# **IBD**

## BrainSeq Phase II: schizophrenia-associated expression differences between the hippocampus and the dorsolateral prefrontal cortex Collado-Torres L, Burke EE, Shin JH, Rajpurohit A, Semick SA, BrainSeq Consortium, Peterson A, Valencia C, Tao R, Deep-Soboslay A, Hyde TM, Kleinman JE, Weinberger DR+, Jaffe AE+ <u>drweinberger@libd.org</u> <u>andrew.jaffe@libd.org</u>

### LIEBER INSTITUTE for BRAIN DEVELOPMENT MALTZ RESEARCH LABORATORIES

### INTRODUCTION

We previously identified widespread genetic, developmental, and schizophrenia-associated changes in polyadenylated RNAs in the dorsolateral prefrontal cortex (DLPFC), but the landscape of hippocampal (HIPPO) expression using RNA sequencing is less well-explored. We performed RNA-seq using RiboZero on 900 tissue samples across 551 individuals (286 with schizophrenia) in DLPFC (N=453) and HIPPO (N=447). We quantified expression of multiple feature summarizations of the Gencode v25 reference transcriptome, including genes, exons and splice junctions. Within and across brain regions, we modeled age-related changes in controls using linear splines, integrated genetic data to perform expression quantitative trait loci (eQTL) analyses, and performed differential expression analyses controlling for observed and latent confounders.



	DLPFC	HIPPO	total
adult (age >= 18)	374	370	744
prenatal	29	28	57
0 <= age < 18	50	49	99
total	453	447	900

Schizophrenia cases			Non-psychiatric controls				
	DLPFC	HIPPO	total		DLPFC	HIPPO	total
adult	152	132	284	adult	222	238	460
prenatal	0	0	0	prenatal	29	28	57
0 <= age < 18	1	1	2	0 <= age < 18	49	48	97
total	153	133	286	total	300	314	614

### METHODS

Focus on being conservative: established processing methods, strict cutoffs, using replication when possible, adjust for RNA quality degradation confounding, avoid potential batch effects and take into account correlation at the individual level.

- **Region-specific** for adult or prenatal ages • Alternative:  $Expr = \beta_0 + age + Sex +$ 
  - $\sum_{i=1}^{5} snpPC_i + mitoRate + totalAssignedGene + RIN + Region$

Development

• Alternative:  $Expr = \beta_0 + age * Region + fetal * Region + birth *$ Region + infant \* Region + child \* Region + teen \* Region + adult \* Region + Sex + $\sum_{i=1}^{5} snpPC_i + mitoRate + totalAssignedGene + RIN + Region$ 

Case-control

p-value threshold

- Alternative:  $Expr = \beta_0 + age + Sex + mitoRate + rRNA_{rate} +$
- $\sum_{i=1}^{5} snpPC_i + totalAssignedGene + RIN + regionSpecificQSVs + Diagnosis$

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Replication using BrainSpan http://www.brainspan.org/



22 0.0 0.2 0.4 2 4 6 8 12 14 16 18 2020 30 40 50 50 55 60 65 70 75 80 Age

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HIPPO control > SCZD

DLPFC control > SCZD