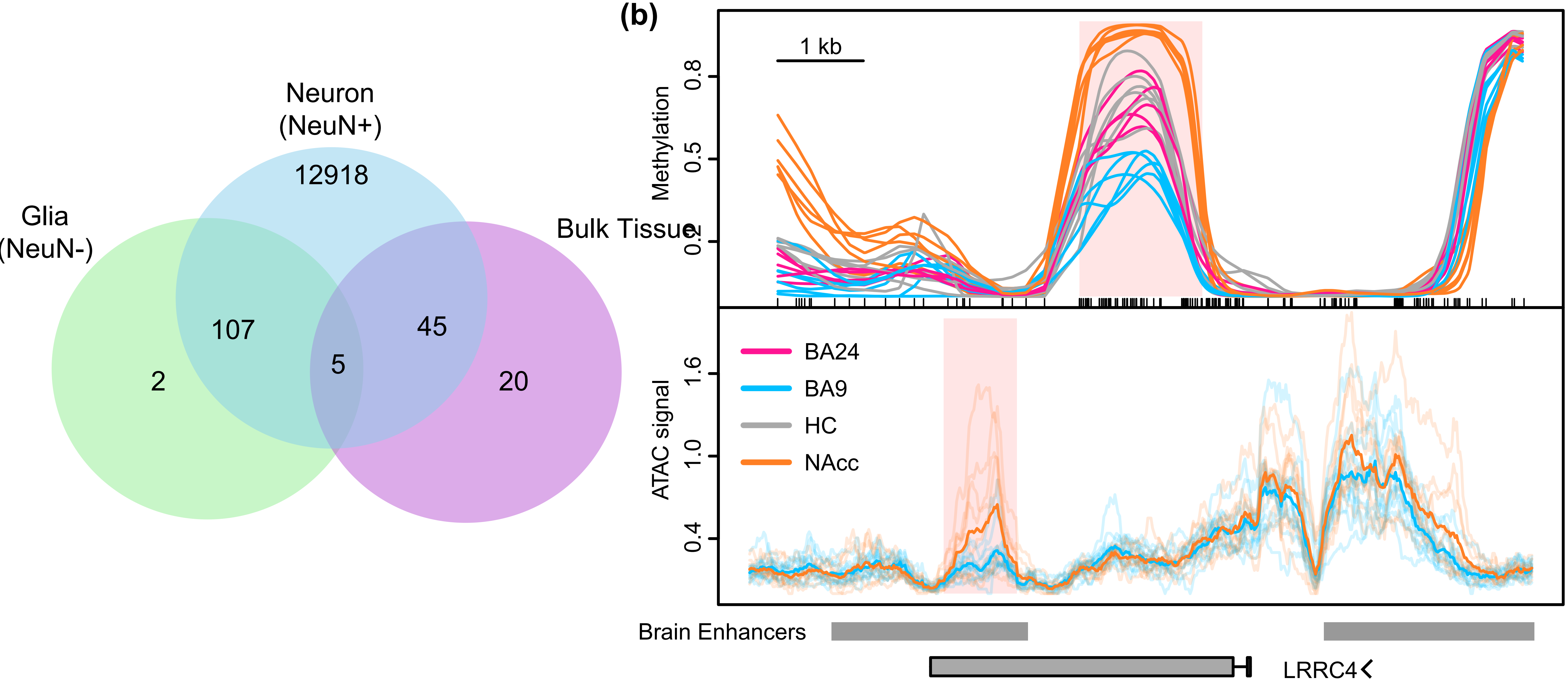
METHOD Open Access

BSmooth: from whole genome bisulfite sequencing reads to differentially methylated regions

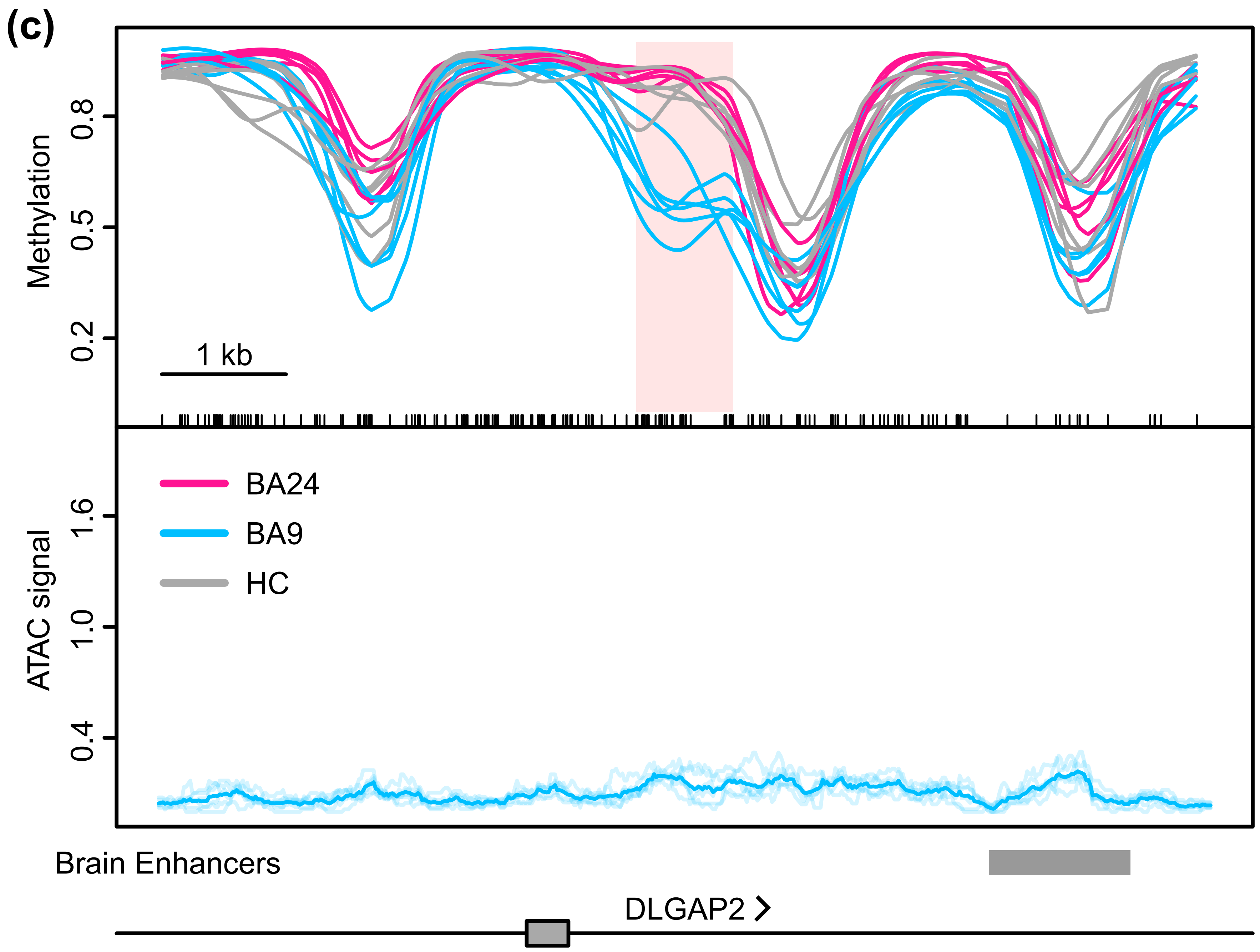
Kasper D Hansen[1*†], Benjamin Langmead[1,2*†] and Rafael A Irizarry[1,2*]

Handles low coverage bisulfite sequencing
We extend the two-group model to handle arbitrary designs
Permutation approach controls FWER (conservative)

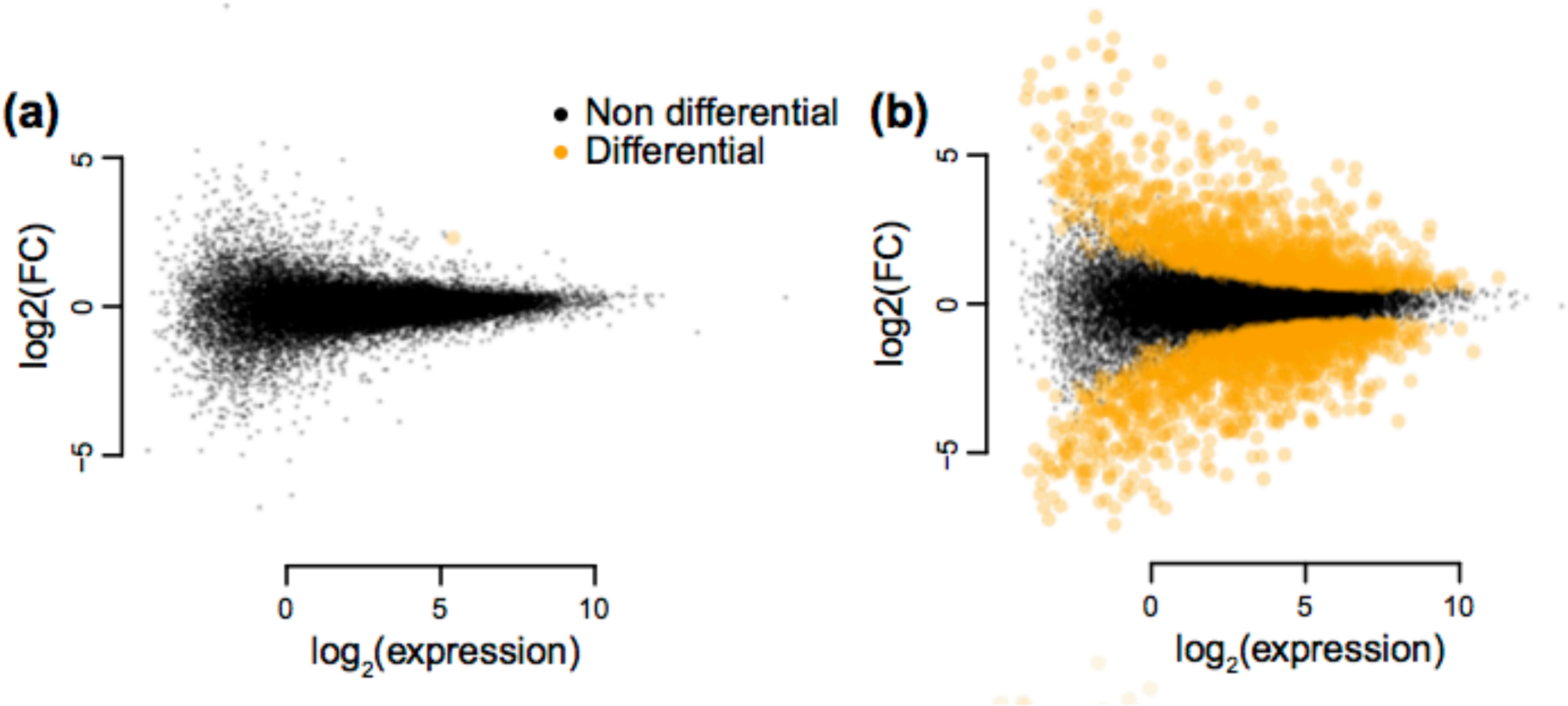
DMRs between brain regions, within cell type



Some (but not many) DMRs between BA9 / BA24 / HC



Differential expression between BA9 and NAcc



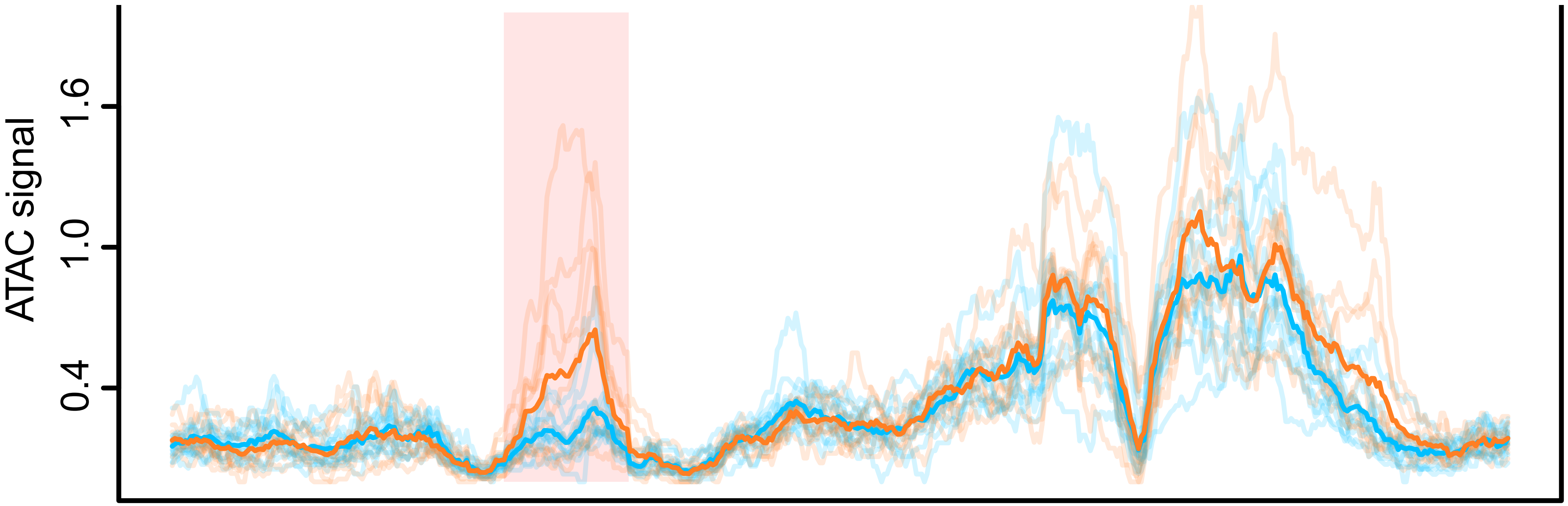
Glial / 1 DEG

Neuron / 2,952 DEG

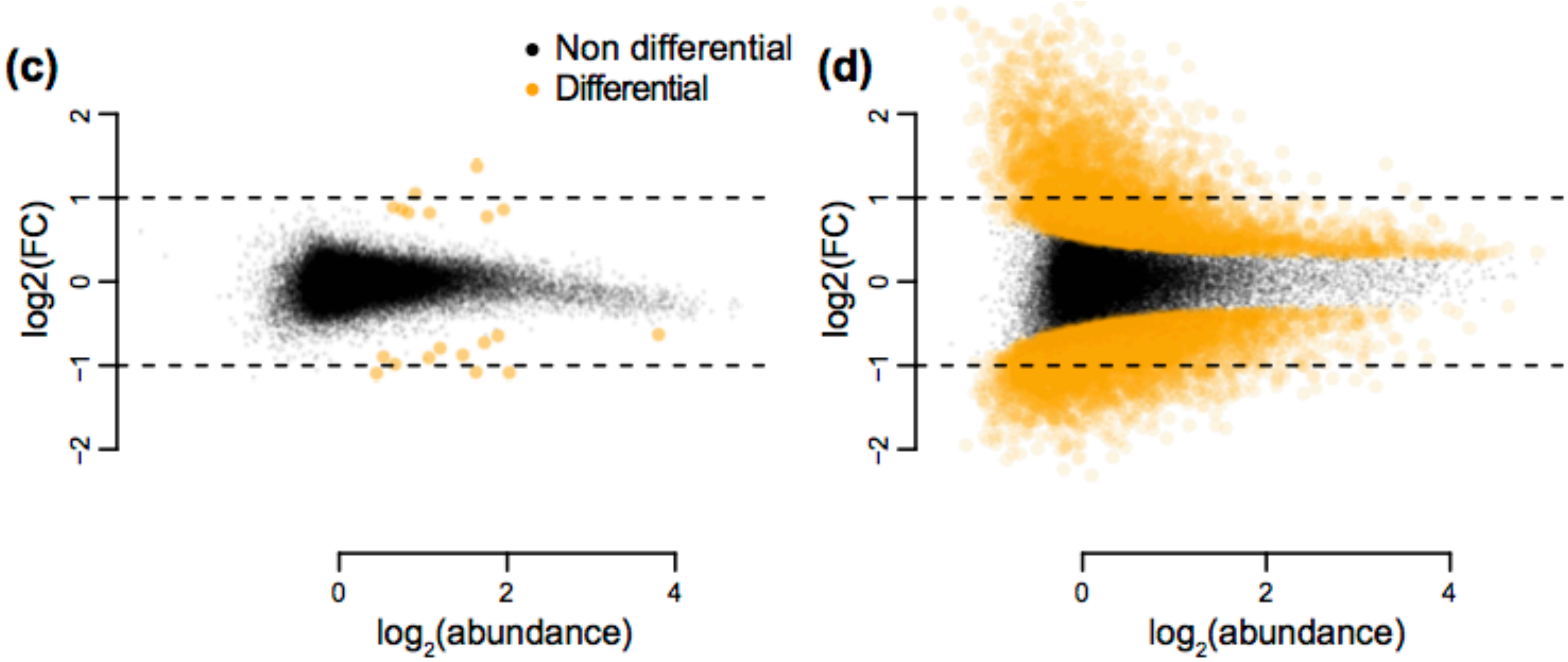
(RNA from nuclei)

Differential accessibility

Merge samples into one "meta" sample
Call peaks on the meta sample -> regions (probably high FP)
Count fragments in each sample and region
Differential "expression"



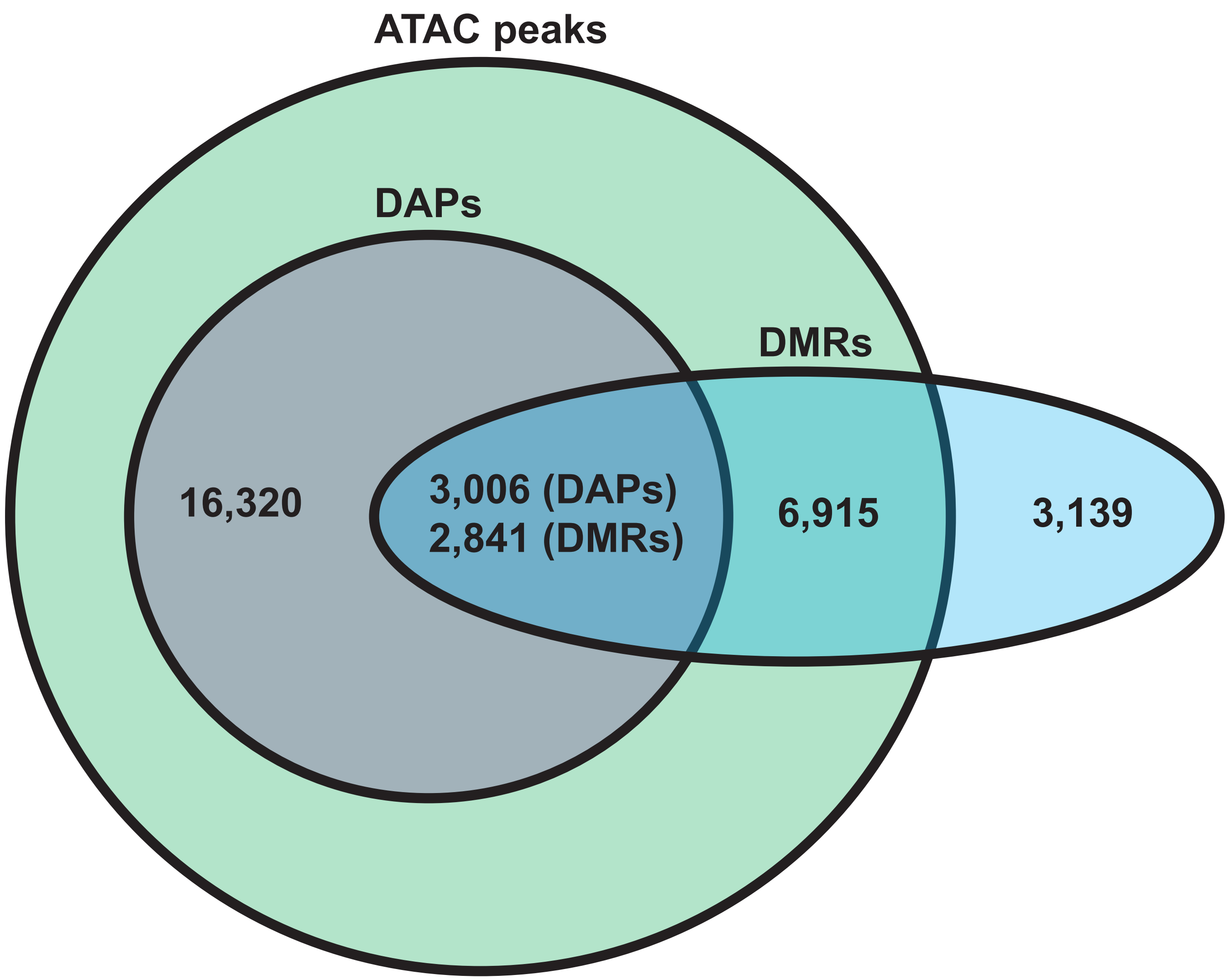
Differential accessibility (DAPs)



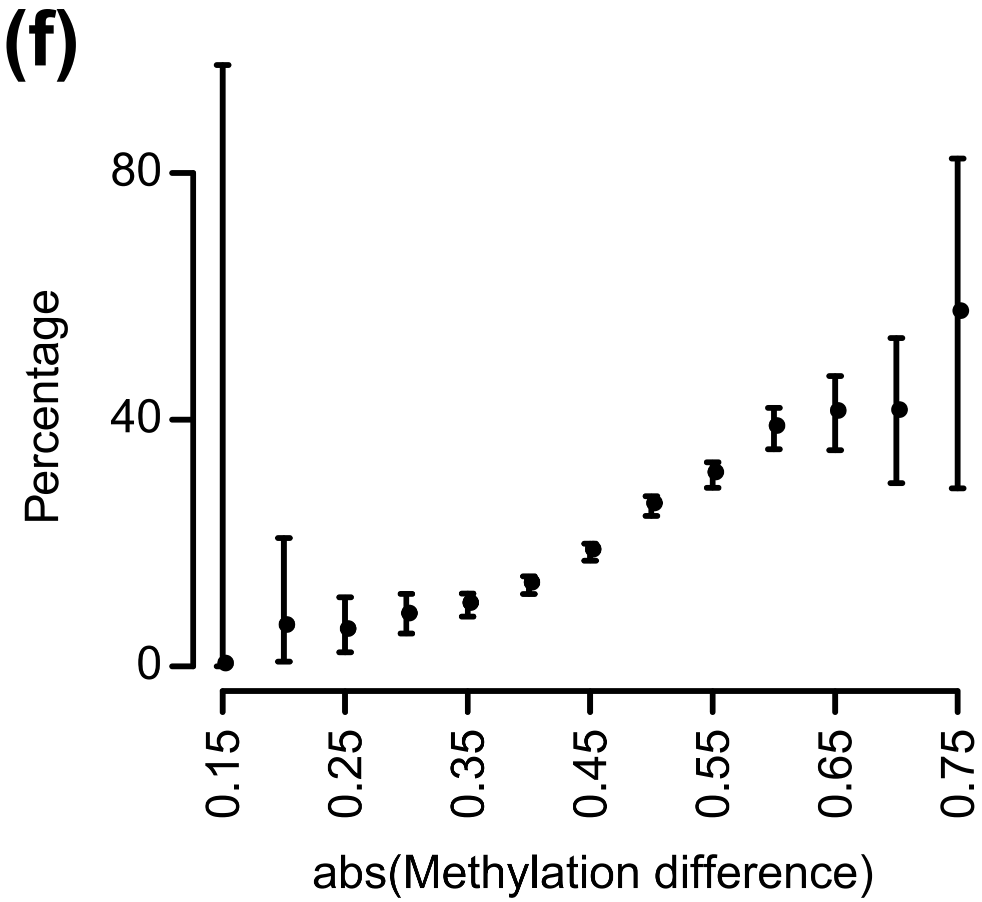
Glial / 19 DAPs

Neuron / 19,326 DAPs

DMRs vs DAPs: limited overlap

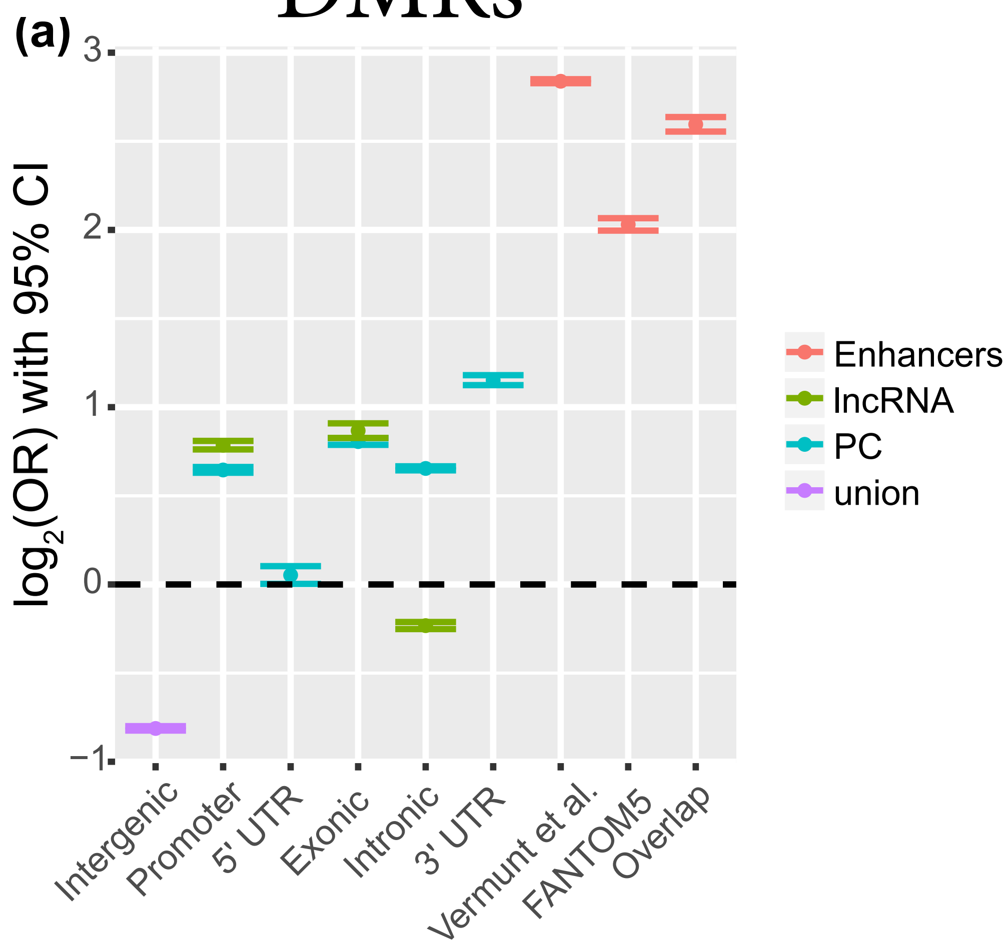


~13k DMRs (12 MB)
~20k DAPs (12 MB)

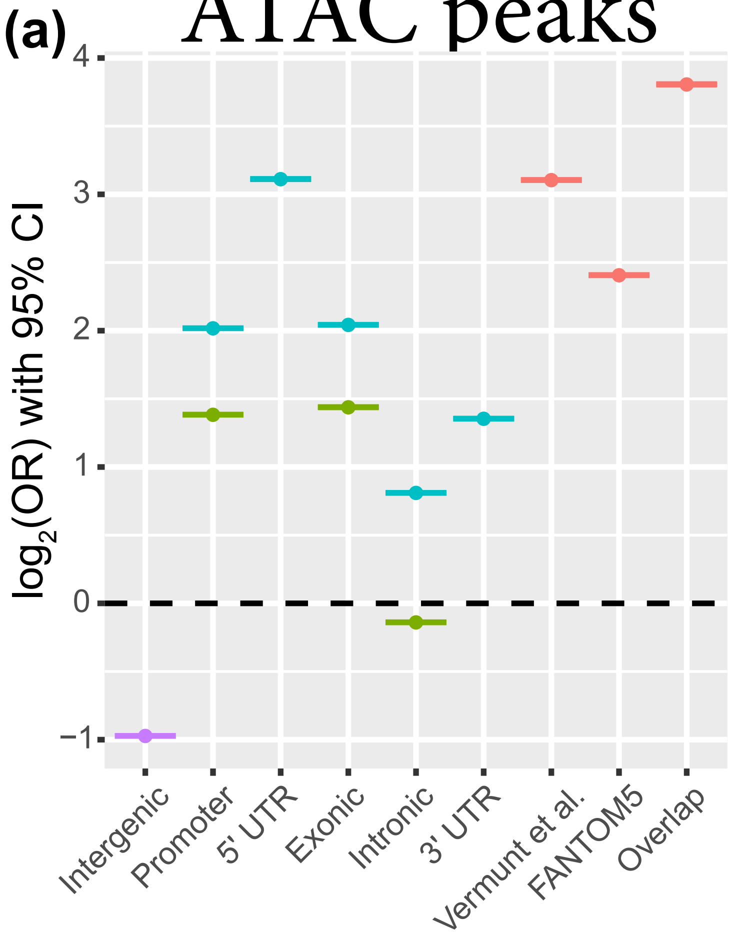


Where?

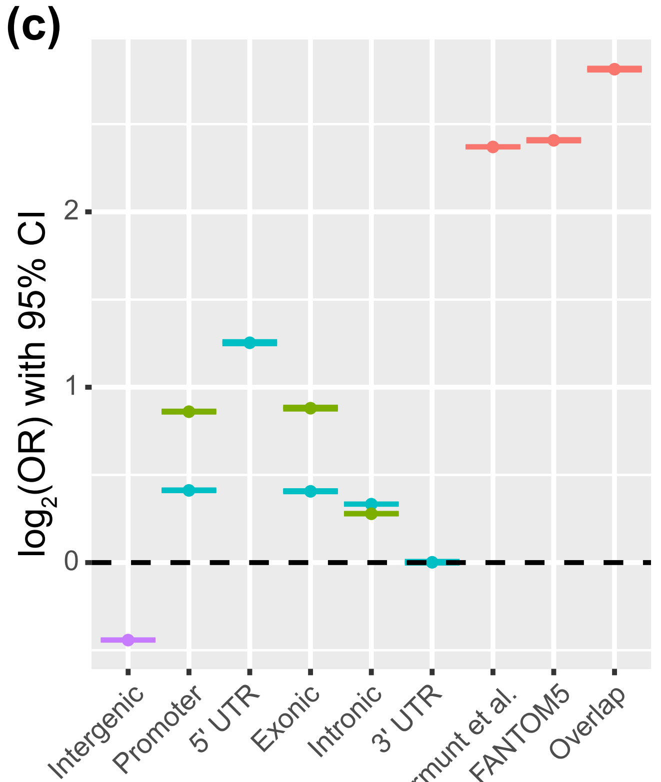
DMRs



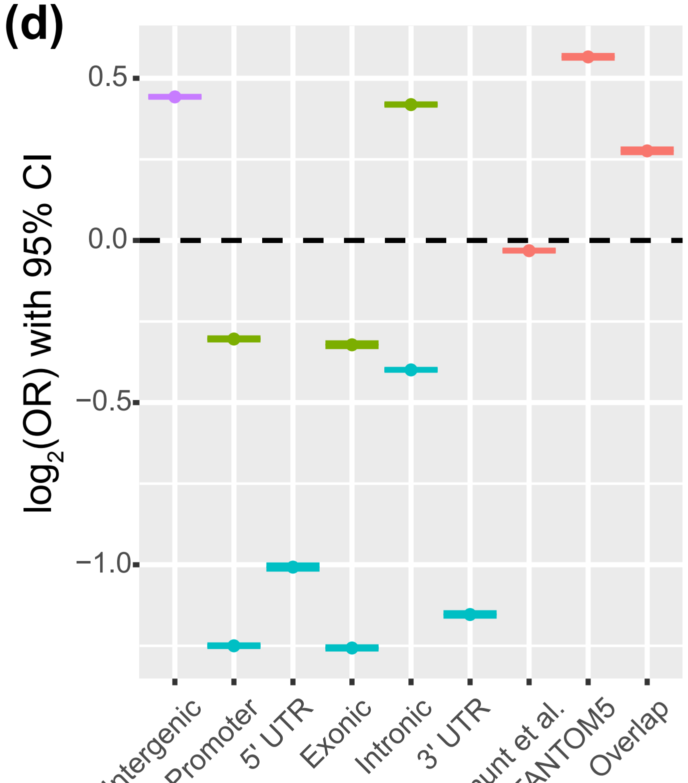
ATAC peaks



DAPs



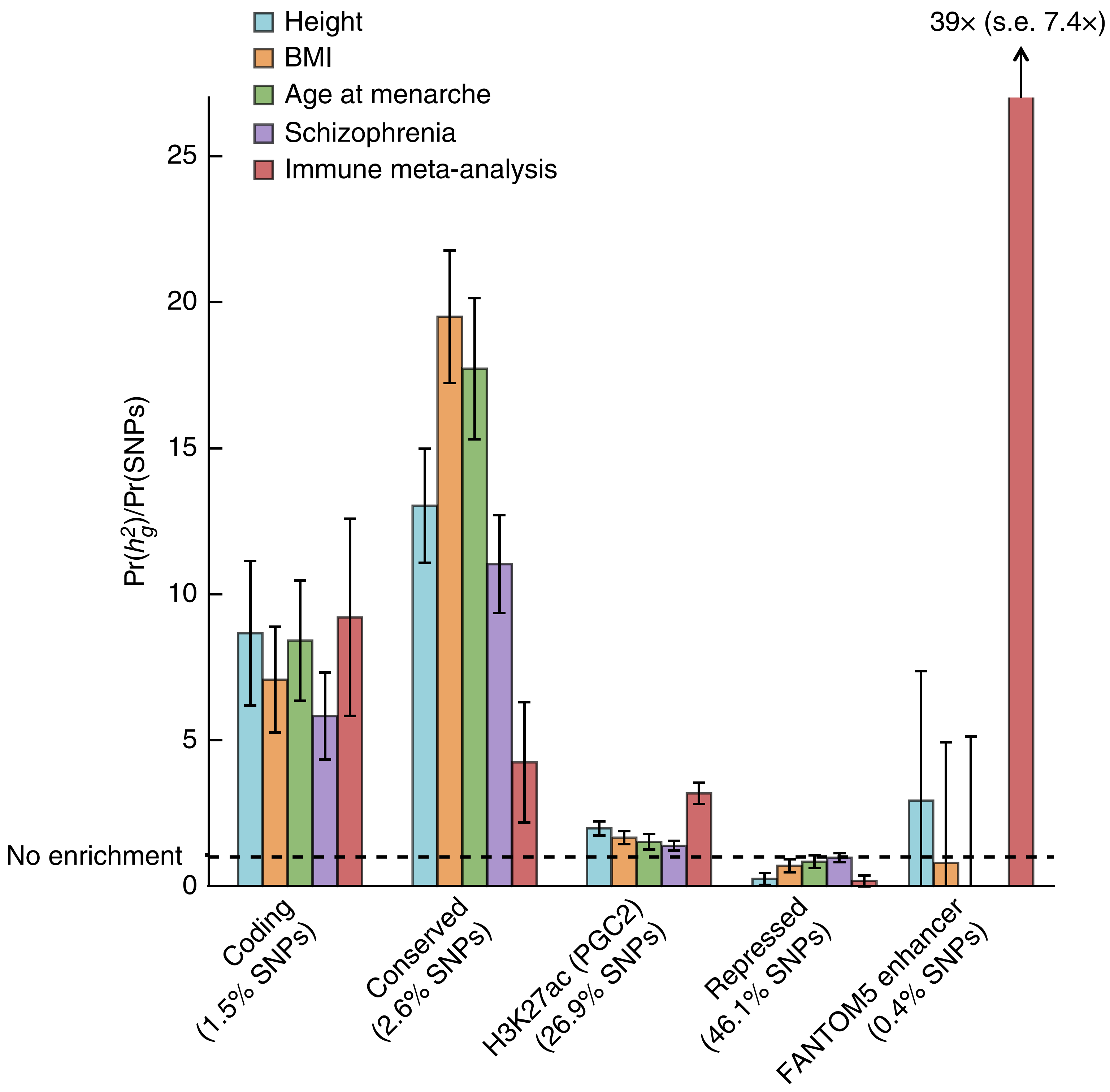
DAPs compared to ATAC peaks



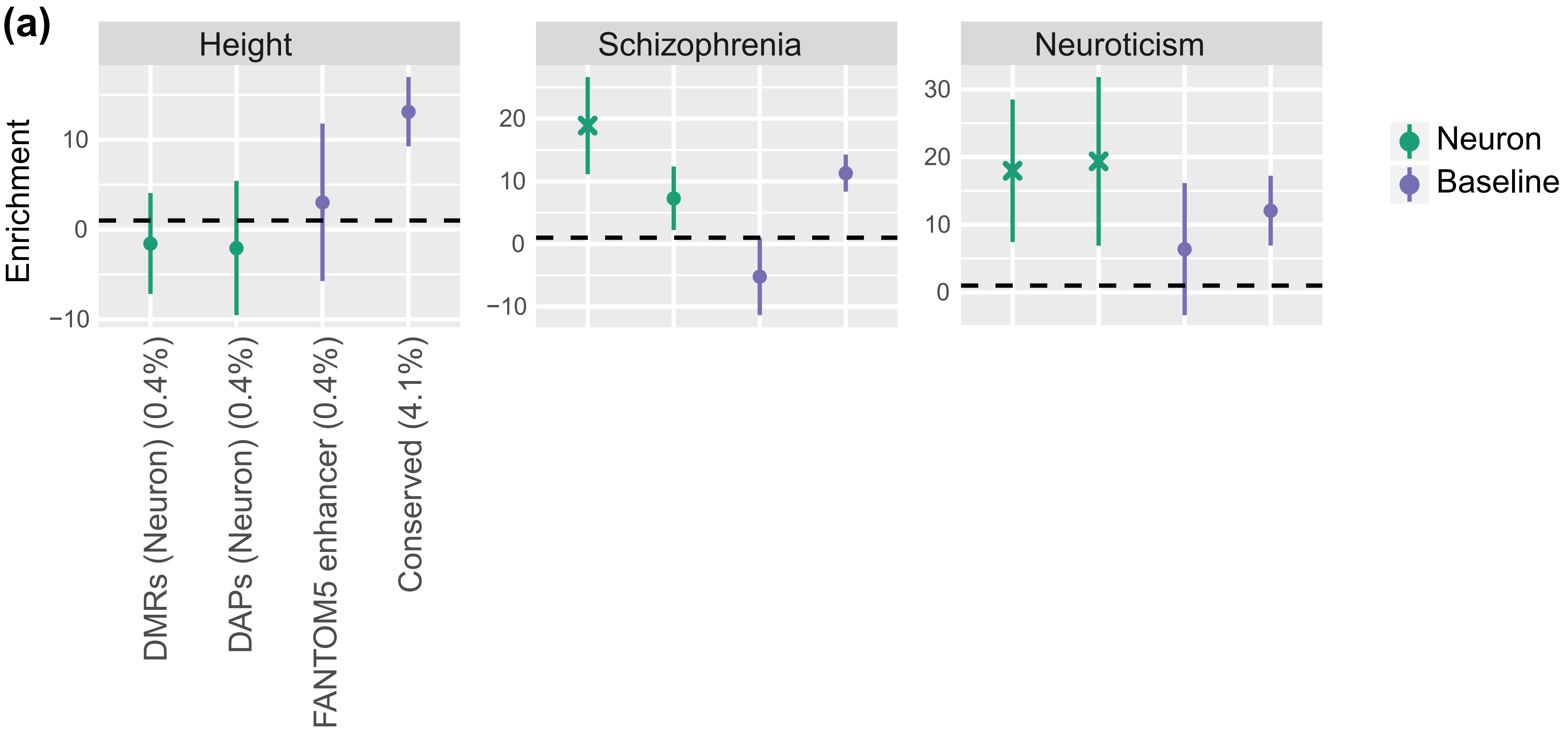
Are these regions genetically important

Partitioning heritability by functional annotation using genome-wide association summary statistics

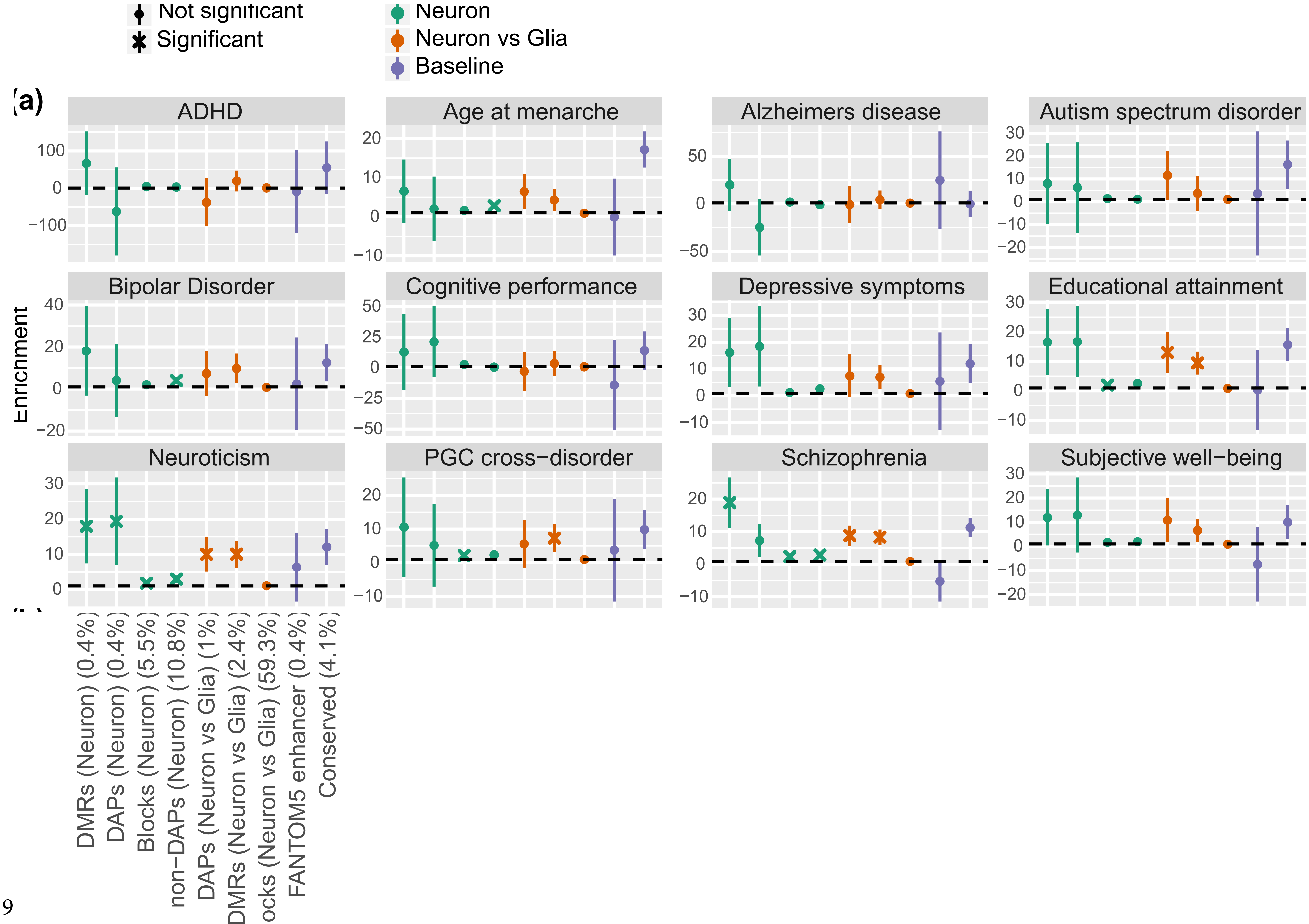
Hilary K Finucane[1,2,19], Brendan Bulik-Sullivan[3,4,19], Alexander Gusev[2], Gosia Trynka[5–9], Yakir Reshef[10], Po-Ru Loh[2], Verneri Anttila[3,4,8], Han Xu[11], Chongzhi Zang[11], Kyle Farh[3,12], Stephan Ripke[3,4], Felix R Day[13], ReproGen Consortium[14], Schizophrenia Working Group of the Psychiatric Genomics Consortium[14], The RACI Consortium[14], Shaun Purcell[5,6,15], Eli Stahl[15], Sara Lindstrom[2], John R B Perry[13], Yukinori Okada[16,17], Soumya Raychaudhuri[5–8,18], Mark J Daly[3,4,8], Nick Patterson[8], Benjamin M Neale[3,4,8,20] & Alkes L Price[2,8,20]



Yes, they are important - for neurological traits



Some "Trends"


Not significant
Significant
Neuron
Neuron vs Glia
Baseline
(a)
Enrichment
ADHD
Age at menarche
Alzheimers disease
Autism spectrum disorder
Bipolar Disorder
Cognitive performance
Depressive symptoms
Educational attainment
Neuroticism
PGC cross−disorder
Schizophrenia
Subjective well−being
100
0
−100
20
10
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−10
50
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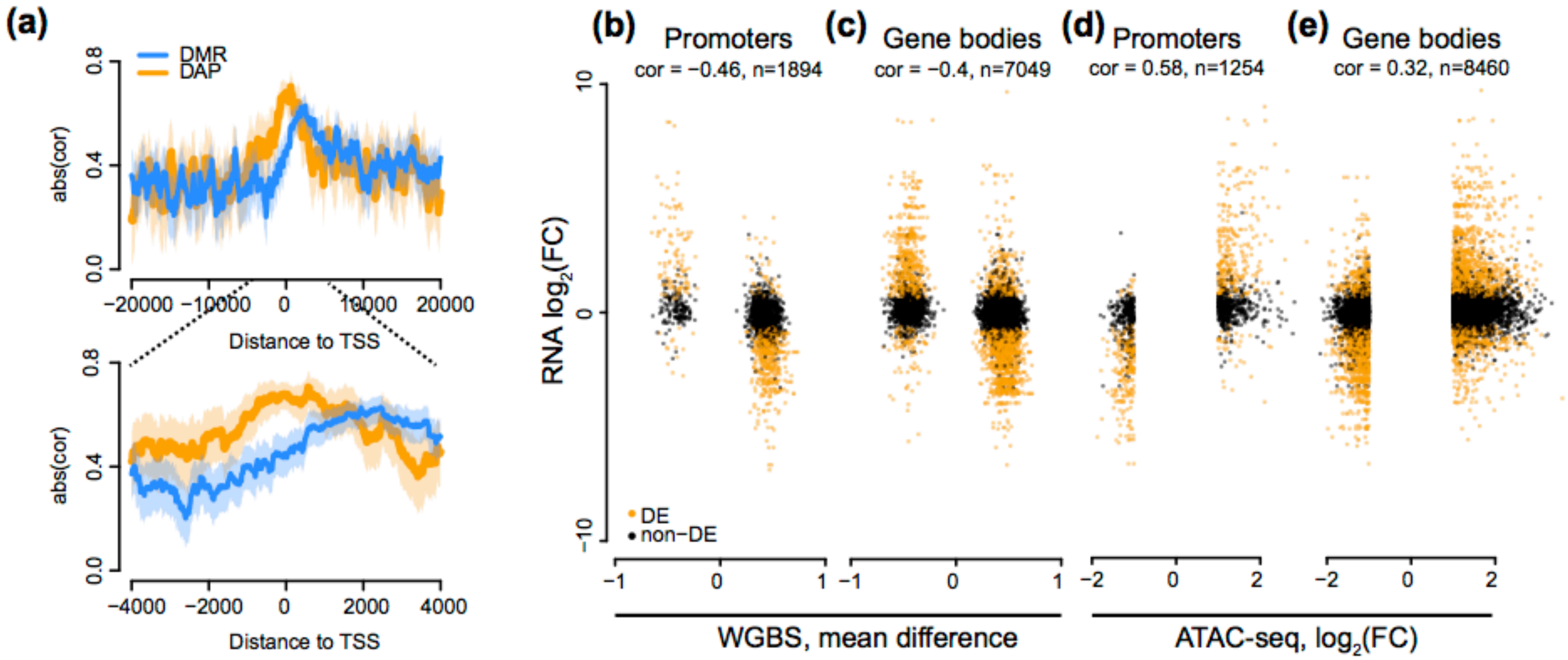
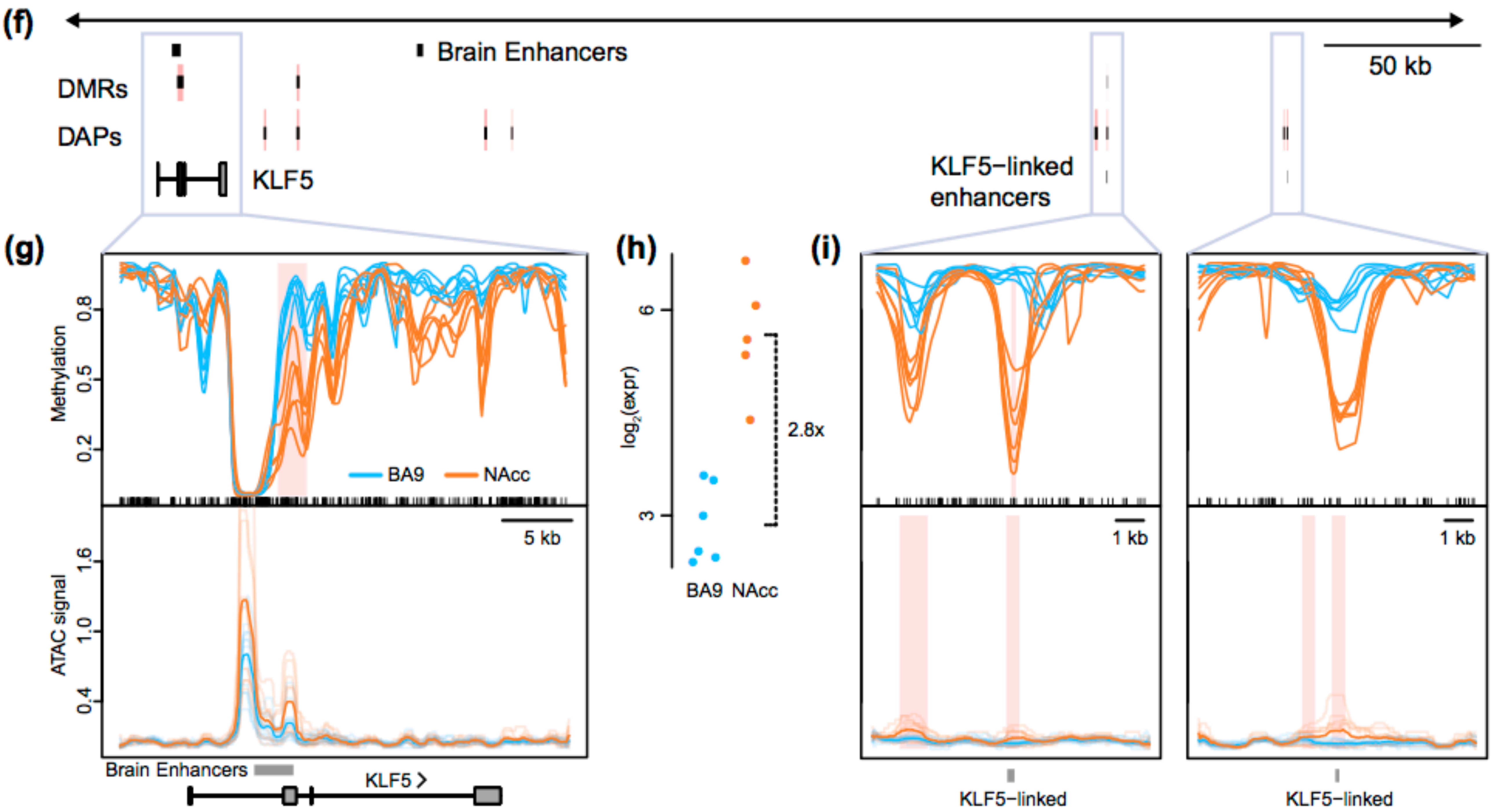
−10
−20
DMRs (Neuron) (0.4%)
DAPs (Neuron) (0.4%)
Blocks (Neuron) (5.5%)
non−DAPs (Neuron) (10.8%)
DAPs (Neuron vs Glia) (1%)
DMRs (Neuron vs Glia) (2.4%)
ocks (Neuron vs Glia) (59.3%)
FANTOM5 enhancer (0.4%)
Conserved (4.1%)

w/Expression in promoters and gene bodies

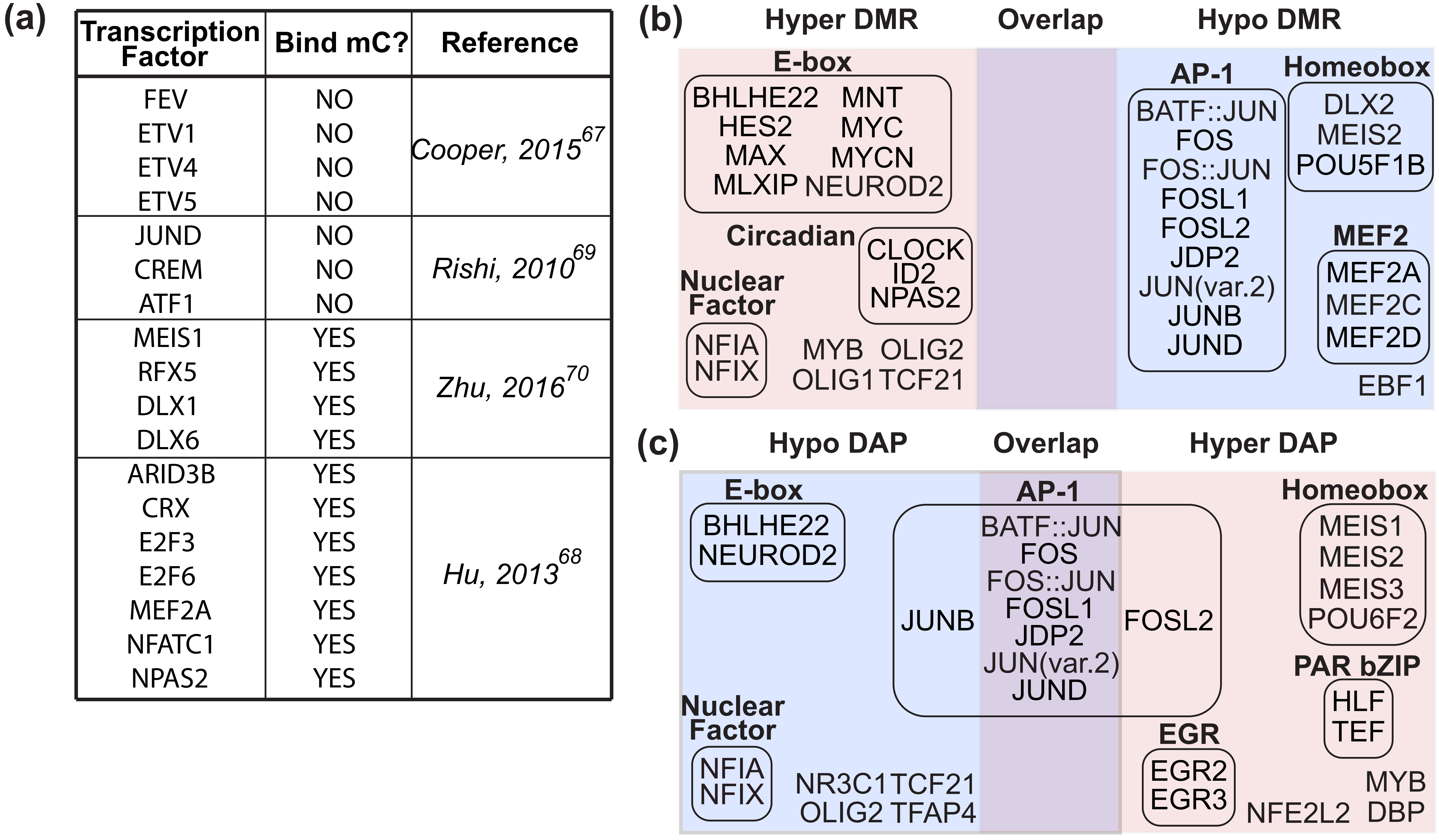


Many genes are differentially expressed without DMRs or DAPs.

FANTOM5 linked enhancers



TFs in promoters



(a)

Transcription Factor	Bind mC?	Reference
FEV	NO	*Cooper, 2015*[67]
ETV1	NO	
ETV4	NO	
ETV5	NO	
JUND	NO	*Rishi, 2010*[69]
CREM	NO	
ATF1	NO	
MEIS1	YES	*Zhu, 2016*[70]
RFX5	YES	
DLX1	YES	
DLX6	YES	
ARID3B	YES	*Hu, 2013*[68]
CRX	YES	
E2F3	YES	
E2F6	YES	
MEF2A	YES	
NFATC1	YES	
NPAS2	YES	