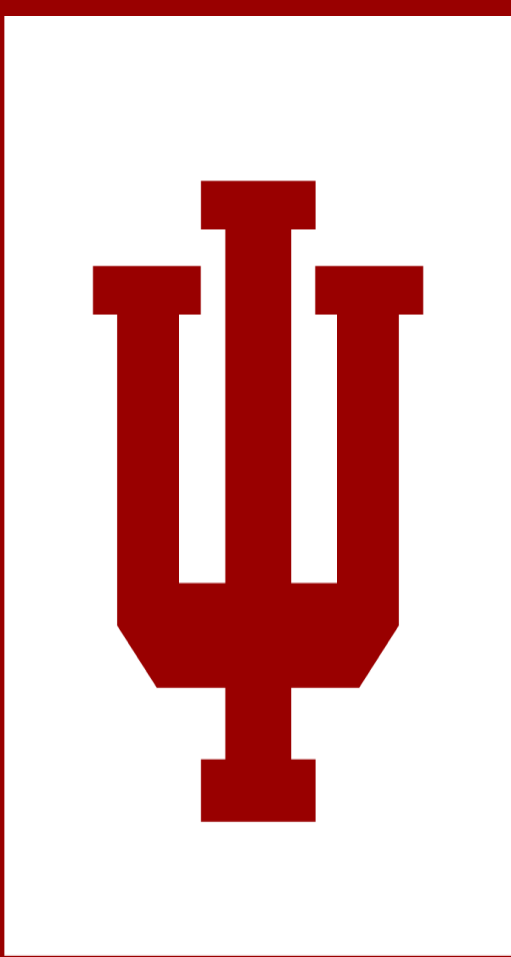




Regional Vulnerability of the Frontal Cortex in Vascular Cognitive Impairment and Dementia

Jessica L. Chalk¹, Erica M. Weekman¹, Brittani R. Price², Tiffany Sudduth³, Donna M. Wilcock¹

¹Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, IN, USA, ²Medical Affairs, Pharmaceutical Diagnostics, GE HealthCare, Marlborough, MA, USA, ³Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA.

INTRODUCTION

Vascular contributions to cognitive impairment and dementia (VCID) is a leading cause of age-related cognitive decline and is characterized by chronic cerebral hypoperfusion, neurovascular unit (NVU) dysfunction, and neuroinflammation. Although cognitive symptoms are largely driven by cortical dysfunction, the molecular mechanisms underlying regional vulnerability and resilience across the brain remain poorly understood. This study aimed to characterize transcriptomic differences between the frontal cortex and cerebellum in VCID to identify region-specific pathological responses.

MATERIALS & METHODS

Post-mortem frontal cortex (FCX) and cerebellum (CER) tissue from 12 VCID cases underwent gene expression profiling using NanoString's Human Neuroinflammatory Panel (784 genes). Differential gene expression analysis was performed using Limma, followed by Gene Ontology (GO) enrichment to identify altered biological pathways. In silico cell-type deconvolution based on established marker genes was used to estimate disease-associated shifts in cellular composition across brain regions.

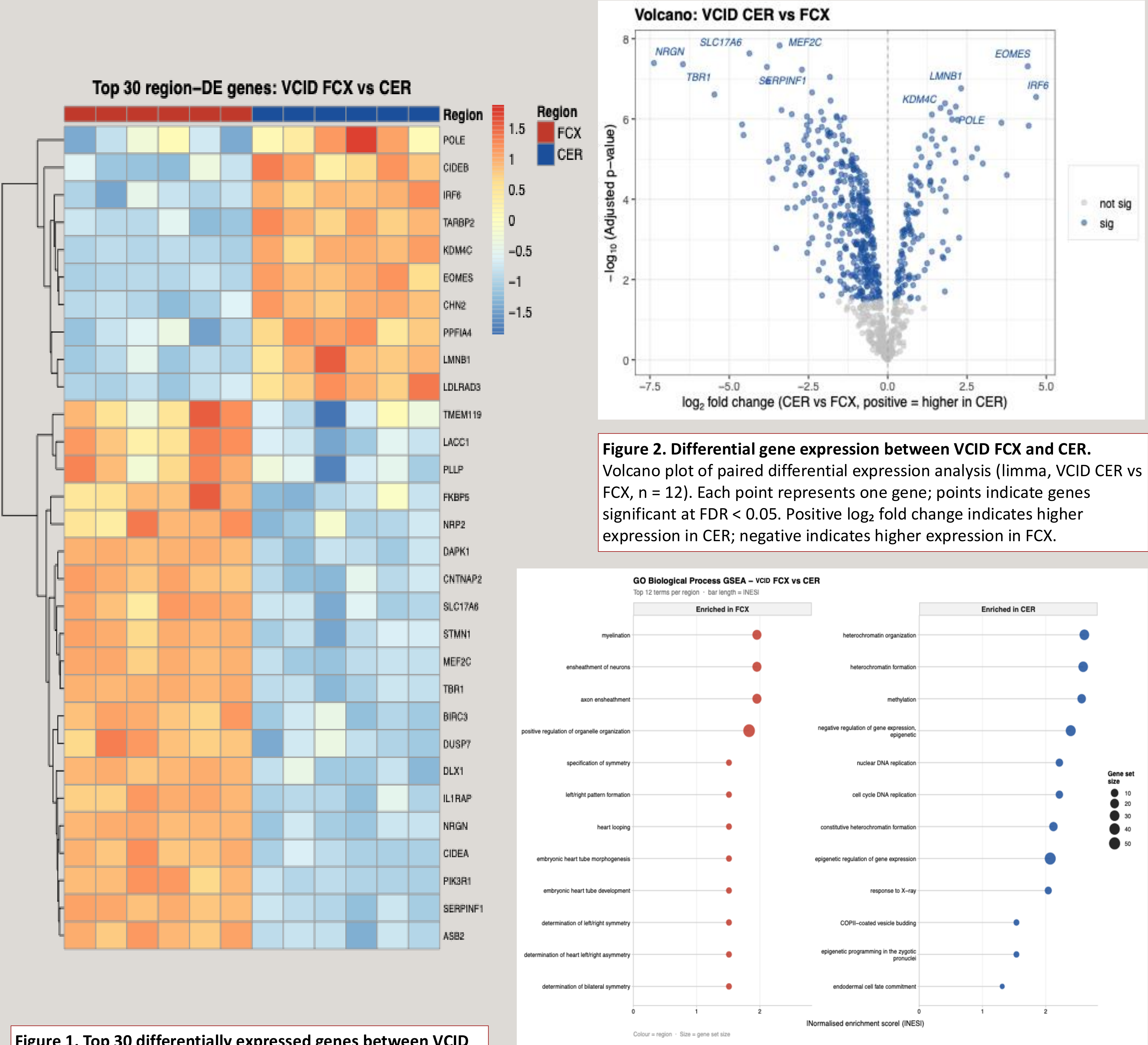


Figure 1. Top 30 differentially expressed genes between VCID FCX and CER. Heatmap of the 30 most significantly region-differentially expressed genes, scaled by row (z-score). Columns represent individual samples grouped by brain region (FCX, red; CER, blue); rows represent genes ordered by significance.

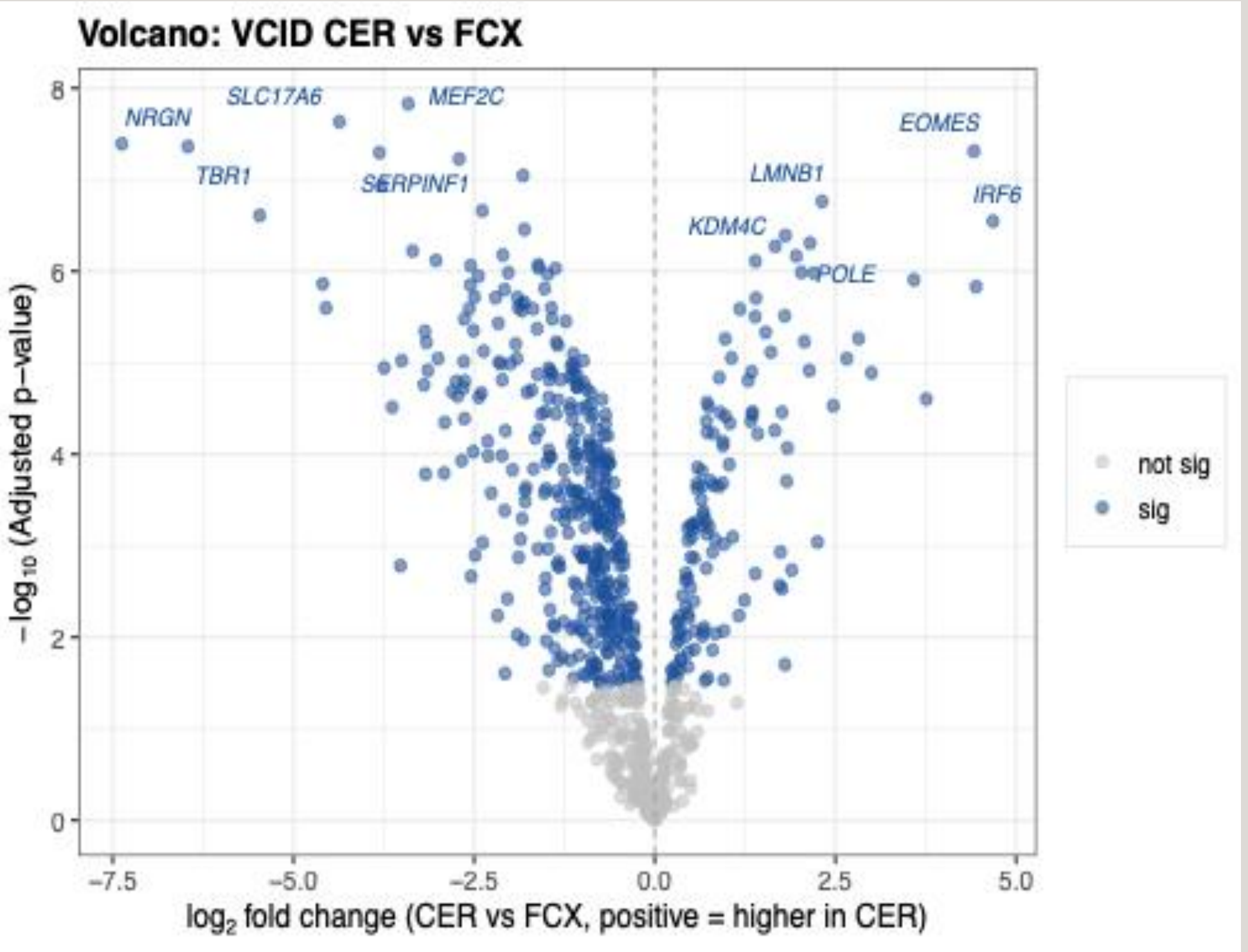


Figure 2. Differential gene expression between VCID FCX and CER. Volcano plot of paired differential expression analysis (limma, VCID CER vs FCX, n = 12). Each point represents one gene; points indicate genes significant at FDR < 0.05. Positive log₂ fold change indicates higher expression in CER; negative indicates higher expression in FCX.

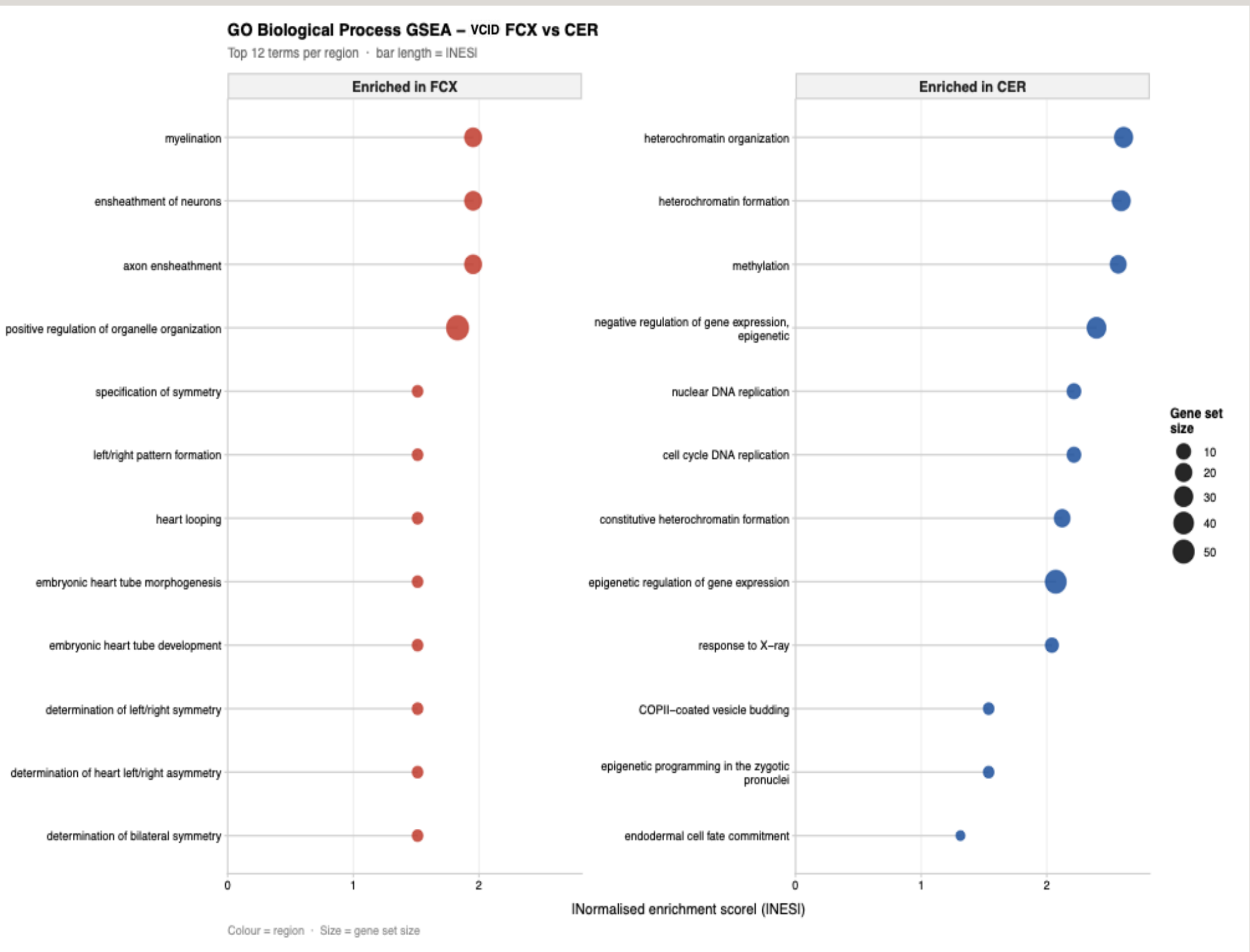


Figure 3. Gene Ontology enrichment of region-specific transcriptional differences in VCID. Gene Set Enrichment Analysis (GSEA) of GO Biological Process terms comparing VCID FCX and CER (n = 12). Bar length indicates the absolute normalized enrichment score (|NES|). Terms enriched in FCX (red) are dominated by neuronal processes including axon ensheathment, myelination, and regulation of organelle organization. Terms enriched in CER (blue) are concentrated in epigenetic regulation, heterochromatin organization, DNA replication, and developmental patterning processes.

CONCLUSIONS

Regional identity drives transcriptional variation in VCID

- **Frontal cortex is enriched for neuronal identity genes:** Upregulated genes include cortical transcription factors (*MEF2C*, *TBR1*, *DLX1*), synaptic markers (*NRGN*), and glutamatergic transporter *SLC17A6*. Pathway analysis confirms enrichment of axon ensheathment and myelination, processes vulnerable to vascular injury.
- **Cerebellum shows a distinct epigenetic and metabolic signature:** Upregulated genes include cell cycle regulators (*POLE*, *LMNB1*), lipid droplet genes (*CIDEA*, *CIDEB*), and chromatin remodelers (*KDM4C*). Pathway analysis reveals enrichment of heterochromatin organization, epigenetic regulation, and DNA replication.

Implications

- VCID does not produce a uniform transcriptional response across brain regions.
- FCX and CER exhibit distinct disease mechanisms, suggesting region-specific therapeutic targets should be considered in VCID research.

FUTURE DIRECTIONS

- MSD multi-array profiling will be used to validate inflammatory and neurovascular markers at the protein level.
- Spatial proteomics will be used to localize markers within the neurovascular niche.

ACKNOWLEDGEMENTS

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