

Mapping the human brain epigenome and its links to disease

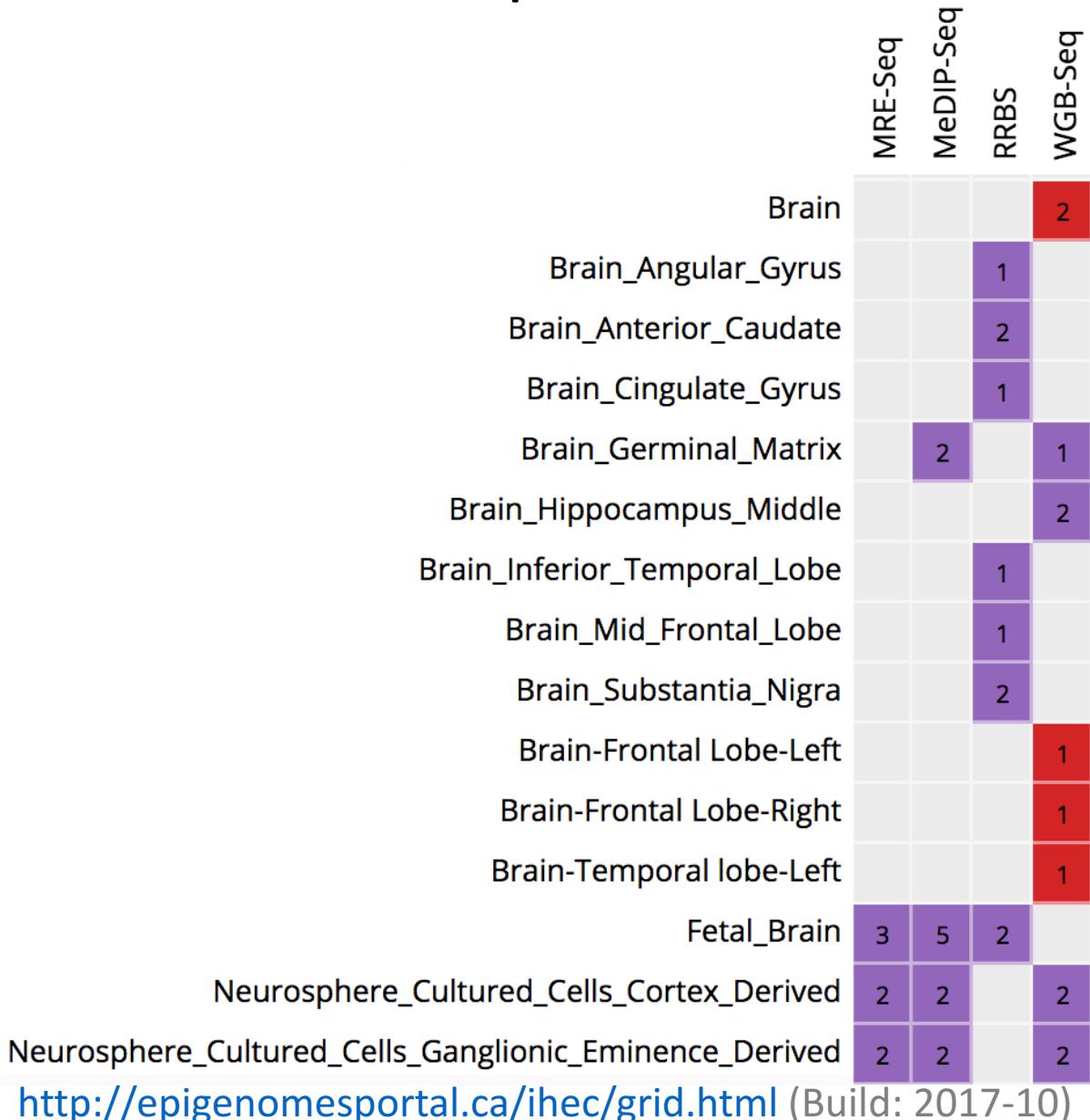
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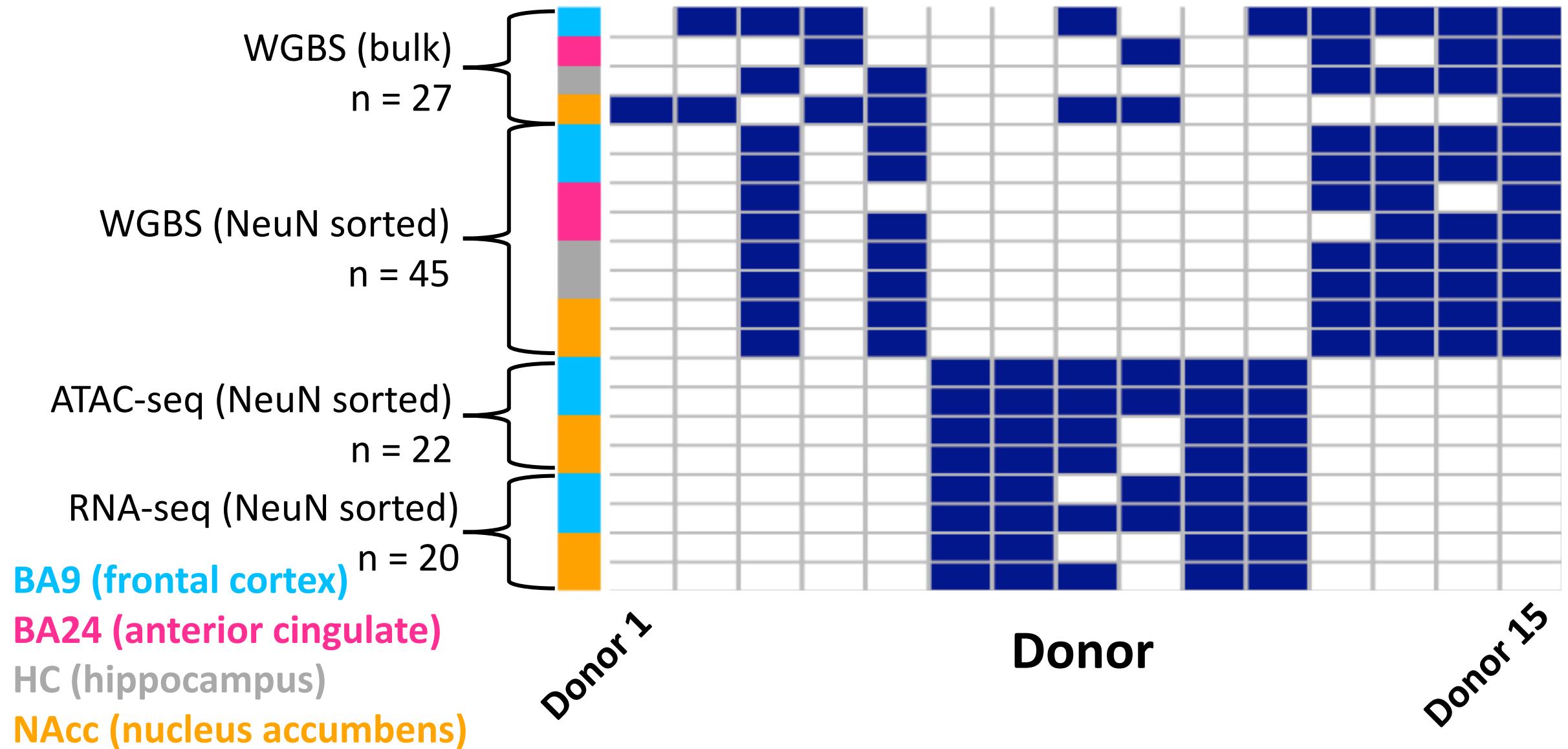
Current map of human brain methylome is limited



- Bulk tissue
- Limited replicates
- Few brain region-specific DMRs^{1,2}

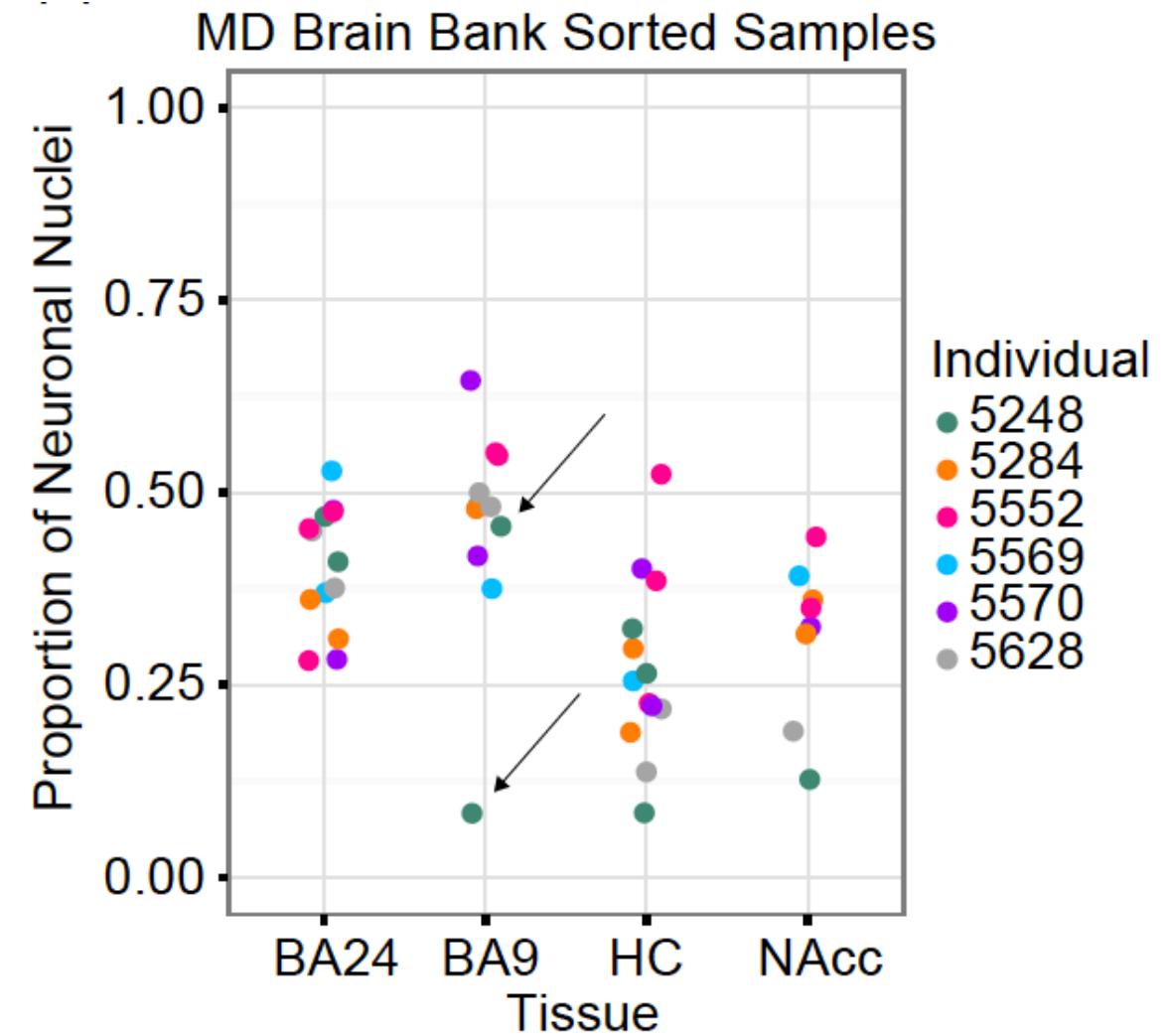
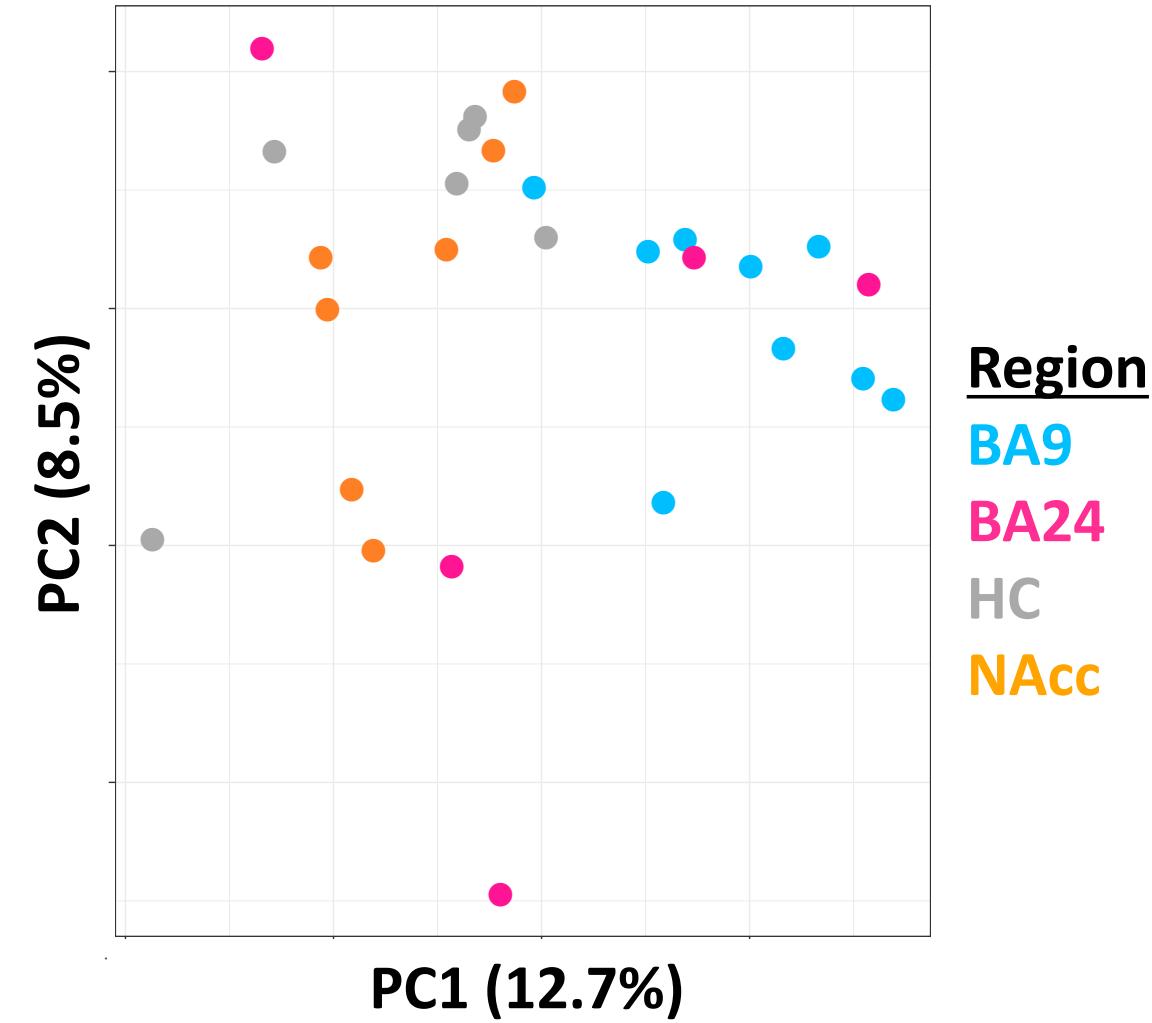
¹Davies, M. N. et al. Functional annotation of the human brain methylome identifies tissue-specific epigenetic variation across brain and blood. *Genome Biol.* **13**, R43 (2012).
²Roadmap Epigenomics Consortium et al. Integrative analysis of 111 reference human epigenomes. *Nature* **518**, 317–330 (2015).

A good map requires biological replicates, multiple brain regions, and multiple cell types



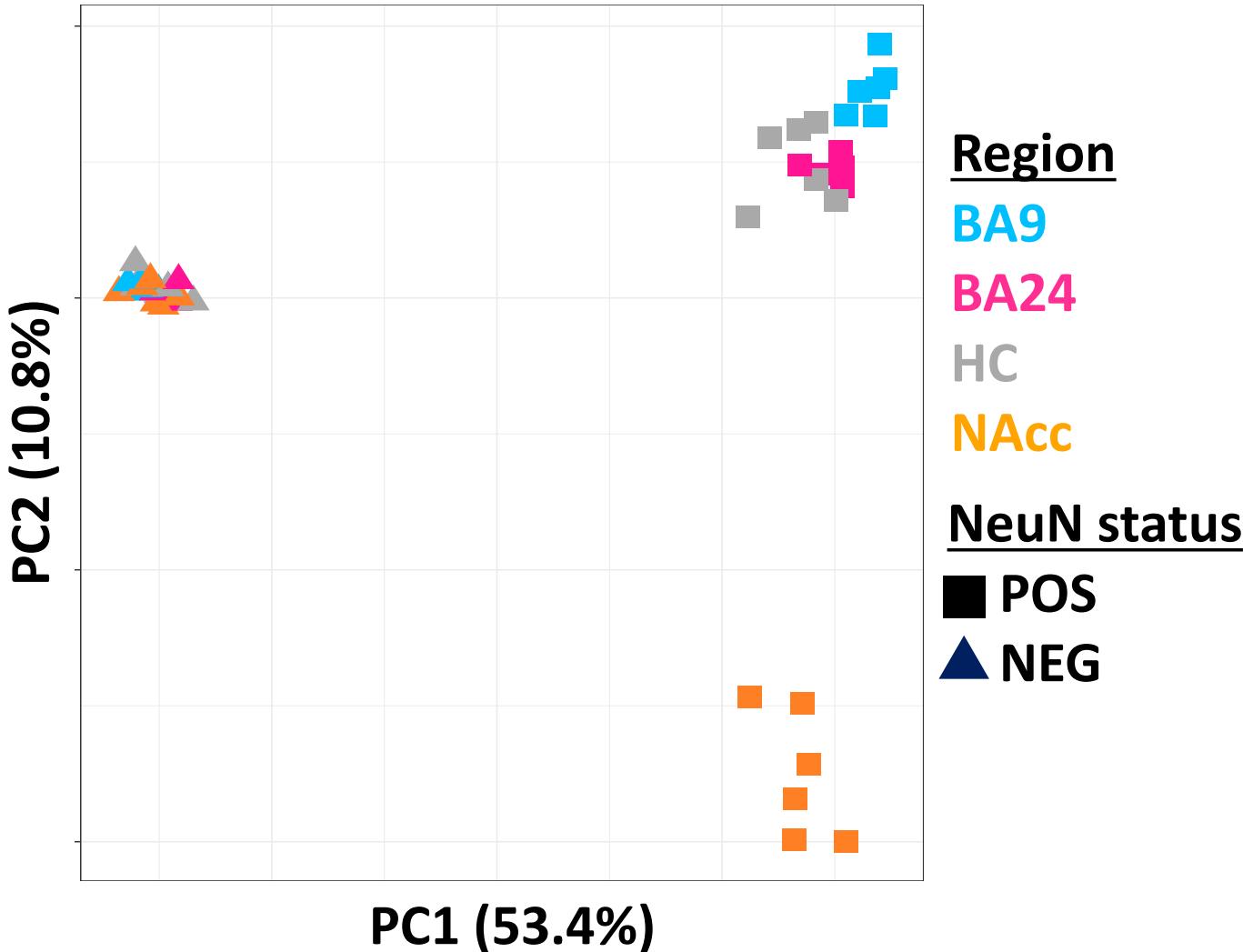
Bulk tissue samples are uninformative for brain region-specificity due to variation of neuronal proportion in sampled tissue

PCA: Bulk Tissue mCG



FANS + WGBS reveals brain region-specificity of mCG
in NeuN+ but not NeuN- samples

PCA: sorted nuclei mCG



Summary of DMRs

	Cell type DMRs	Brain region DMRs		
	CG-DMRs (NeuN+ vs. NeuN-)	CG-DMRs (NeuN+)	CG-DMRs (NeuN-)	CH-DMRs (NeuN+)
n	100,875*	13,074	114	15,029 ⁺
Total size (Mb)	70.0	11.9	0.1	39.6 ⁺⁺
Median (10-90%)	612	809	767	3558
width (bp)	(296 – 1157)	(671 – 3267)	(459 – 1789)	(2421 – 9269)

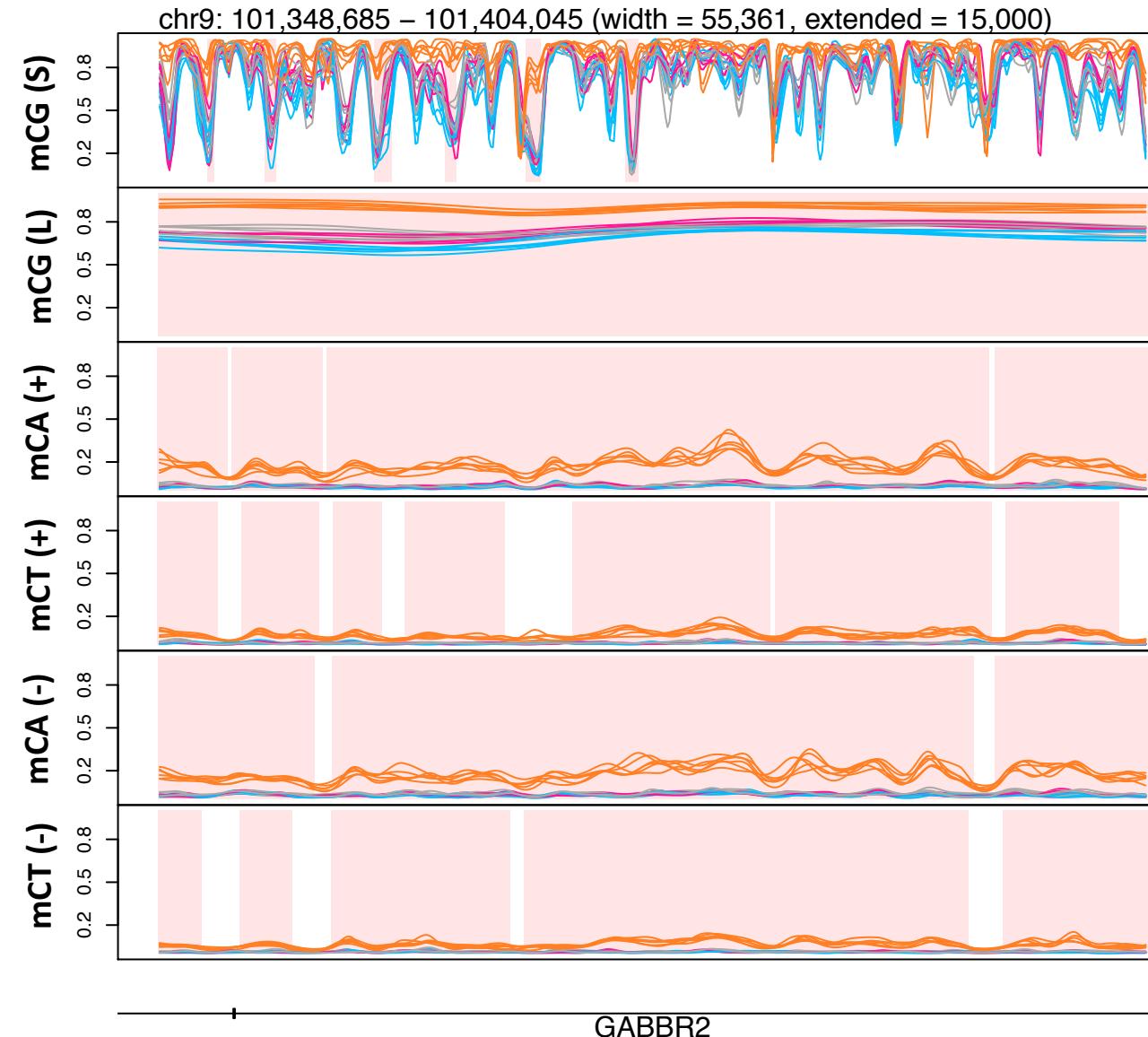
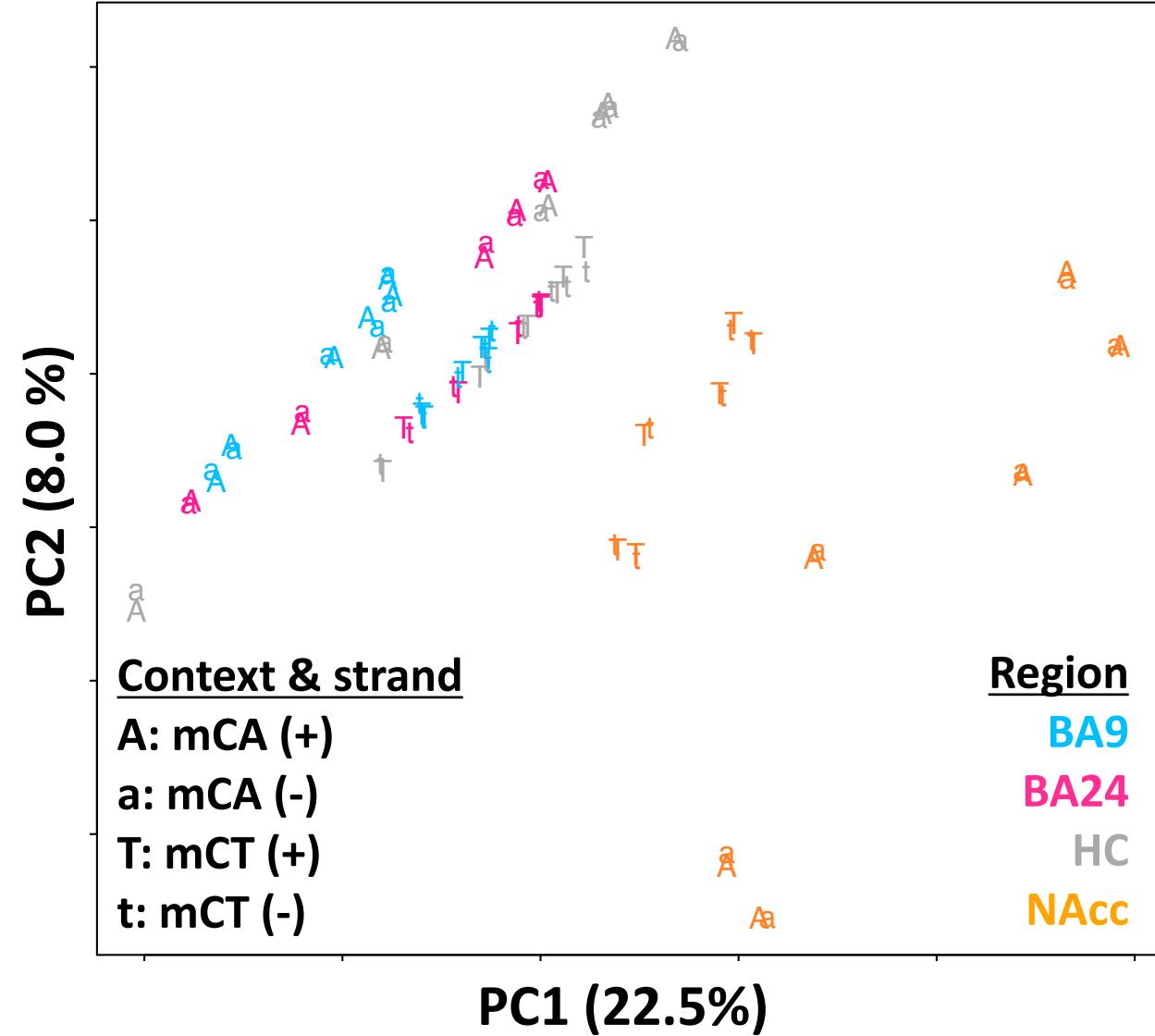
* 21,802 novel DMRs

⁺Before merging across strand and context

⁺⁺After merging across strand and context

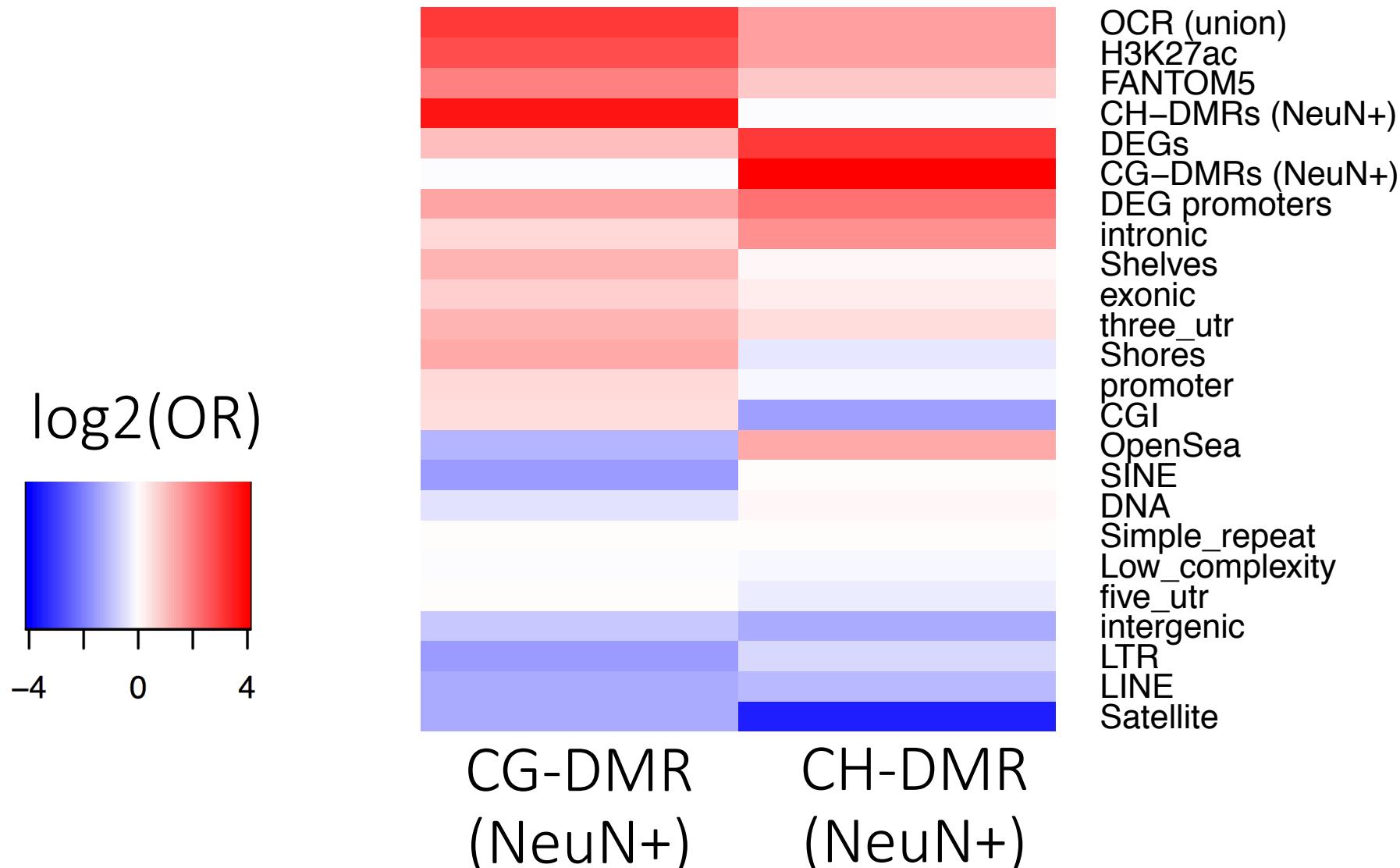
mCH shows little strand specificity and ‘tracks’ mCG (L)

PCA: NeuN+ mCH (1kb bins)



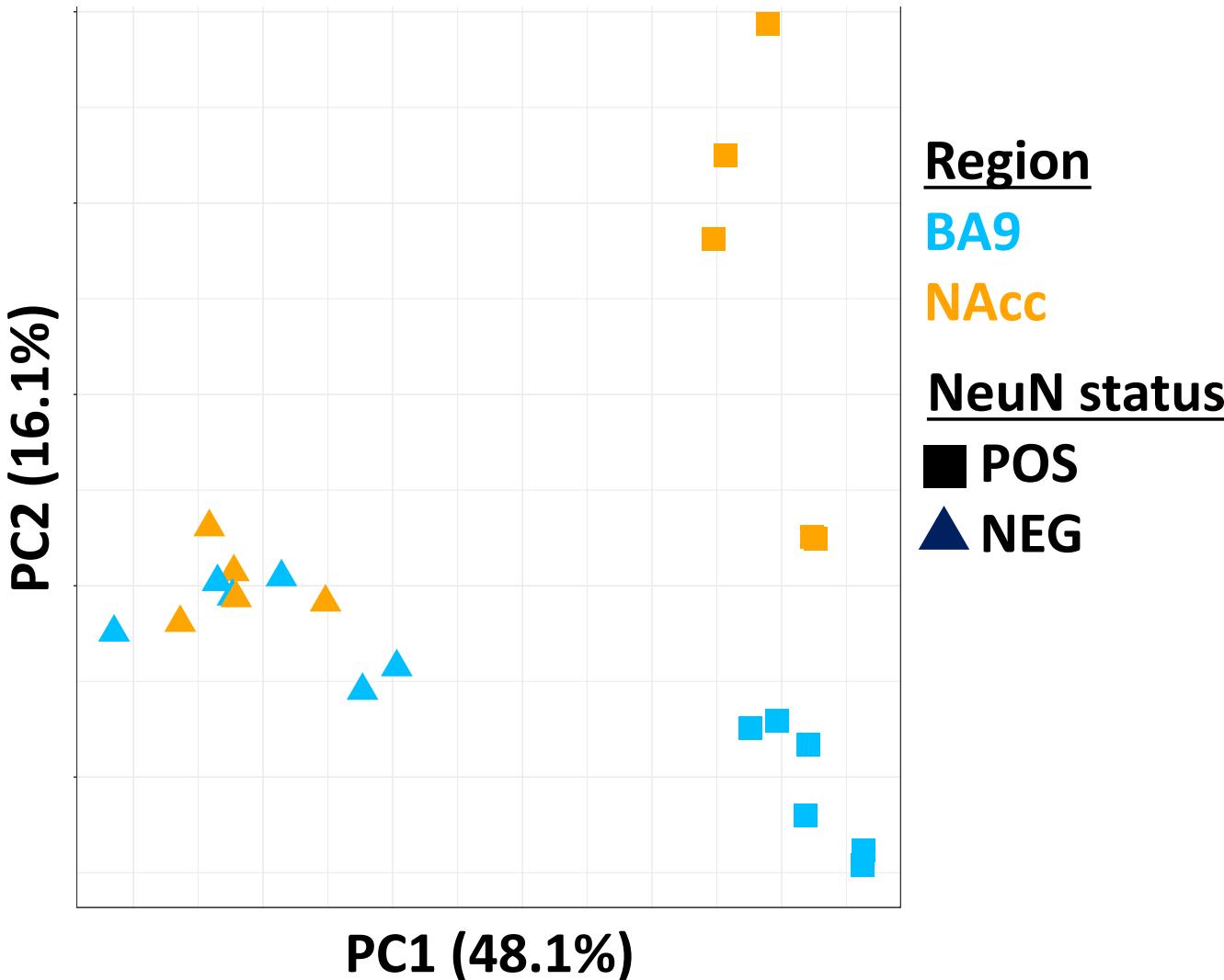
CG-DMRs and CH-DMRs co-occur

CG-DMRs are enhancer-centric, CH-DMRs are enriched over differentially expressed genes (DEGs) relative to non-DEGs



FANS + ATAC-seq reveals brain region-specificity of chromatin accessibility in NeuN+ but not NeuN- samples

PCA: sorted nuclei ATAC



FANS + ATAC-seq reveals brain region-specificity of chromatin accessibility in NeuN+ but not NeuN- samples

	OCRs (overall)	DARs (NeuN+ vs. NeuN-)	DARs (NeuN+)	DARs (NeuN-)
n	836,627	163,026	68,021	13
Total size (Mb)	619.5	275.8	118.1	0.05
Median (10-90%)	447	1176	1243	3739
width (bp)	(228 – 1459)	(659 – 3202)	(671 – 3267)	(1303 – 7541)

OCRs = Open Chromatin Regions are enriched over genic and regulatory-like features

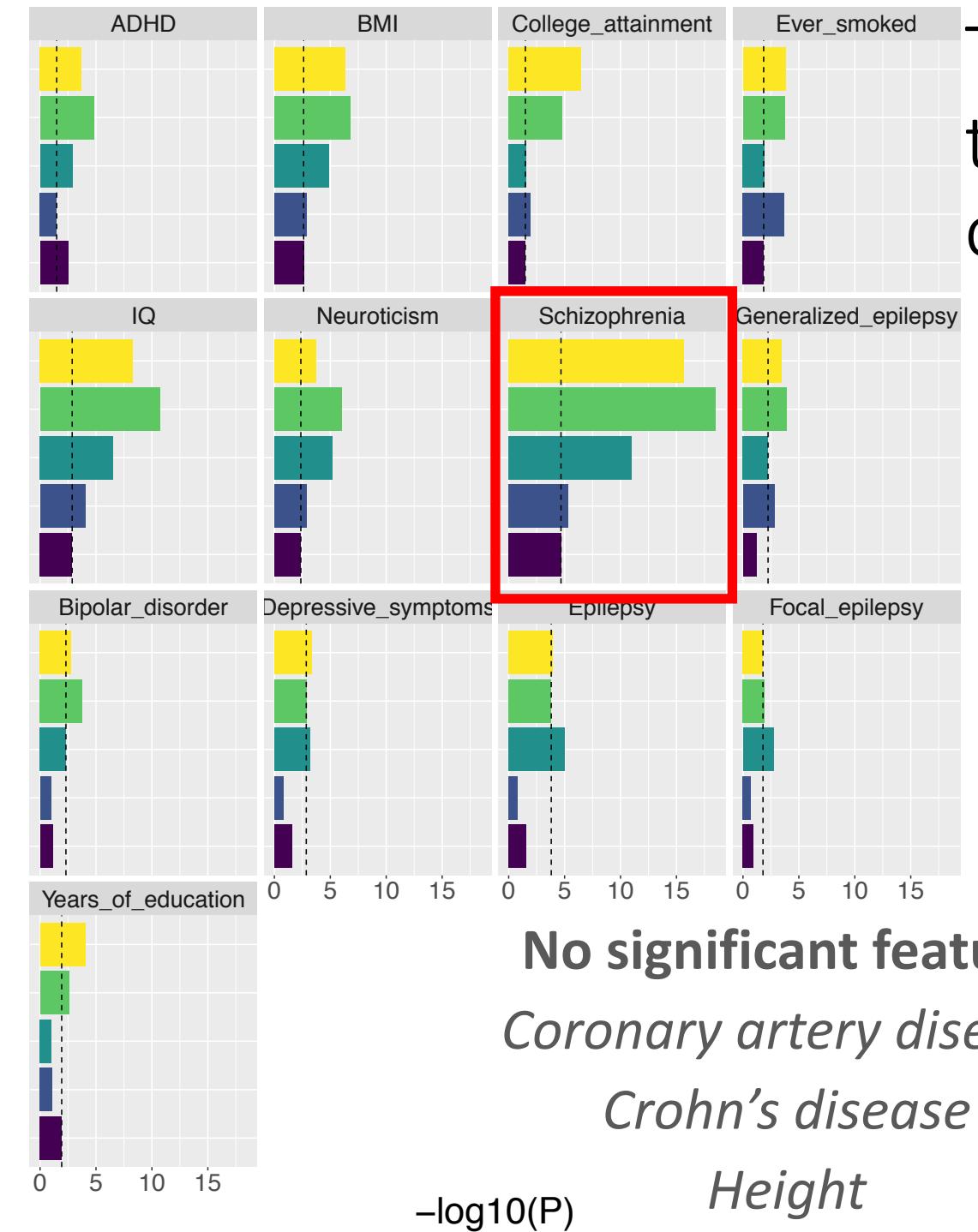
DARs = Differentially Accessible Regions are enriched over CG-DMRs

Linking brain region-specific epigenetic differences to disease

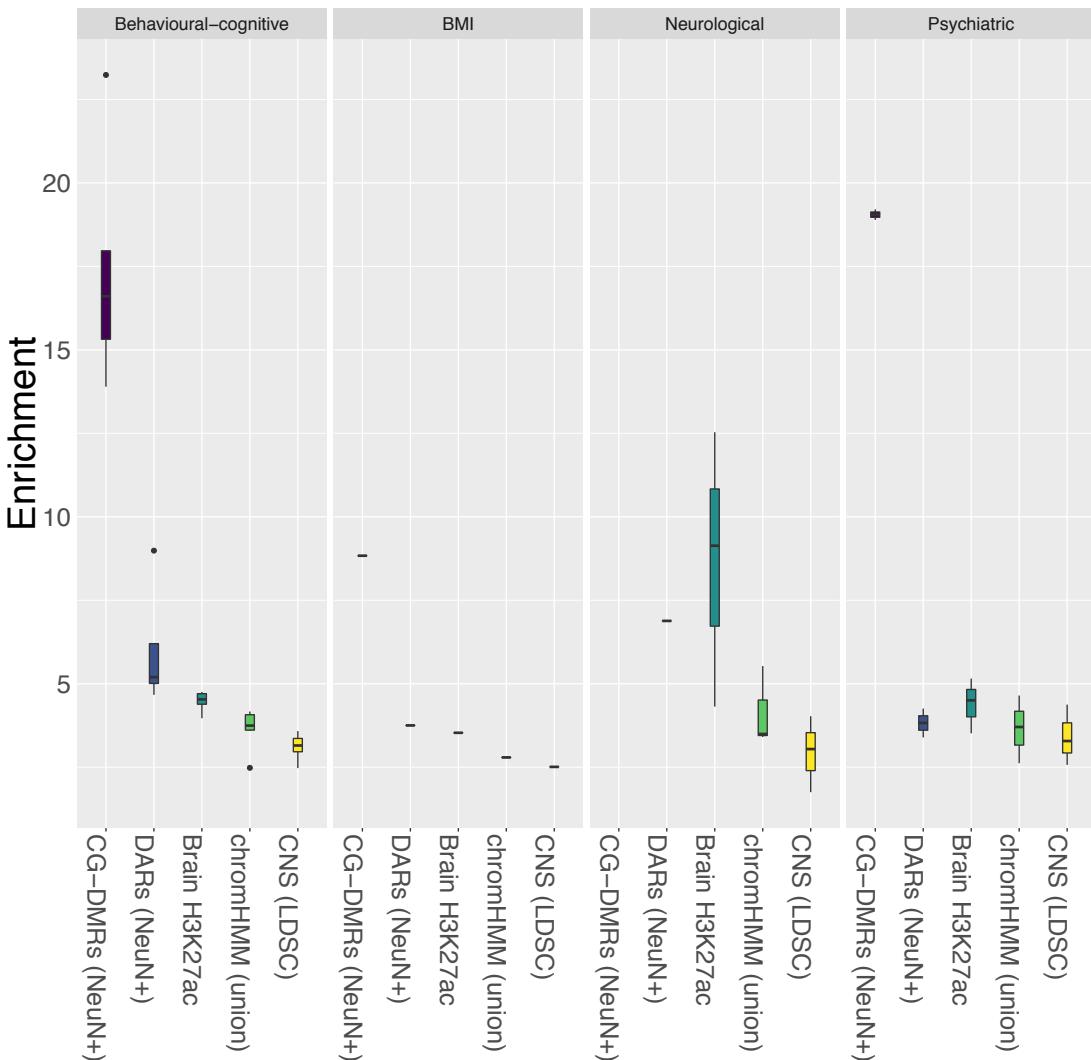
- Hypothesis: Regulatory regions in relevant cell types contain ‘GWAS signal’
- Stratified Linkage Disequilibrium Score Regression (SLDSR)¹
 - Estimate per-SNP heritability of trait from genome wide association study data
 - Partition the heritability by genomic features
- Traits (n = 30): E.g., schizophrenia, neuroticism, ADHD,
- Baseline features (n = 53): E.g., **conserved regions**, promoters, DHS
- Brain-derived features (n = 5): E.g., CG-DMRs, DARs, H3K27ac³
- Questions:
 - Does adding the brain-derived feature explain additional heritability over the 53 baseline features?
 - Are the brain-derived features enriched for heritability of the trait?

¹ Finucane, H. K. et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat. Genet.* 47, 1228–1235 (2015).

² Vermunt, M. W. et al. Large-scale identification of coregulated enhancer networks in the adult human brain. *Cell Rep.* 9, 767–779 (2014)



Traits with a brain-derived feature
that explains additional heritability
over baseline features



Summary

- Sorting is critical to identify brain region-specific epigenomic and transcriptomic changes
- More diverse brain regions brings lots to the party
- Little brain region-specificity of NeuN- data (WGBS, ATAC, RNA)
 - Additional sorting will help but not currently feasible
- CG-DMRs enriched for heritability of brain traits
- Data will be available as custom track hub on UCSC

Acknowledgements



Dr. Lindsay Rizzardi



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Summary

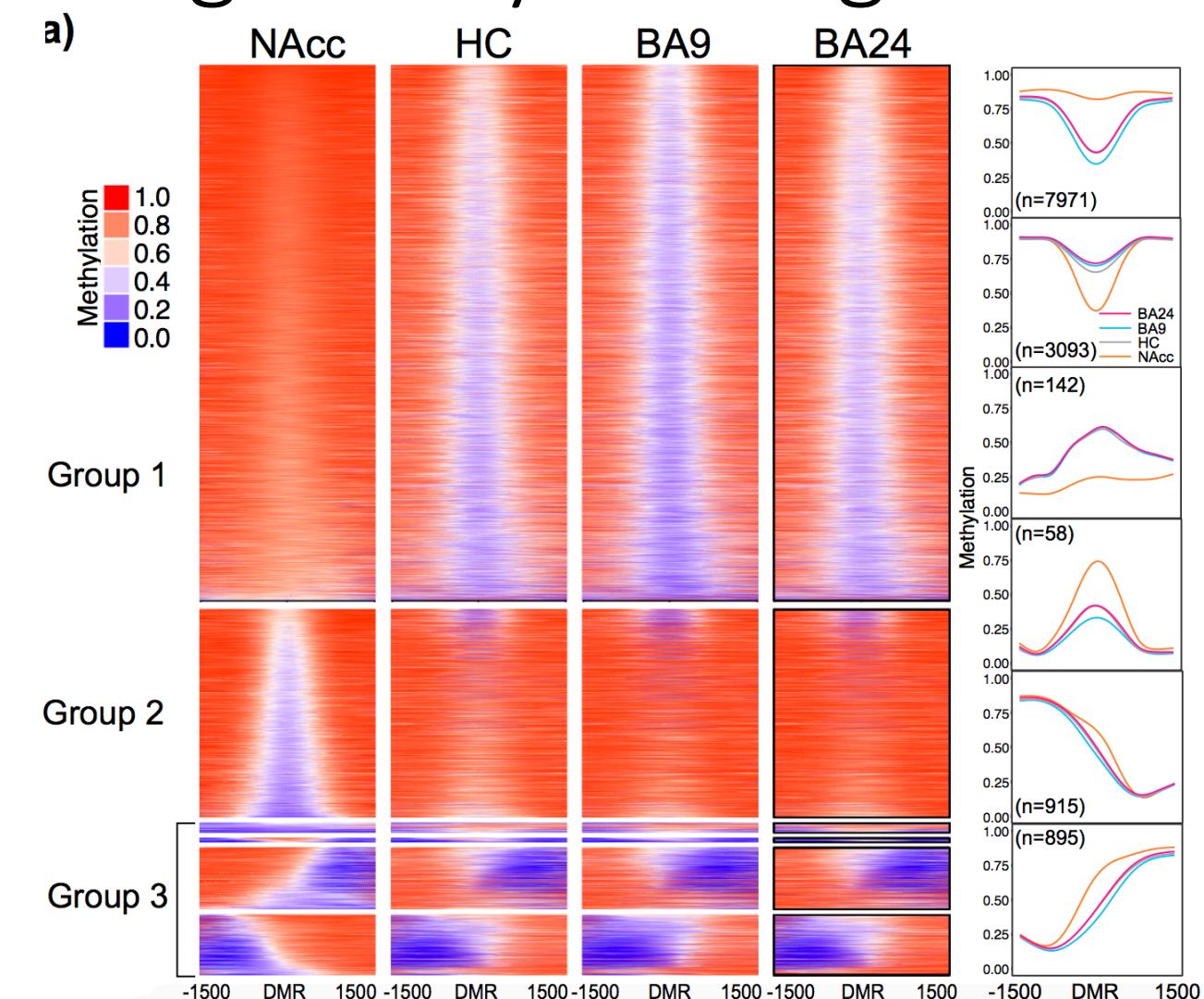
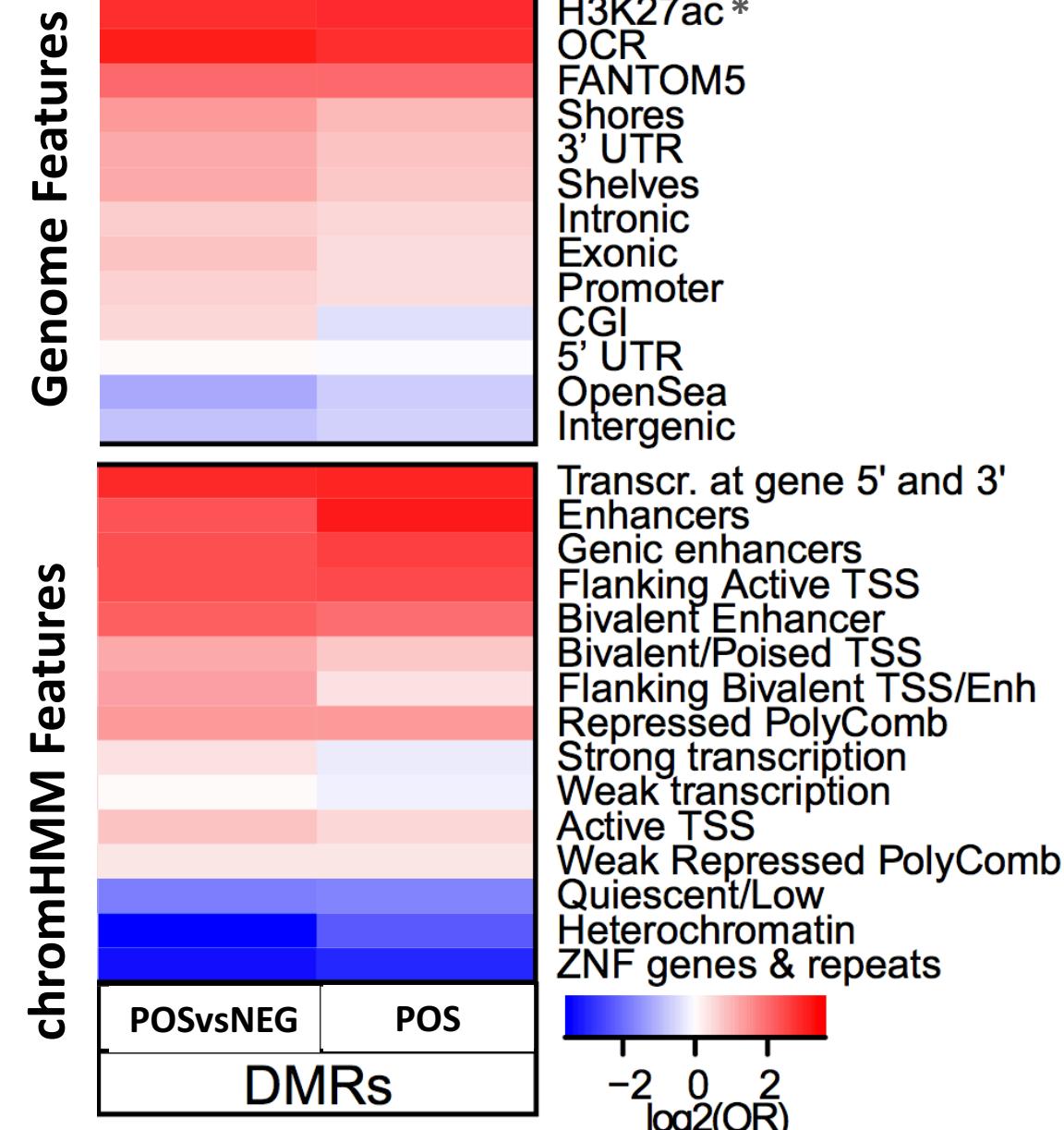
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<http://biorxiv.org/content/early/2017/03/24/120386>

Supplementary slides

CG-DMRs are enriched over regulatory-like regions



Group 1 & 2 enriched over enhancers

Group 3 are promoter enriched over promoters, CGI shores

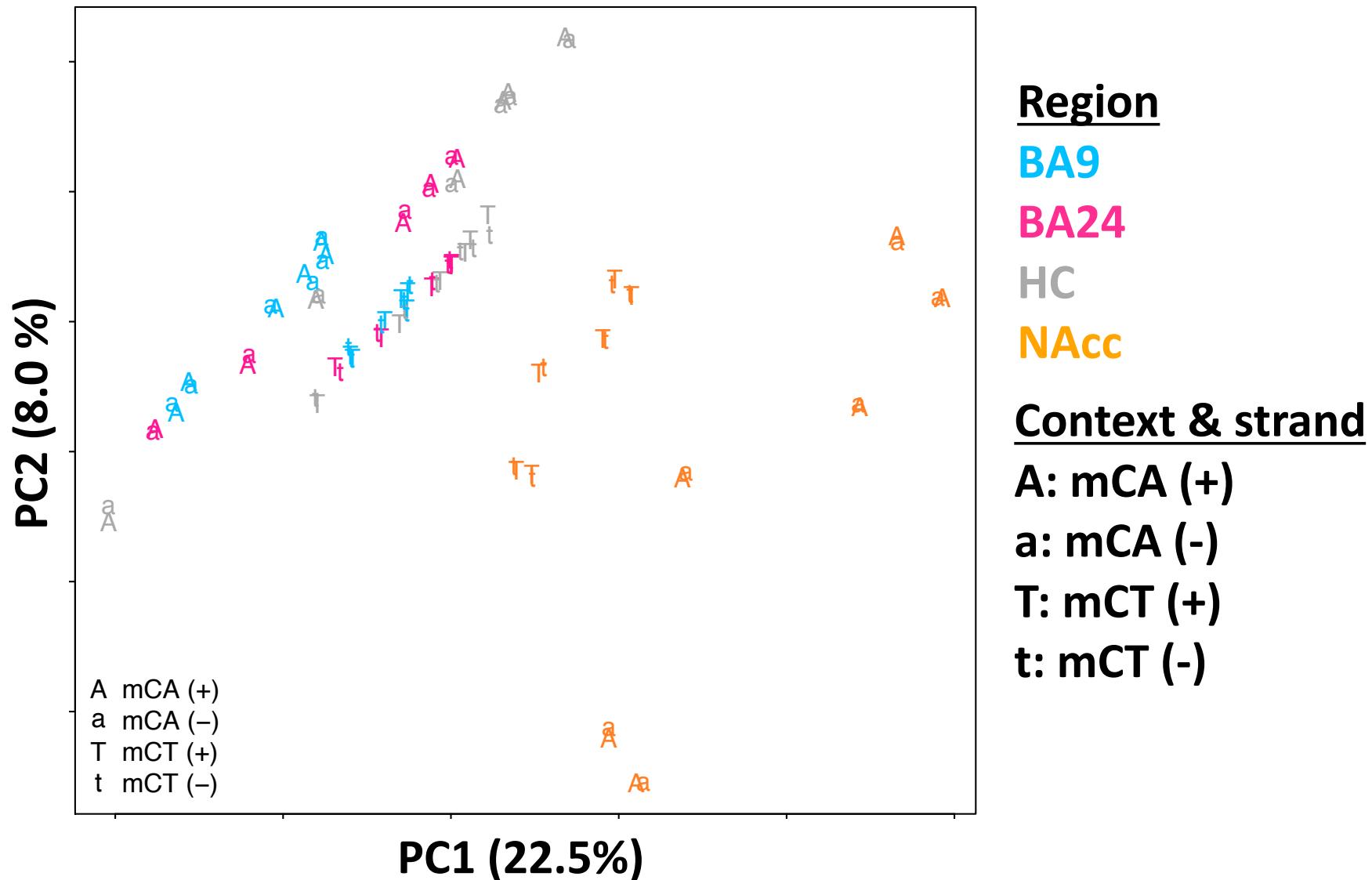
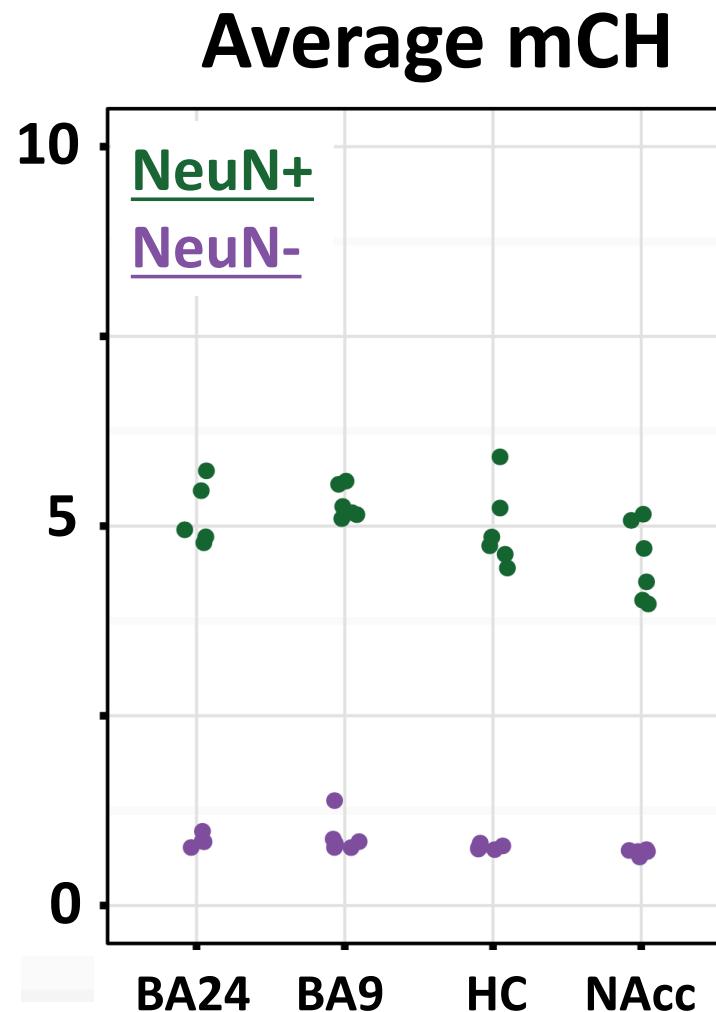
OCRs enriched over genic and regulatory-like features

DARs enriched over CG-DMRs

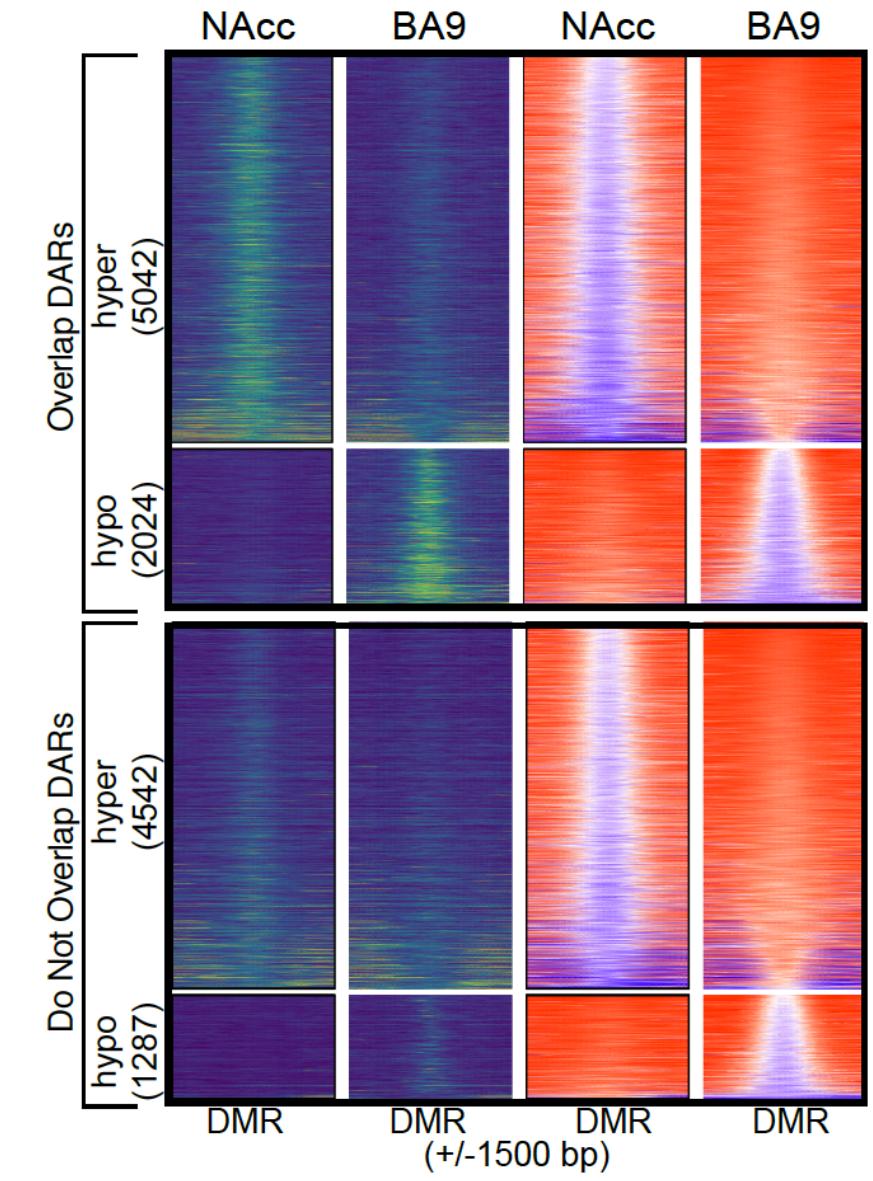
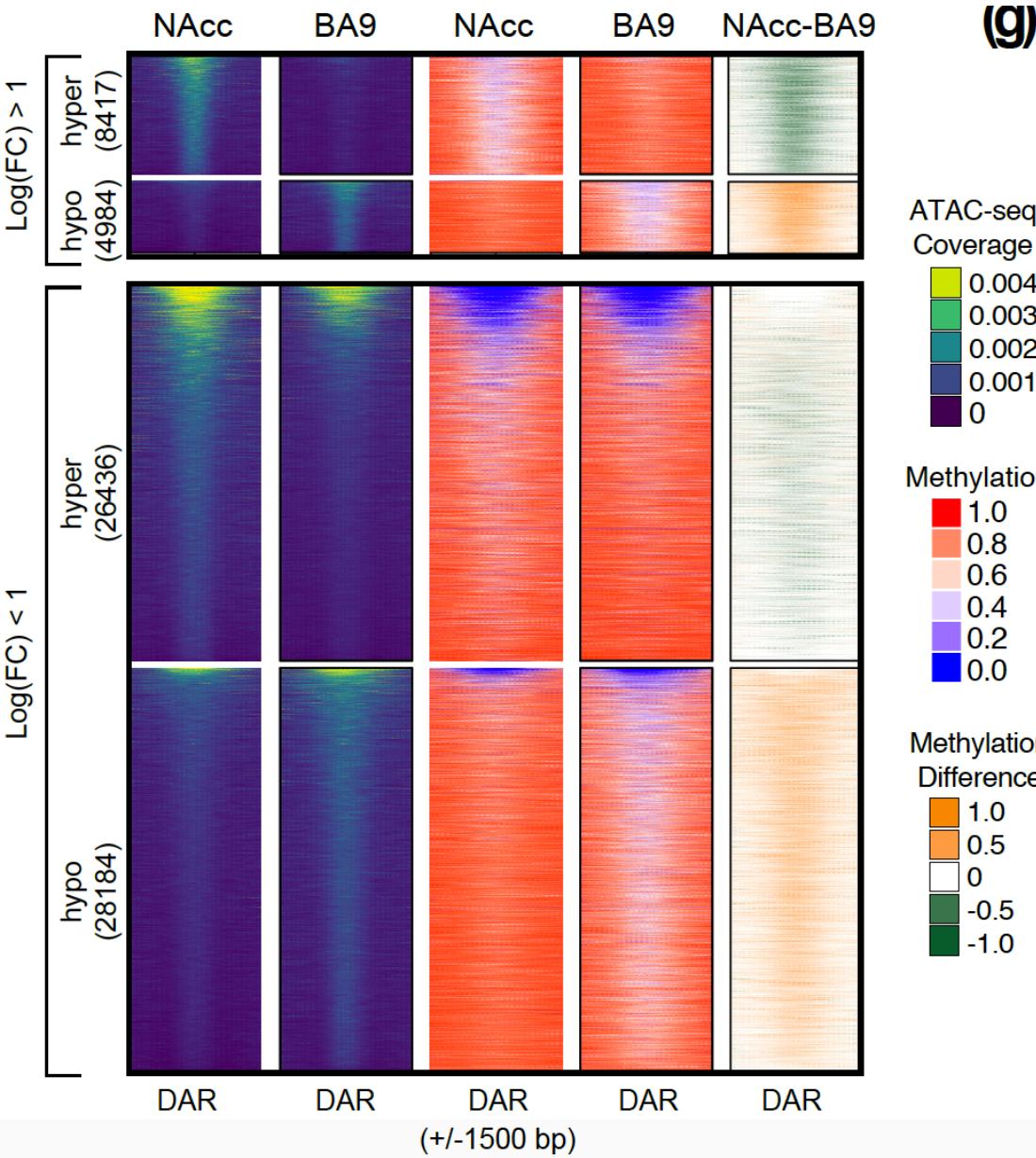


mCH is restricted to NeuN+ and shows little strand specificity

PCA: NeuN+ mCH (1kb bins)

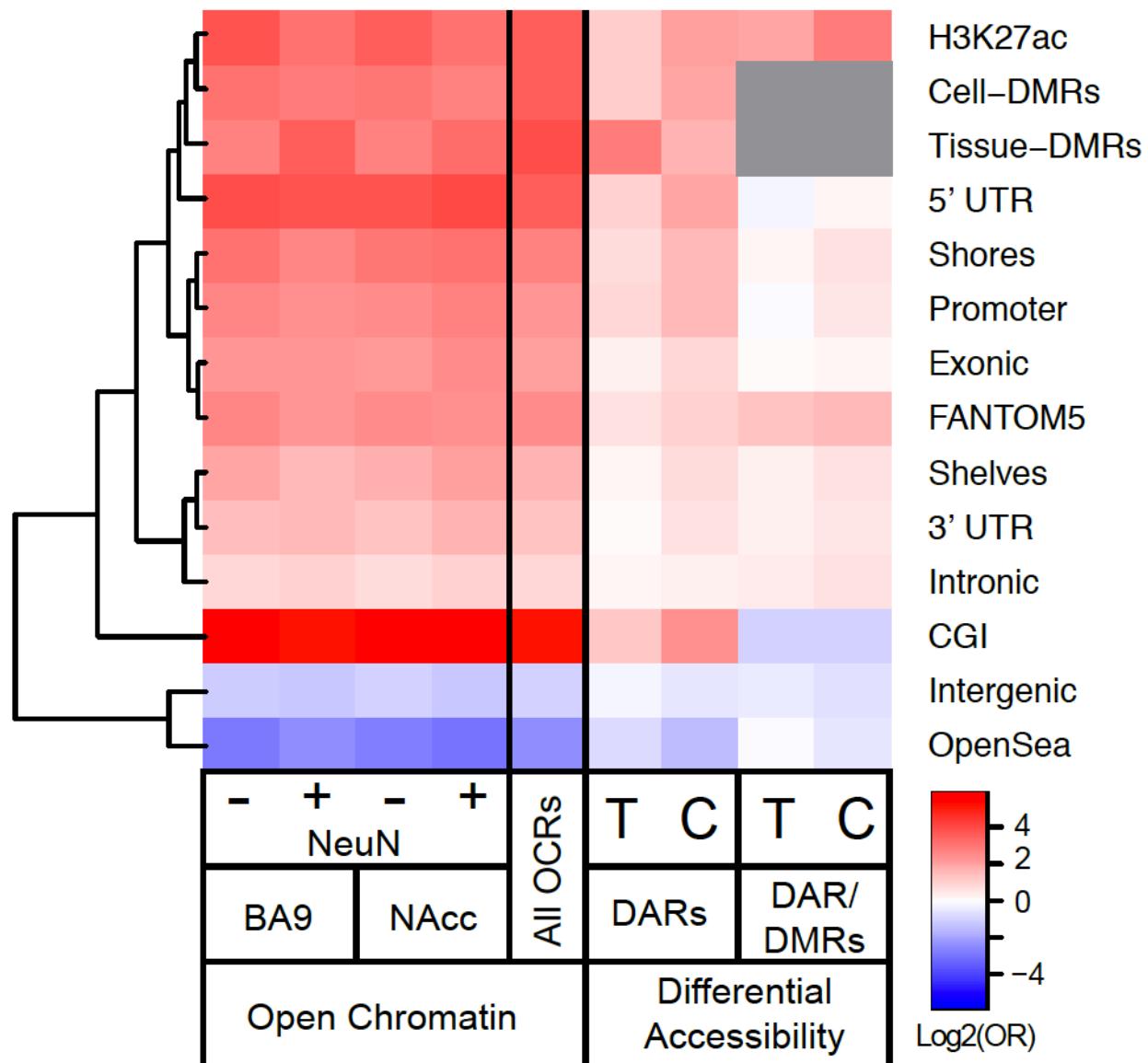


Consistent changes in chromatin accessibility and mCG within CG-DMRs and DARs



OCRs enriched over genic and regulatory-like features

DARs enriched over CG-DMRs



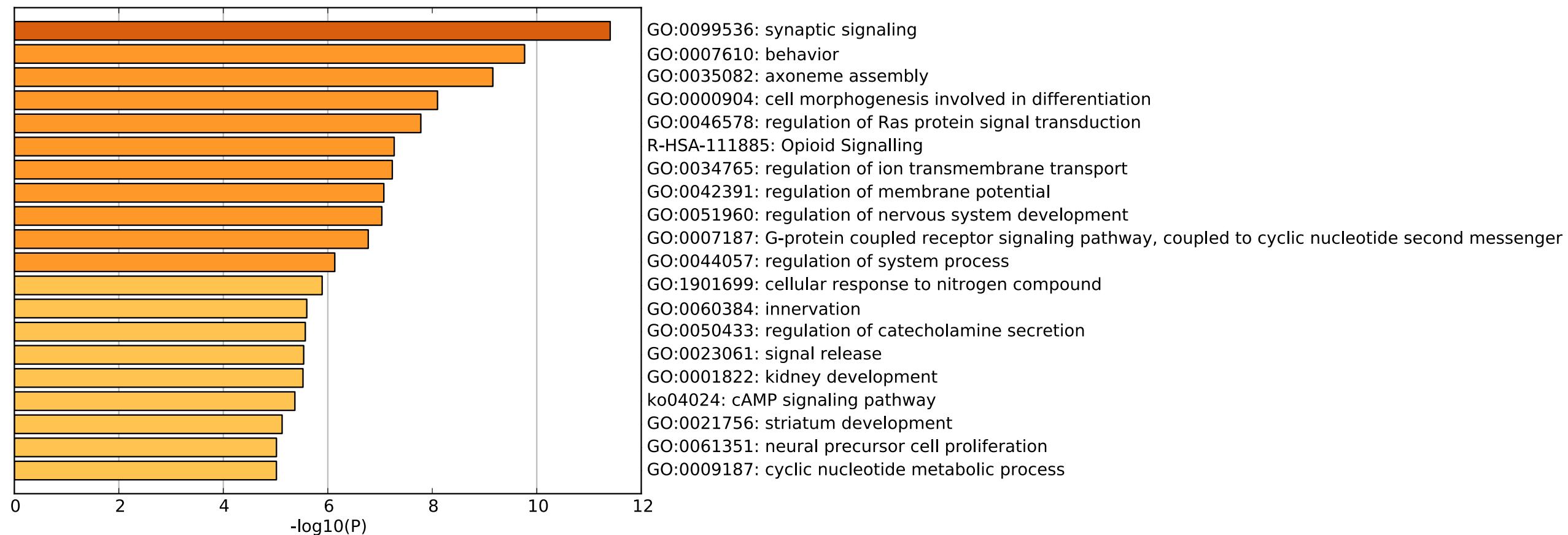


Feature

- yellow chromHMM (union)
- green CNS (LDSC)
- teal Brain H3K27ac
- blue DARs (NeuN+)
- purple CG-DMRs (NeuN+)

No significant feature
 Alzheimer's disease
 Anorexia nervosa
 Anxiety disorder
 Autism spectrum disorder
 Childhood cognitive performance
 Cigarettes per day
 Conscientiousness
 Extraversion
 Intracerebral hemorrhage
 Ischemic stroke
 Major depressive disorder
 Openness
 PTSD
 Subjective well-being
Coronary artery disease
Crohn's disease
Height

Up in NAcc_pos



Down in NAcc_pos

