

Female-Biased Mitochondrial Dysfunction and Glucose Stress in Drug-Naïve First-Episode Schizophrenia

Angela Rooks¹, Aidan R. Butler¹, Selah G. McKenney¹, Grant Nelson¹, Roshan Sirole¹, John M. Vergis¹, Robert E. McCullumsmith^{1,2}

¹Department of Neurosciences and Psychiatry, The University of Toledo College of Medicine, Toledo, OH, U.S.A., ²Neuroscience Institute, ProMedica, Toledo, OH 43606, USA

Cognitive Disorders Research Laboratory

Introduction

Schizophrenia is increasingly recognized as a systemic disorder, not solely a brain-based illness. Peripheral blood leukocytes provide a minimally invasive window into disease-related immune, metabolic, and transcriptional changes. Because schizophrenia also shows clear sex differences in onset and course, we examined whether metabolic abnormalities are already present at first episode and whether they differ by sex.

Significance

1. Define sex-specific metabolic disruptions and identify actionable control points in first-episode, drug-naïve schizophrenia.
2. Females showed broader mitochondrial suppression and glucose-stress signaling, highlighting bioenergetic pathways as candidate therapeutic targets.
3. Incorporating sex as a planned analytic variable may improve mechanistic precision and translational relevance.

Methods

We reanalyzed RNA-seq data from peripheral blood leukocytes of 84 first-episode, drug-naïve schizophrenia patients and 97 controls using an integrated GSEA, EnrichR, and LINCS workflow.

Conclusion

First-episode, drug-naïve schizophrenia shows sex-related metabolic differences, with females demonstrating broader mitochondrial downregulation and reduced glucose-ketone switching, highlighting mitochondria and fuel handling as potential therapeutic targets.

Overview of Workflow

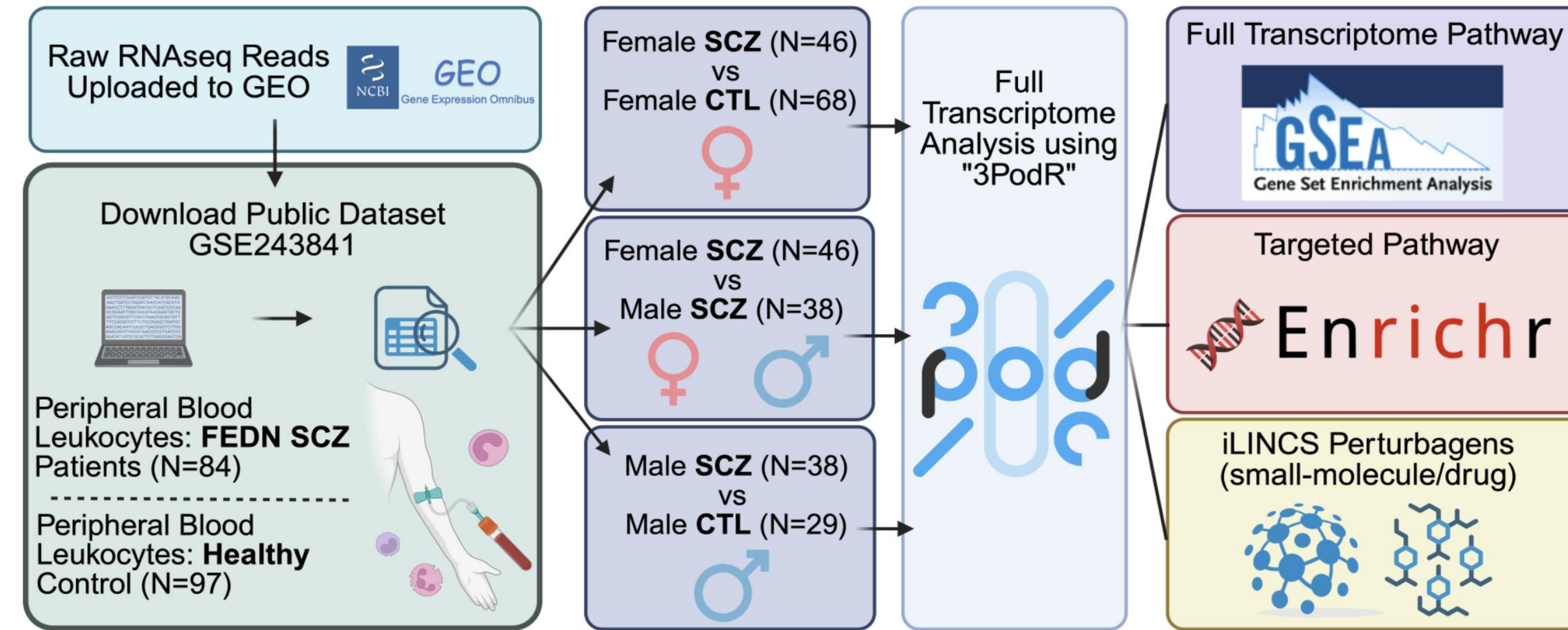


Figure 1. Workflow of analysis.

Results

Mitochondrial Programs in Females	NES
Mitochondrial matrix	-1.73
Inner membrane	-1.56
Mitochondrial gene expression	-1.75
Mitochondrial translation	-1.77
Mitochondrial ribosomes	-1.81

Figure 2. In GSEA, females showed coordinated downregulation of mitochondrial programs.

Mitochondrial Programs in Males	NES
Regulation of mitochondrial translation	-1.81

Figure 3. In GSEA, males showed downregulation that was more restricted and centered on regulation of mitochondrial translation.

Females showed broad mitochondrial downregulation and upregulated glucose-stress pathways with reduced ketone metabolism. Males showed narrower mitochondrial downregulation, mainly in translation. EnrichR supported insulin-axis involvement in both sexes, stronger in males, and LINCS implicated glucose transport in both sexes.

Glucose stress with reduced ketone pathways in Females	NES
Glucose starvation response	2.1
Intracellular glucose homeostasis	2.06
Ketone metabolic processes	-1.65

Figure 4. In GSEA, females showed glucose stress with reduced ketone pathways.

Sex	Perturbagen	Similarity	MOA
male	Phloretin	-0.359	Sodium/glucose cotransporter inhibitor
female	Phloretin	-0.284	Sodium/glucose cotransporter inhibitor

Figure 5. In LINCS, glucose transport was prioritized with phloretin among top discordant signatures in both sexes.

DEG Analysis

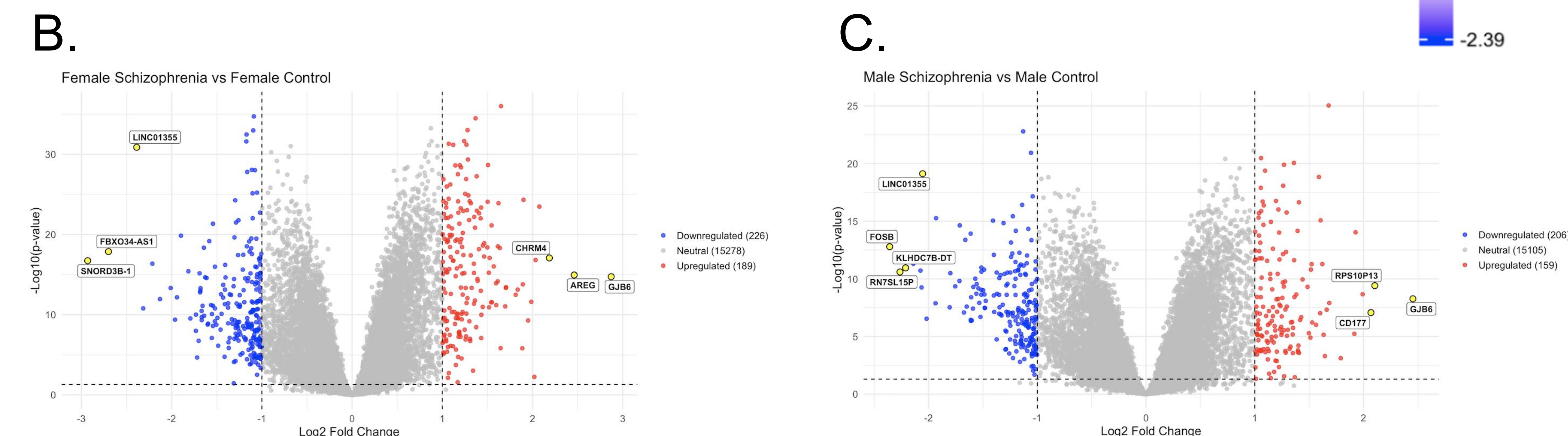
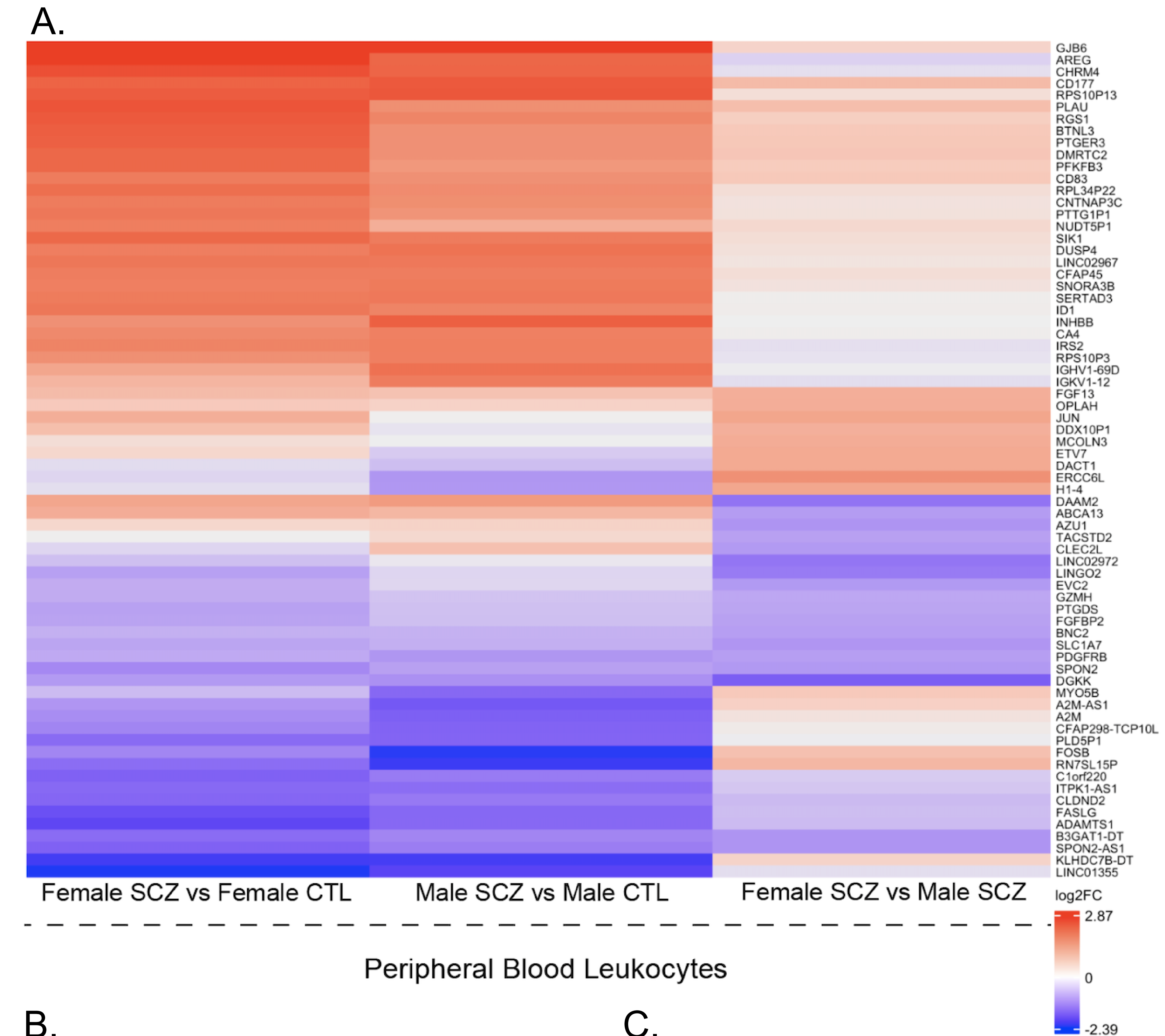


Figure 6. Top 50 significantly (adjusted for p-value <= 0.05) differentially expressed genes (DEGs) for each comparison determined by greatest absolute log2FoldChange (A.); Volcano plots showing male SCZ versus male CTL (B), and female SCZ vs female CTL (C).