UTJMS 2026 February 03, 14(S4):e1-e18 doi:10.46570/utjms-2025-1899

Sex-Based Transcriptomic Variations in Schizophrenia: Prospects for Targeted Therapy

Eire Chen[1*], Jasleen Mann[1*], Fred Muler[1*], Henry Sun[1*], Eleza Zaidi[1*], Robert McCullumsmith[2,3], Jacob Schmieder[4], Hunter Eby [1#]

[1] Summer Biomedical Science Program in Bioinformatics, Department of Neurosciences and Psychiatry, College of Medicine & Life Sciences, Toledo, OH, USA
[2] Department of Neurosciences and Psychiatry, University of Toledo, College of Medicine and Life Sciences, 3000 Arlington Avenue, Toledo OH 43614
[3] Promedica, 2130 W. Central Ave., Toledo, Ohio 43606 Toledo, Ohio, USA
[4] Department of Anesthesiology, College of Medicine and Life Sciences, 3000 Arlington Avenue, Toledo OH 43614
*Authors contributed equally

Email: Hunter.Eby@rockets.utoledo.edu
Received: 12/12/2025
Accepted: 12/12/2025
Published: 02/03/2026

Abstract

Schizophrenia is a complex neuropsychiatric disorder with significant sex differences in onset, symptoms, and outcomes, suggesting that biological sex may influence disease mechanisms. However, molecular differences between males and females with schizophrenia remain poorly defined. This study examined sex-specific transcriptional alterations in the dorsolateral prefrontal cortex (DLPFC) of individuals with schizophrenia using publicly available RNA-sequencing data (GSE208338). Differential gene expression (DGE) analyses were performed separately for male and female cohorts, followed by gene set enrichment analysis (GSEA), leading-edge (LE) gene analysis, and perturbagen signature matching using the Library of Integrated Network-Based Cellular Signatures (iLINCS). No genes reached significance after correction, but unadjusted analyses revealed marked sex differences. Using the uncorrected analysis, Males exhibited over 2,000 differentially expressed genes distributed evenly between up- and downregulation, whereas females showed a smaller set of differentially expressed genes that were skewed towards upregulation. Pathway-level analyses showed that males displayed upregulation of metabolic pathways and downregulation of synaptic transport processes, while females exhibited upregulation of immune pathways alongside downregulation of vesicle organization and phosphoinositide metabolism. LE gene analysis supported the pathway changes. iLINCS analysis further highlighted sex-specific drug candidates whose expression profiles were discordant schizophrenia-associated signatures. FDA approved medications with high discordance included JAK2/mTOR pathway inhibitors and metabolic regulators in males, and immune or hormonal modulators in females. Taken together, these results reveal divergent molecular signatures that may underlie sex differences in schizophrenia pathophysiology. The identification of candidate drugs with discordant transcriptomic effects suggests potential therapeutic avenues and emphasizes the importance of sex stratified approaches in schizophrenia research.

Keywords: Schizophrenia, Drug repurposing, RNAseq, Sex Differences, Pathway Analysis

UTJMS 2026 February 03, 14(S4):e1-e18 doi:10.46570/utjms-2025-1899

1. Introduction

Schizophrenia (SCZ) is a severe neuropsychiatric disorder characterized by disturbances in thought, perception, and cognition that often lead to lifelong social and functional impairment (1). Although the clinical presentation can vary widely, schizophrenia remains among the leading causes of disability worldwide, with affected individuals experiencing reduced life expectancy due to suicide, metabolic disease, and limited access to healthcare (1). Despite decades of research, the biological mechanisms driving schizophrenia remain only partially understood.

A growing body of evidence suggests that schizophrenia is not a single, uniform entity but a syndrome shaped by biological sex and molecular context. Men and women exhibit distinct patterns in disease onset, symptom severity, and long-term outcomes: men typically experience earlier onset and more severe negative symptoms, while women tend to present later with more affective features and better functional recovery. These clinical observations imply that sex-specific biological processes, hormonal, genetic, and neuroimmune, may influence disease pathogenesis (2,3). However, most large-scale molecular studies of schizophrenia are not stratified results by sex, leaving critical gaps in understanding how male and female brains diverge at the transcriptomic level.

Emerging data point toward schizophrenia as a disorder rooted in dysregulated neurodevelopment and immune signaling (4, 5). Aberrant synaptic pruning altered glutamatergic and dopaminergic transmission, and microglial activation are implicated in disease progression (6). Genetic studies link risk variants to pathways involved in synaptic function and immune regulation, including complement-mediated pruning and cytokine signaling. It's unclear whether these molecular disturbances manifest differently between males and females.

To address this knowledge gap, we reanalyzed postmortem dorsolateral prefrontal cortex (DLPFC) RNA-sequencing data from individuals with schizophrenia and neurotypical controls, stratified by sex (7). Next, we interrogate sex-specific transcriptional dysregulation for a cortical region central to cognition and executive function. We used differential gene expression analysis and gene set enrichment analysis (GSEA) to identify biological pathways altered in male and female patients, followed by leading-edge (LE) analysis to pathway changes (8). Finally, we leveraged the Library of Integrated Network-Based Cellular Signatures (iLINCS) to identify FDA-approved compounds whose gene expression profiles were discordant with schizophrenia signatures in a sex-specific manner, highlighting potential therapeutic candidates (9). This integrated transcriptomic and perturbagen analysis provides a framework for understanding how schizophrenia manifests differently in men and women at the molecular level and identifies drug candidates that may inform precision, sex-aware treatment strategies.

2. Methods

We reanalyzed bulk RNA-sequencing data from the dorsolateral prefrontal cortex (DLPFC; Brodmann area 9) using a publicly available dataset (GEO accession: GSE208338) (7). This dataset includes postmortem DLPFC tissue from 130 individuals aged 18–87 years, comprising individuals diagnosed with schizophrenia (n = 68, 54 Male, 14 Female) and demographically matched neurotypical controls (n = 62, 49 = Male, 13= Female). Tissue was dissected from the lateral surface of the frontal lobe, encompassing the middle frontal gyrus to the inferior frontal sulcus of the left hemisphere. Diagnostic classifications were determined using the Diagnostic Instrument for Brain Studies (DIBS), and all tissue collection and processing procedures were performed according to protocols described in the original dataset.

Differential Gene Expression Analysis

All computational analyses were conducted in R (version 4.4.0) using Rstudio (10). Raw count matrices were imported, and gene-level normalization and filtering were performed prior to differential expression analysis. Sex-stratified comparisons were conducted between SCZ and control groups: SCZ females vs. control females, and SCZ males vs. control males. Differential gene expression was assessed using the DGE package (11), and results were visualized via volcano plots with ggplot. The x-axis of the plots represents log2 fold change (log2FC), while the y-axis denotes –log10(p-value). No fold-change threshold were applied, as emphasis was placed on unfiltered p-value distributions to capture the full spectrum of transcriptional variation.

To account for multiple hypothesis testing, p-values were adjusted using false discovery rate (FDR) threshold of 0.05. Adjusted p-values (padj) were derived by ranking raw p-values in ascending

order and applying the formula (i/m)Q, where i is the rank, m is the total number of tests, and Q is the target FDR.

Pathway Enrichment Analysis

Gene Set Enrichment Analysis (GSEA) was employed to identify biological pathways differentially enriched in schizophrenia as a function of sex (12). Top 10% of differentially expressed genes were ranked based on their log2FC between SCZ and control samples. For each comparison, enrichment scores (ES) were computed to quantify the degree to which pathway-associated genes were concentrated at the top (upregulated) or bottom (downregulated) of the ranked list. Normalized enrichment scores (NES) were calculated to allow cross-pathway comparisons, and pathway significance was determined using padj values derived from BH-corrected p-values.

Leading Edge Gene Analysis

To identify genes most responsible for driving pathway enrichment, leading edge (LE) analysis was performed using the GSEA algorithm (12). For each enriched pathway, the LE subset was defined as the group of genes contributing to the maximum ES. The frequency of each gene's appearance across the top 100 enriched pathways (ranked by absolute NES) was calculated separately for upregulated and downregulated gene sets in males and females. Genes with high recurrence were interpreted as key molecular contributors to sex-specific transcriptional dysregulation in SCZ.

LINCS Perturbagen Analysis

The Library of Integrated Network-based Cellular Signatures (LINCS)(9) platform was utilized to identify small molecules with discordant signatures to SCZ. Differential gene expression results were mapped to L1000 landmark genes, and inverse signature analysis was performed using the iLINCS database. Compounds generating gene expression profiles discordant with the SCZ DEG signatures were prioritized as potential therapeutic candidates. Analyses were stratified by sex to evaluate the presence of sex-specific drug-pathway interactions. Discordant compounds were further analyzed for differences in their mechanisms of action between male and female cohorts.

3. Results

Differential Gene Expression.

A total of 19,728 genes were analyzed across the four different subject populations. The female (SCZ vs Control) and male (SCZ vs Control) subjects were analyzed separately in 2 distinct analyses. In both the male and female populations, no genes met significance with adjusted p-values. To provide additional information for subsequent analyses, differential gene expression was done using raw p-values in addition to the adjusted p-values. Volcano plots (Fig 2) show the differential gene expression across the male and female cohorts using a raw p-value threshold of 0.05. In females, just over 300 genes met the raw significance level. Among these genes, there were over double the number of upregulated genes (212) than downregulated genes (102) (Fig 2A). Across the male population, over 2,000 genes met significance, split nearly evenly with 1,009 downregulated genes and 1,075 upregulated genes (Fig 2B).

The difference in the relative distribution of up versus downregulated genes and the number of significant genes are notable between the male and female cohorts. The female group showed less differential gene expression as noted by the modest 314 total genes that had significant changes in comparison to the 2,084 significant genes in the males. Further, the male cohort had similar counts of up and downregulated genes while upregulated genes outnumbered downregulated genes in the females at a rate of 2:1.

Pathway Analysis.

Pathway analysis in both cohorts aimed to identify significant pathways changes based on differential gene expression results with a total of 6,582 pathways analyzed. Males and females had differing changes in their altered pathways. Table 1 and table 2 show the downregulated pathways in males and females, respectively. Similarly, table 3 and table 4 show the upregulated pathways in males and females. In analysis of male control versus male SCZ there was significant upregulation of metabolic activity-linked pathways in SCZ patients in comparison to controls. Upregulated pathways included purine nucleobase metabolic process, mitochondrial RNA processing, glucosyltransferase activity and phosphotransferase activity (Table 3). Downregulated pathways in males with SCZ versus control males were highlighted by cellular transport pathways including positive regulation of neurotransmitter secretion, positive regulation of excitatory postsynaptic potential, and protein

localization to postsynaptic specialization membrane (Table 1).

These pathways were distinct from the pathways found in female subjects. Upregulated pathways in the female SCZ versus female control were dominated by immune-related pathways. These included antigen processing pathways like the peptide antigen assembly with MHC class II protein complex pathway and antigen processing and presentation via MHC class Ib pathway as well as immune signaling pathways such as immune response-regulating signaling pathway and regulation of immune response (Table 4).

Downregulated pathways in females were also distinct from the downregulated pathways in males, with phosphatidylinositol biosynthetic and metabolic processes downregulated in females but not in males. The female group also had downregulation in myelin assembly, secretory granule localization, and nuclear localization signal mediated protein import into nucleus, highlighting intracellular transport mechanisms pathways (Table 2).

Male and female cohorts were contrasted to determine how the top 10 up- and down-regulated pathways in one group were represented in the other (Figure 5-6). Pathways that were among the top upregulated in males were often among the least upregulated in females. For example, the amino acid metabolic process pathway, which ranked among the top 10 most upregulated pathways in males, was only the 4,225th most upregulated pathway in females, the highest ranking among the top 10 male pathways. Conversely, among the top 10 upregulated pathways in females, six appeared within the top 1,000 upregulated pathways in males, with only the blood microparticle pathway reaching the top 100. Regarding downregulation, three of the top 10 most downregulated pathways in males were also ranked within the top 1,000 in females. In contrast, only one of the top 10 most downregulated female pathways, vesicle organization, was shared in the top 1,000 downregulated pathways in males.

LE Gene Analysis.

Leading edge gene analysis showed different genes contribute towards up- and downregulation in the male and female cohorts (Fig. 4). All of the top 10 LE genes contributing towards downregulation in males contributed to over 10 different pathways. Similar results are seen in the downregulation LE genes in females. Genes contributing towards downregulation in females saw within the top 10 genes contributing to at least 14 pathways, many immune related, specifically to the HLA complex. Downregulation in males saw LE genes contribute to fewest pathways out of the four LE gene analyses with no gene contributing to more than nine pathways.

LINCS Analysis

Perturbagen analysis using iLINCS identified several FDA-approved drugs with discordant gene expression signatures relative to those observed in schizophrenia in male and female postmortem brain samples (Table V, Table VI). The male cohort yielded numerous immune-modulating medications, including fedratinib, everolimus, deracoxib, and valdecoxib. Fedratinib showed the greatest discordance signature of -0.387 among the male group. Five of these top 10 compounds have previously been studied in SCZ, two of which have results from clinical studies (13-19).

In females, the perturbagens with the greatest discordance signatures were frequently related to cellular metabolism, including compounds such as methazolamide, rosuvastatin, cholic acid, and floxuridine. The carbonic anhydrate activity inhibitor, methazolamide, showed the greatest discordance of -0.387. Four of the top female perturbagens have been studied in SCZ and three of these four have clinical data (20-24).

4. Discussion

Differences in Gene Expression

Analysis of gene expression differences between SCZ patients and controls revealed distinct sex-specific patterns. Limited transcriptional changes were observed and no genes in the males nor females were significant using the adjusted p-values. When the analysis was restricted to using the unadjusted p-values, there were distinct changes among the sexes.

In males, over 2,000 genes meeting the unadjusted p-value significance were equally split between being up- or downregulated, highlighting a broad transcriptional change in males with SCZ (Figure 2A). In contrast, females showed a more modest profile, with about 300 genes differentially expressed which were predominantly upregulated

(Figure 2B). This suggests a narrower scope of transcriptional changes in female SCZ patients. The differences between sexes imply that SCZ's molecular impact on gene expression is more extensive and unbiased towards up- or downregulation in males, whereas females exhibit fewer changes that are skewed toward upregulation. This sex-specific transcriptional divergence supports hypotheses about biological differences in disease mechanisms between males and females, progression, or compensatory responses, highlighting the importance of considering sex as a critical factor in SCZ research and potentially in developing targeted treatments. However, since no genes survived multiple-testing correction, more rigorous work should be conducted to confirm these findings. Sex differences in schizophrenia have been increasingly recognized at the molecular level, with prior studies identifying distinct gene expression patterns in male and female patients. Several investigations report sex-dependent alterations in genes related to dopamine signaling and synaptic function, while other studies observe limited overlap between male and female differentially expressed genes (25-27). The current findings are consistent with these observations, demonstrating divergent DEG profiles in males and females within the dorsolateral prefrontal cortex.

Pathway Analysis

Sex specific differences in pathway analysis inform possible mechanisms that differ in the pathophysiology of SCZ across sex. In males with SCZ, upregulated pathways were primarily associated with metabolic activity, suggesting increased or unregulated energy-related processes in the DLPFC. On the contrary, downregulated pathways were enriched for cellular transport functions, including those with sodium-potassium ATPase activity. This reduction may impair ion balance and neuronal excitability, possibly contributing to functional disruptions in cortical signaling seen in schizophrenia.

In females with SCZ, the transcriptomic profile showed predominant upregulation of immune-related pathways, particularly those involved in peptide antigen binding and antigen processing. These changes suggest elevated or unregulated immune activity within the DLPFC on top of known estrogen effects on the immune system already present in females. Conversely, downregulated pathways were mainly associated with protein catabolism and vesicle organization, leading to potential impairments in protein turnover and intracellular transport. The overall imbalance, where upregulated pathways outnumbered downregulated ones two-to-one, highlights a pronounced shift toward immune activation in the SCZ brain of females.

By conducting a cross-sex comparisons of pathway ranking, changes in one sex relative to the other were able to further demonstrate sex-specific differences. Immune receptor activity was highly upregulated in females but was only the 614th most upregulated pathway in males. Conversely, the mitochondrial gene expression pathway was among the most upregulated in males but was downregulated in females, making the pathway the 6,002nd most upregulated in females. Downregulated pathways further reflected these sex biases, with males showing reduced expression in neurodevelopmental and transcriptional regulation, while females showed decreased proteasomal and synaptic processes. Such differences emphasize the importance of sex-stratified analyses in uncovering distinct biological mechanisms that may contribute to disease risk or progression and could have a meaningful impact on treatment for the disease.

Pathway-level analyses in this study reveal that immune and oxidative stress pathways are predominantly upregulated in females, whereas males exhibit dysregulation in metabolic and inflammatory signaling cascades, including JAK2 and mTOR pathways. These results align with existing literature implicating immune system activation and metabolic dysfunction as prominent features in SCZ pathology (28-38). Importantly, the differing alteration in these pathways between males and females is understudied in prior work. Evidence of a sex-specific distinction in immune and metabolic function expands on previous findings.

These findings support other work in SCZ pathway analysis, although frequently analysis of males and females are done together. A study of single-cell DEG in SCZ with equal male and female subjects had three major biological themes that DEGs were grouped into, and while not explicitly pathways, that are similar to the results obtained from this work; neuron development, cell projection organization, and anterograde-synaptic signaling (39).These transport and organizational themes are similar to the cellular transport pathways found in our male cohort. A multi-omics study comparing SCZ subjects to healthy controls also found similar results with changes to regulation of ion transport, sodium ion transport, anion transport, tissue morphogenesis, monocarboxylic acid metabolic process, and

cellular modified amino acid metabolic process (40). While the sex of subjects was not reported in this study, the transport pathway themes again match our results. Finally, a review compiled DEG and pathway studies related to the immune system in SCZ (41). The results from the review support our findings in the female cohort, with many changes to immune related genes. Some studies analyzed in the review did note some immune-related pathway changes, while other studies did not find significant changes. However, since most studies do not sex-dependent analysis, it is possible that the immune related pathways that were found in our female cohort may not have strong enough effects when the sexes are analyzed together.

LE Gene Analysis

The LE gene profiles revealed distinct sex-specific molecular patterns associated with schizophrenia. In females downregulated genes included vesicle transport and phosphoinositide signaling related genes which included the PI3K family, OCRL, STXBP1, SYNJ1/2, and FIG4. These findings suggest possible disruption in intracellular and intracellular signaling pathways. Among upregulated genes in males, the predominance of genes associated with metabolic processing, including aldo-keto reductases and enzymes involved in nucleotide metabolism. In contrast, upregulated genes in females showed strong involvement of HLA genes and FCGR2B, highlighting adaptive immune pathway activation. This supports prior findings of immune and metabolic dysregulation in SCZ patients and builds upon findings sexual dimorphism at the gene level (28-33).

Analysis of iLINCS-Identified Drugs

Experimental validation of identified pathways and discordant drugs, especially those targeting immune responses in females and metabolic systems in males is critical for moving beyond transcriptional correlations toward actionable insights. Among the top discordant compounds identified for males, drugs such as fedratinib (a JAK2 kinase pathway inhibitor), everolimus (an mTOR pathway suppressor), and auranofin (a thioredoxin reductase enzyme inhibitor) suggest a theme of metabolic and inflammatory pathway disruption (15). Additional agents like vorinostat (a histone deacetylase blocker) and gemcitabine (a DNA synthesis chain terminator) have demonstrated positive preclinical evidence for modulating disease-relevant pathways (13, 14, 42-44). These results highlight mitochondrial dysfunction and glucose metabolism as critical biological factors in males with schizophrenia.

For females, the LINCS analysis highlights a different set of discordant drugs, with immune-modulating agents such as nebivolol (a beta-1 adrenergic receptor blocker) and enoxolone (a 11β-HSD cortisol modulator) showing distinct transcriptomic effects. However, other work has shown possible adverse effects when nebivolol is taken in patients with SCZ (45). Other compounds like rosuvastatin (an HMG-CoA reductase inhibitor) and cholic acid (a bile acid metabolism regulator) exhibit positive preclinical or clinical signals, pointing toward novel and previously underappreciated therapeutic avenues specific to females (46-48). Cholic acid has been explored as a biomarker for SCZ, making it an interesting compound for further study (49, 50).

5. Limitations

Several limitations should be acknowledged in interpreting these findings. First, the sample size for females was relatively small (n=14 SCZ, n=13 controls), which may reduce statistical power and limit the generalizability of female-specific findings. Additionally, the small cohort size restricts the ability to explore heterogeneity within the female SCZ population, such as variations related to symptom subtypes and medication status. Second, the reliance on raw p-values in gene-level analyses, while informative for identifying trends, inherently increases the risk of false positives. Without correction for multiple testing, some genes identified as significant may reflect random variation rather than true biological differences. This necessitates cautious interpretation of these results and emphasizes the need for replication in larger, independent cohorts with rigorous statistical adjustments. Since no genes survived multiple-testing correction, the results are limited due to the use of unadjusted p-values. This further highlights the need for additional, more rigorous studies to confirm the findings. Third, while pathway enrichment and drug signature analyses provide compelling hypotheses, they remain computational predictions and do not confirm causal relationships or functional effects without validation through molecular and cellular experiments. Without such validation, the clinical relevance and applicability of these pathway findings remain speculative. Finally, due to the data being derived from postmortem brain tissue samples, dynamic molecular processes are unable to be captured, limiting the ability to visualize molecular changes that occur during disease

progression or in response to treatment. Postmortem factors such as medication exposure, tissue degradation, and agonal state may also confound gene expression measurements. Longitudinal studies and in vivo models are necessary to better understand the temporal and mechanistic aspects of transcriptional dysregulation in SCZ.

Future Considerations

Our findings underscore the potential for sex-specific approaches in the treatment of schizophrenia. Future studies should prioritize expanding female cohorts to strengthen the reliability of sex-comparative analyses. Increasing female representation in clinical trials and molecular studies will not only improve statistical power for sex-stratified analyses but also help identify previously overlooked therapeutic targets and biosignatures specific to female patients. This expanded representation is particularly crucial given that females may present different symptom profiles, age of onset, and treatment responses compared to their male counterparts (51).

Our LINCS-based analysis identified different sets of drugs for males and females whose gene expression signatures oppose those seen in schizophrenia. These sex-specific drug profiles suggest distinct biological pathways that may be therapeutically relevant including metabolic and mitochondrial targets in males, and immune or hormonal targets in females. Several identified compounds are FDA-approved for other uses, presenting a unique opportunity for rapid drug repurposing with fewer regulatory hurdles. Future research should focus on testing these candidates in sex-stratified models to experimentally explore their relevance and effectiveness. In addition, integrating these results with neuroimaging and clinical phenotype data could aid in identifying biomarkers that predict treatment response. Ultimately, early-phase clinical trials should be designed with sex as a stratification variable from the outset to evaluate efficacy and tolerability in males and females separately. This multi-tiered, sex-informed approach could streamline the development of more precise, biologically grounded treatment algorithms and move the field closer to personalized care in schizophrenia.
Conclusions Transcriptomic analysis identified sex-specific transcriptional signatures in the DLPFC in SCZ, revealing distinct molecular mechanisms in males and females. Males exhibited widespread dysregulation of metabolic and cellular transport pathways, while females demonstrated upregulation of genes involved in inflammatory and immune-related processes. These findings align with prior evidence implicating sex-specific crosstalk between immune activation, oxidative stress, and lipid metabolism in schizophrenia. In males, widespread disruption of metabolic and transport-related genes may reflect altered energy demands, mitochondrial function, or other cellular mechanisms relevant to cognitive processes. In contrast, many immune-associated genes upregulated in females, including those linked to microtubule dynamics and lipid signaling, may reflect unique vulnerability pathways or compensatory mechanisms shaped by hormonal and chromosomal influences.

While interpretation of these findings is limited by factors such as lack of detailed medication data, use of postmortem bulk RNA sequencing, and the need for experimental validation of LINCS-derived therapeutic predictions, taken together the results of this study support a model in which immune dysregulation in females and metabolic disruption in males represent divergent but biologically plausible mechanisms contributing to SCZ pathophysiology. The identification of distinct perturbagen profiles reinforces the potential of sex-informed therapeutic strategies and further investigation of candidate compounds identified through iLINCS is needed to evaluate therapeutic relevance and potential sex-specific efficacy. Continued integration of sex as a biological variable in psychiatric transcriptomic research.

6. References

1. Saha, S., D. Chant, and J. McGrath, *A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time?* Arch Gen Psychiatry, 2007. **64**(10): p. 1123-31.
2. Giordano, G.M., et al., *Gender Differences in Clinical and Psychosocial Features Among Persons With Schizophrenia: A Mini Review.* Front Psychiatry, 2021. **12**: p. 789179.
3. Ochoa, S., et al., *Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review.* Schizophr Res Treatment, 2012. **2012**: p. 916198.
4. Khandaker, G.M., et al., *Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment.* Lancet Psychiatry, 2015. **2**(3): p. 258-270.

5. Salter, M.W. and B. Stevens, *Microglia emerge as central players in brain disease.* Nat Med, 2017. **23**(9): p. 1018-1027.
6. Lisman, J.E., et al., *Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia.* Trends Neurosci, 2008. **31**(5): p. 234-42.
7. Worf, K., et al., *Exon-variant interplay and multi-modal evidence identify endocrine dysregulation in severe psychiatric disorders impacting excitatory neurons.* Transl Psychiatry, 2025. **15**(1): p. 153.
8. Shi, J. and M.G. Walker, *Gene set enrichment analysis (GSEA) for interpreting gene expression profiles.* Current Bioinformatics, 2007. **2**(2): p. 133-137.
9. Koleti, A., et al., *Data Portal for the Library of Integrated Network-based Cellular Signatures (LINCS) program: integrated access to diverse large-scale cellular perturbation response data.* Nucleic Acids Res, 2018. **46**(D1): p. D558-D566.
10. Ryan, W., *3PodR Bookdown.* Accessed From: [last cited updated on 2025-06-04]; Available from: https://github.com/willgryan/3PodR_bookdown.git.
11. Robinson, M.D., D.J. McCarthy, and G.K. Smyth, *edgeR: a Bioconductor package for differential expression analysis of digital gene expression data.* Bioinformatics, 2010. **26**(1): p. 139-40.
12. Subramanian, A., et al., *Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles.* Proc Natl Acad Sci U S A, 2005. **102**(43): p. 15545-50.
13. Kurita, M., et al., *HDAC2 regulates atypical antipsychotic responses through the modulation of mGlu2 promoter activity.* Nature Neuroscience, 2012. **15**(9): p. 1245-1254.
14. Martínez-Peula, O., et al., *A method for HDAC activity screening in postmortem human brain. A proof-of-concept study with antipsychotics.* Journal of Neuroscience Methods, 2025. **416**: p. 110365.
15. Kim, Y. and S. Kim, *Target Discovery Using Deep Learning-Based Molecular Docking and Predicted Protein Structures With AlphaFold for Novel Antipsychotics.* Psychiatry Investig, 2023. **20**(6): p. 504-514.
16. Ximenis, M., et al. *Natural Polyhydroxy Flavonoids, Curcuminoids, and Synthetic Curcumin Analogs as α7 nAChRs Positive Allosteric Modulators*. International Journal of Molecular Sciences, 2021. **22**, DOI: 10.3390/ijms22020973.
17. Ostrow, D. G., Pandey, G. N., Davis, J. M., Hurt, S. W., & Tosteson, D. C. *A heritable disorder of lithium transport in erythrocytes of a subpopulation of manic-depressive patients.* American Journal of Psychiatry, 1978. **135**(9): p. 1070-1078. Doi:10.1176/ajp.135.9.1070
18. Benoit, C.-E., et al., *Loss of Quinone Reductase 2 Function Selectively Facilitates Learning Behaviors.* The Journal of Neuroscience, 2010. **30**(38): p. 12690.
19. Asit, K.C., et al., *Progress in COX-2 Inhibitors: A Journey So Far.* Current Medicinal Chemistry, 2010. **17**(15): p. 1563-1593.
20. Wang, X., et al., *The relationship between alterations in plasma metabolites and treatment responses in antipsychotic-naïve female patients with schizophrenia.* The World Journal of Biological Psychiatry, 2024. **25**(2): p. 106-115.
21. Zhuo, C., et al., *Acid sphingomyelinase/ceramide system in schizophrenia: implications for therapeutic intervention as a potential novel target.* Translational Psychiatry, 2022. **12**(1): p. 260.
22. Mohammed, A., et al., *Rosuvastatin improves olanzapine's effects on behavioral impairment and hippocampal, hepatic and metabolic damages in isolated reared male rats.* Behavioural Brain Research, 2020. **378**: p. 112305.
23. Siwek, M., et al., *Adverse effects of interactions between antipsychotics and medications used in the treatment of cardiovascular disorders.* Pharmacological Reports, 2020. **72**(2): p. 350-359.
24. Yoshida, Y., et al., *Selective and competitive inhibition of kynurenine aminotransferase 2 by glycyrrhizic acid and its analogues.* Scientific Reports, 2019. **9**(1): p. 10243.
25. Williams, O.O.F., et al., *Sex Differences in Dopamine Receptors and Relevance to Neuropsychiatric Disorders.* Brain Sci, 2021. **11**(9).
26. Mayer, F.P., A. Stewart, and R.D. Blakely, *Leaky lessons learned: Efflux prone dopamine transporter variant reveals sex and circuit specific contributions of D2 receptor signalling to neuropsychiatric disease.* Basic Clin Pharmacol Toxicol, 2024. **134**(2): p. 206-218.
27. Carceller, H., et al., *The impact of sex on gene expression in the brain of schizophrenic patients: a systematic review and meta-analysis of transcriptomic studies.* Biol Sex Differ, 2024. **15**(1): p. 59.
28. Ermakov, E.A., et al., *Chemokine Dysregulation and Neuroinflammation in Schizophrenia: A Systematic Review.* Int J Mol Sci, 2023. **24**(3).
29. Ermakov, E.A., et al., *Immune System Abnormalities in Schizophrenia: An Integrative View and Translational Perspectives.* Front Psychiatry, 2022. **13**: p. 880568.
30. Jones, A.L., et al., *Immune dysregulation and self-reactivity in schizophrenia: do some cases of*

schizophrenia have an autoimmune basis? Immunol Cell Biol, 2005. **83**(1): p. 9-17.
31. Michel, M., M.J. Schmidt, and K. Mirnics, *Immune system gene dysregulation in autism and schizophrenia.* Dev Neurobiol, 2012. **72**(10): p. 1277-87.
32. Strous, R.D. and Y. Shoenfeld, *Schizophrenia, autoimmunity and immune system dysregulation: a comprehensive model updated and revisited.* J Autoimmun, 2006. **27**(2): p. 71-80.
33. Yu, S., et al., *The expression of immune related genes and potential regulatory mechanisms in schizophrenia.* Schizophr Res, 2024. **267**: p. 507-518.
34. Bryll, A., et al., *Oxidative-Antioxidant Imbalance and Impaired Glucose Metabolism in Schizophrenia.* Biomolecules, 2020. **10**(3).
35. Fizíková, I., J. Dragašek, and P. Račay, *Mitochondrial Dysfunction, Altered Mitochondrial Oxygen, and Energy Metabolism Associated with the Pathogenesis of Schizophrenia.* Int J Mol Sci, 2023. **24**(9).
36. Konradi, C. and D. Öngür, *Role of mitochondria and energy metabolism in schizophrenia and psychotic disorders.* Schizophr Res, 2017. **187**: p. 1-2.
37. Pruett, B.S. and J.H. Meador-Woodruff, *Evidence for altered energy metabolism, increased lactate, and decreased pH in schizophrenia brain: A focused review and meta-analysis of human postmortem and magnetic resonance spectroscopy studies.* Schizophr Res, 2020. **223**: p. 29-42.
38. Steen, N.E., et al., *Metabolic dysfunctions in the kynurenine pathway, noradrenergic and purine metabolism in schizophrenia and bipolar disorders.* Psychol Med, 2020. **50**(4): p. 595-606.
39. Ruzicka, W.B., et al., *Single-cell multi-cohort dissection of the schizophrenia transcriptome.* Science. **384**(6698): p. eadg5136.
40. Wang, T., et al., *An integrated pathological research for precise diagnosis of schizophrenia combining LC-MS/1H NMR metabolomics and transcriptomics.* Clinica Chimica Acta, 2022. **524**: p. 84-95.
41. Van Mierlo, H.C., et al., *The association between schizophrenia and the immune system: Review of the evidence from unbiased 'omic-studies'.* Schizophrenia Research, 2020. **217**: p. 114-123.
42. de la Fuente Revenga, M., et al., *HDAC2-dependent Antipsychotic-like Effects of Chronic Treatment with the HDAC Inhibitor SAHA in Mice.* Neuroscience, 2018. **388**: p. 102-117.
43. Kennedy, A.J., et al., *Tcf4 Regulates Synaptic Plasticity, DNA Methylation, and Memory Function.* Cell Rep, 2016. **16**(10): p. 2666-2685.
44. Kurita, M., et al., *HDAC2 regulates atypical antipsychotic responses through the modulation of mGlu2 promoter activity.* Nat Neurosci, 2012. **15**(9): p. 1245-54.
45. Siwek, M., et al., *Adverse effects of interactions between antipsychotics and medications used in the treatment of cardiovascular disorders.* Pharmacol Rep, 2020. **72**(2): p. 350-359.
46. De Hert, M., et al., *Treatment with rosuvastatin for severe dyslipidemia in patients with schizophrenia and schizoaffective disorder.* J Clin Psychiatry, 2006. **67**(12): p. 1889-96.
47. Mohammed, A., et al., *Rosuvastatin improves olanzapine's effects on behavioral impairment and hippocampal, hepatic and metabolic damages in isolated reared male rats.* Behav Brain Res, 2020. **378**: p. 112305.
48. Shen, H., et al., *Adjunctive therapy with statins in schizophrenia patients: A meta-analysis and implications.* Psychiatry Res, 2018. **262**: p. 84-93.
49. Koike, S., et al., *Plasma unconjugated bile acids as novel biomarker for schizophrenia.* Biochem Biophys Res Commun, 2022. **634**: p. 70-74.
50. Tao, Y., et al., *A combination of three plasma bile acids as a putative biomarker for schizophrenia.* Acta Neuropsychiatr, 2021. **33**(1): p. 51-54.
51. Li, X., W. Zhou, and Z. Yi, *A glimpse of gender differences in schizophrenia.* Gen Psychiatr, 2022. **35**(4): p. e100823.

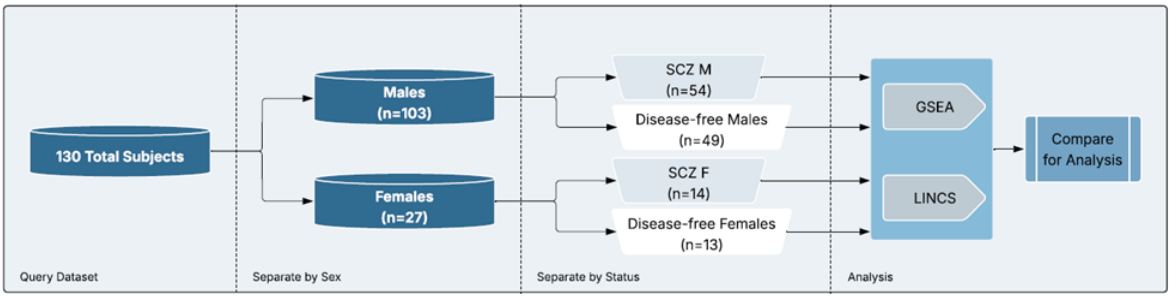

Figure 1. Study design and gene set enrichment analysis workflow.
Postmortem brain samples from individuals with schizophrenia (SCZ) and matched disease-free controls were separated by sex and diagnosis. Differential gene expression analysis was performed for schizophrenia vs. control within each sex, followed by gene set enrichment analysis (GSEA). Resulting enrichment signatures were compared to perturbagen profiles from the LINCS database to identify potential therapeutic candidates.

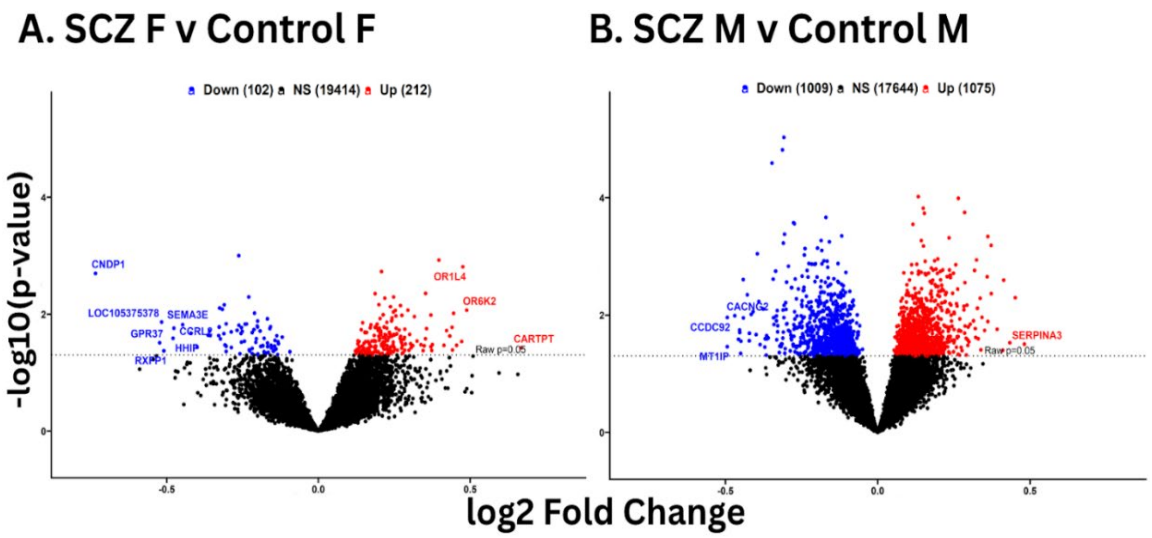

Figure 2. Volcano Plots of Differential Gene Expression in Male and Female SCZ Patients vs Controls

Differential gene expression analysis in schizophrenia (SCZ) patients compared to controls, stratified by sex. Volcano plots show log2 fold change (x-axis) versus -log10 p-value (y-axis) for (A) male SCZ patients vs male controls and (B) female SCZ patients vs female controls. Blue points represent significantly downregulated genes (Down), red points represent significantly upregulated genes (Up), and black points represent non-significant genes (NS). The dotted horizontal line indicates the significance threshold ($p<0.05$). Selected genes of interest are labeled. Sample sizes are indicated in parentheses for each group: (A) Down (1009 genes), NS (17644 genes), Up (1075 genes); (B) Down (102 genes), NS (19414 genes), Up (212 genes). Notable sex-specific differences are observed, with males showing more extensive differential expression patterns compared to the females.

UTJMS 2026 February 03, 14(S4):e1-e18 doi:10.46570/utjms-2025-1899

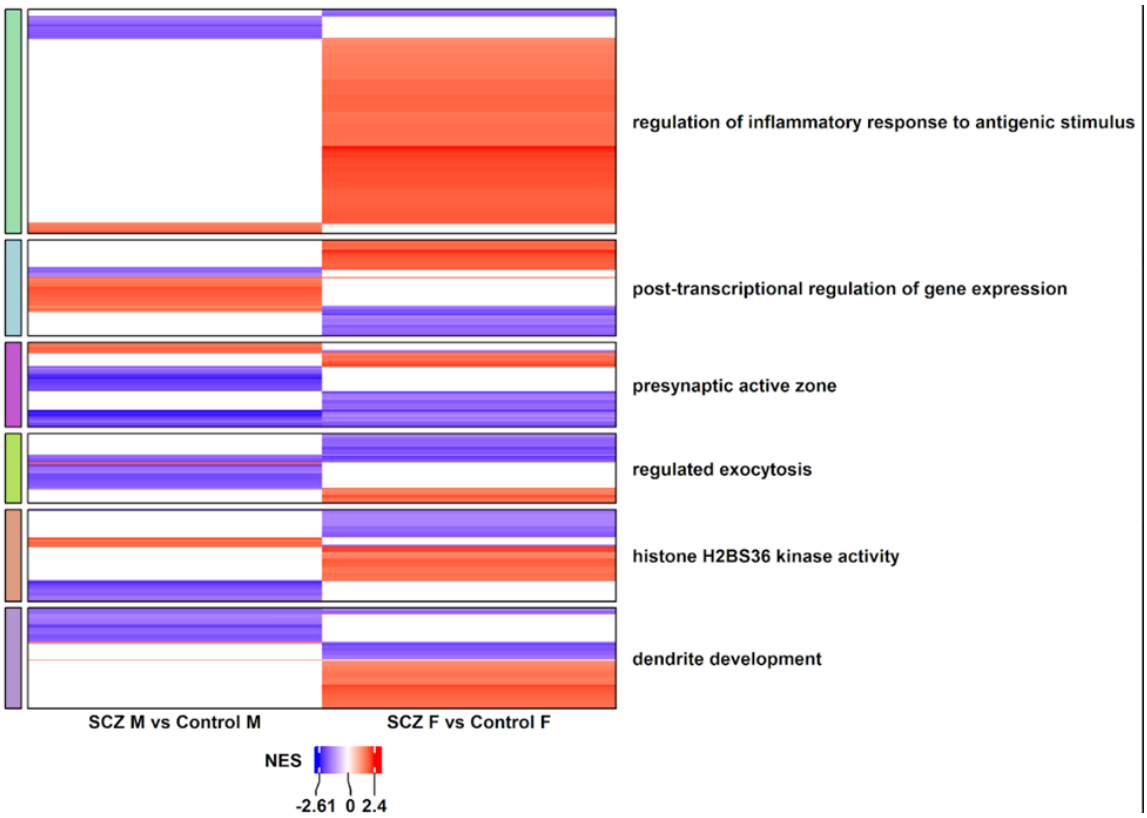

Figure 3. Normalized Enrichment Scores of Key Pathways between Male and Female SCZ Patients v. Control.

Using normalized enrichment score (NES), the pathway heat map illustrates the direction and intensity of pathway regulation. Pathways involved in the study were grouped by similar biological themes. The column on the left compares male schizophrenia (SCZ) patients with male controls and the right compares female SCZ patients with female controls. NES is shown using a blue-red color scale, as blue represents down regulated pathways and red represents upregulated pathways. Notably, inflammatory response in females is highly regulated while dendrite development and regulated exocytosis in males is predominantly downregulated.

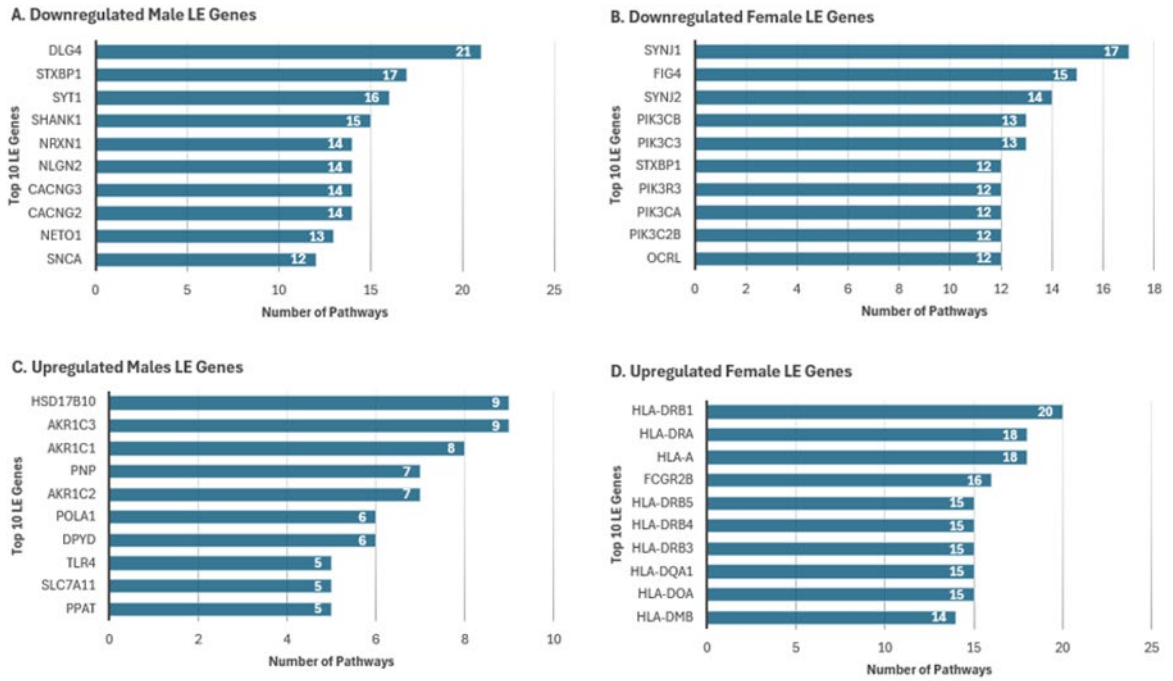

Figure 4. Leading Edge (LE) genes by sex and direction of regulation.

Representative charts of the top 10 leading-edge (LE) genes from the first 100 pathways (ranked by enrichment score) are shown. The x-axis indicates the number of pathways in which each gene appeared as part of the leading-edge subset. (A) shows the presence of genes in the top 100 downregulated pathways in males, (B) shows the presence of genes in the top 100 downregulated pathways in females, (C) shows the presence of genes in the top 100 upregulated pathways in males, and (D) shows the presence of genes in the top 100 upregulated pathways in females.

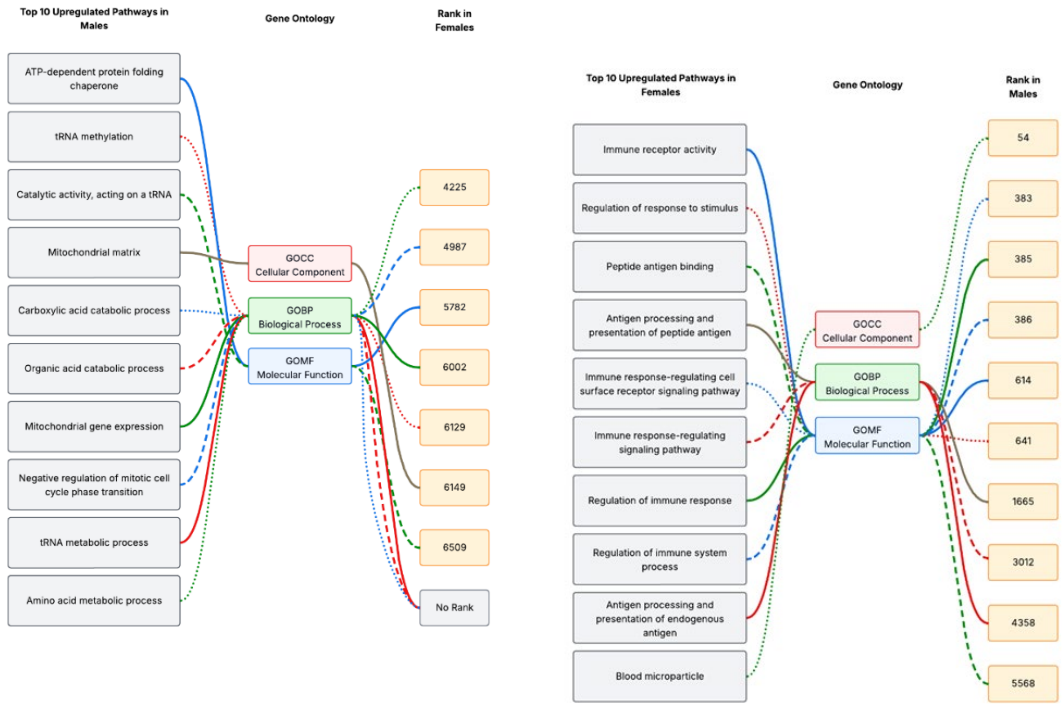

Figure 5. Sex-specific enrichment of upregulated pathways and cross-sex ranking comparison.
Sankey diagrams show the relationship between the top 10 upregulated pathways in schizophrenia (SCZ) for each sex and how those same pathways rank in the opposite sex and are color coded by ontology terms. Each diagram visualizes Gene Ontology categories and traces specific enrichment or lack thereof in the other sex, highlighting both overlapping and divergent molecular signatures across sexes. On the left, the top 10 upregulated pathways in males are connected to where the pathway ranks among the upregulated pathways in females. On the right, the top 10 upregulated pathways in females are connected to the rank of the pathway in males

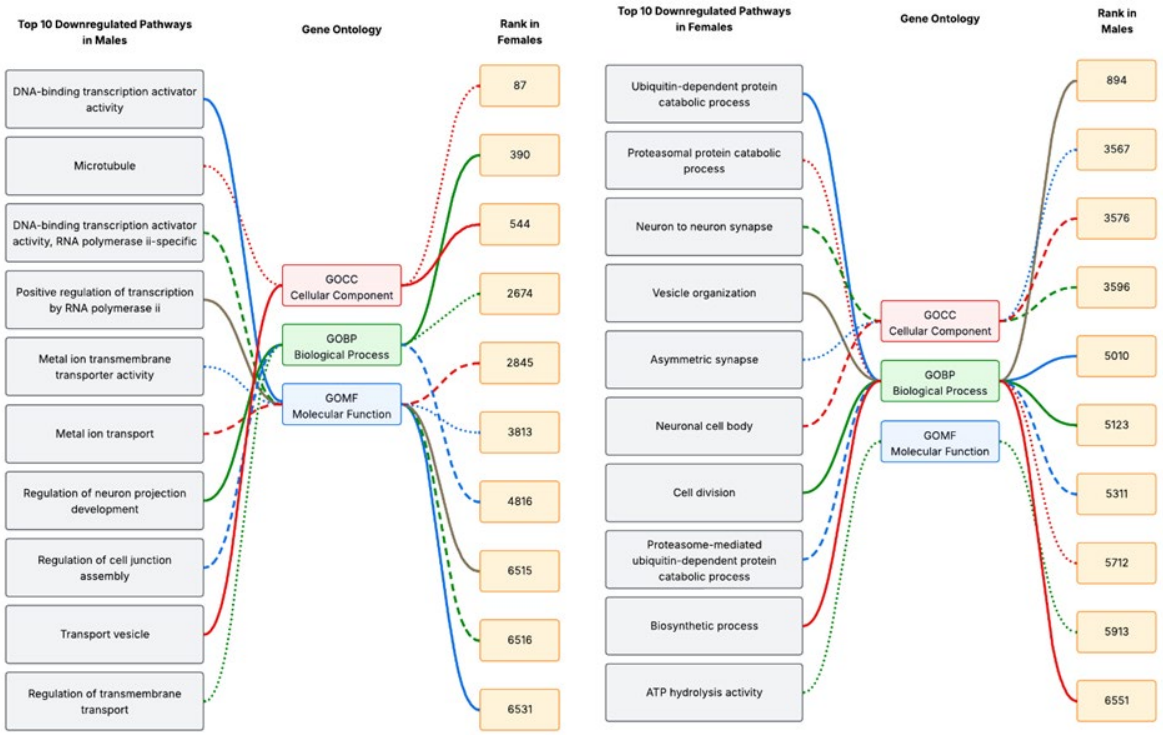

Figure 6. Sex-specific enrichment of downregulated pathways and cross-sex ranking comparison.

Sankey diagrams show the relationship between the top 10 upregulated pathways in schizophrenia (SCZ) for each sex and how those same pathways rank in the opposite sex and are color coded by ontology terms. Each diagram visualizes Gene Ontology categories and traces specific enrichment or lack thereof in the other sex, highlighting both overlapping and divergent molecular signatures across sexes. On the left, the top 10 downregulated pathways in males are connected to where the pathway ranks among the downregulated pathways in females. On the right, the top 10 downregulated pathways in females are connected to the rank of the pathway in males.

UTJMS 2026 February 03, 14(S4):e1-e18 doi:10.46570/utjms-2025-1899

Downregulated Pathways (SCZ M)	Enrichment Score
Regulation of Neurotransmitter Receptor Activity	-0.819
Synaptic Vesicle Priming	-0.796
Positive Regulation of Neurotransmitter Secretion	-0.764
Positive Regulation of Synaptic Transmission, Glutamatergic	-0.747
Positive Regulation of Calcium Ion-Dependent Exocytosis	-0.743
Positive Regulation of Excitatory Postsynaptic Potential	-0.743
Arachidonate Epoxygenase Activity	-0.739
Neurotransmitter Receptor Localization to Postsynaptic Specialization Membrane	-0.733
Protein Localization to Postsynaptic Specialization Membrane	-0.733
AMPA Glutamate Receptor Complex	-0.727

Table I. Downregulated Pathways for Males Diagnosed with Schizophrenia (SCZ)
This table presents categories of downregulated pathways identified by Gene Set Enrichment Analysis (GSEA) in males with schizophrenia. Enrichment scores quantify the degree of downregulation for each pathway category.

Downregulated Pathways (SCZ F)	Enrichment Score
Node of Ranvier	-0.763
Nuclear Localization Signal (NLS)-Mediated Protein Import into Nucleus	-0.673
Secretory Granule Localization	-0.671
Intraciliary Anterograde Transport	-0.663
Myelin Assembly	-0.651
Phosphatidylinositol Biosynthetic Process	-0.65
Phosphatidylinositol Metabolic Process	-0.65
Phosphatidylinositol Phosphate Biosynthetic Process	-0.65
Phosphatidylinositol-3-Phosphate Biosynthetic Process	-0.65
Proteasome Regulatory Particle	-0.647

Table II. Downregulated Pathways for Females Diagnosed with Schizophrenia (SCZ)

This table presents categories of downregulated pathways identified by Gene Set Enrichment Analysis (GSEA) in females with schizophrenia. Enrichment scores quantify the degree of downregulation for each pathway category.

Upregulated Pathways (SCZ M)	Enrichment Score
Estradiol 17-Beta-Dehydrogenase [NAD(P)+] Activity	0.748
Purine Nucleobase Metabolic Process	0.689
Mitochondrial RNA Processing	0.689
Ribosomal Small Subunit Assembly	0.679
Glucosyltransferase Activity	0.667
Golgi Cis Cisterna	0.666
Tertiary Alcohol Metabolic Process	0.665
Cytoplasmic Side of Endoplasmic Reticulum Membrane	0.657
Phosphotransferase Activity, for Other Substituted Phosphate Groups	0.648
Regulation of Plasminogen Activation	0.638

Table III. Upregulated Pathways for Males Diagnosed with Schizophrenia (SCZ)

This table presents categories of upregulated pathways identified by Gene Set Enrichment Analysis (GSEA) in males with schizophrenia. Enrichment scores quantify the degree of upregulation for each pathway category.

UTJMS 2026 February 03, 14(S4):e1-e18 doi:10.46570/utjms-2025-1899

Upregulated Pathways (SCZ F)	Enrichment Score
MHC Class II Protein Complex	0.768
MHC Class II Protein Complex Assembly	0.767
Peptide Antigen Assembly with MHC Class II Protein Complex	0.767
Immune Response-Regulating Cell Surface Receptor Signaling Pathway	0.766
Immune Response-Regulating Signaling Pathway	0.766
Regulation of Immune Response	0.766
Regulation of Immune System Process	0.766
MHC Protein Complex	0.76
Antigen Processing and Presentation via MHC Class Ib	0.76
MHC Class I Receptor Activity	0.75

Table IV. Upregulated Pathways for Females Diagnosed with Schizophrenia (SCZ)

This table presents categories of upregulated pathways identified by Gene Set Enrichment Analysis (GSEA) in females with schizophrenia. Enrichment scores quantify the degree of upregulation for each pathway category.

Drug Name	Discordance Signature	Mechanism of Action	Studied in Schizophrenia?	Preclinical Evidence	Clinical Evidence?
Fedratinib	-0.387	JAK2 kinase pathway inhibitor			
Vorinostat	-0.38	Histone deacetylase (HDAC) blocker	✓	Positive	Positive
Everolimus	-0.353	mTOR signaling pathway suppressor	✓		
Auranofin	-0.322	Thioredoxin reductase enzyme inhibitor			
Gemcitabine	-0.304	DNA synthesis chain terminator			
Deracoxib	-0.303	COX-2 selective inflammation blocker			
Phloretin	-0.301	Glucose transporter (GLUT) inhibitor	✓	Positive	No effect
Niclosamide	-0.299	Mitochondrial uncoupler, Wnt blocker			
Menadione	-0.292	ROS generator, redox agent	✓	No effect	
Valdecoxib	-0.292	Selective COX-2 enzyme inhibitor	✓		

Table V. Discordant Drugs for Males Diagnosed with Schizophrenia

Top 10 FDA approved compounds identified through iLINCS perturbagen analysis that exhibit the most discordant transcriptional signatures relative to those observed in males diagnosed with schizophrenia. The table also provides information regarding investigations of each compound in the context of schizophrenia, including evidence from preclinical studies conducted in animal models and the clinical evaluation in human subjects.

UTJMS 2026 February 03, 14(S4):e1-e18 doi:10.46570/utjms-2025-1899

Drug Name	Discordance Signature	Mechanism of Action	Studied in Schizophrenia?	Preclinical Evidence	Clinical Evidence?
Methazolamide	-0.387	Carbonic anhydrase activity inhibitor			
Rimantadine	-0.371	M2 proton channel blocker			
Cholic acid	-0.36	Bile acid metabolism regulator	✓		Positive
Rosuvastatin	-0.348	HMG-CoA reductase cholesterol inhibitor	✓	Positive	No effect
Floxuridine	-0.336	Thymidylate synthase DNA disruptor			
Vinorelbine	-0.33	Microtubule polymerization suppressor			
Nebivolol	-0.329	Beta-1 adrenergic receptor blocker	✓		Negative
Enoxolone	-0.315	11β-HSD cortisol modulator	✓		
Elvitegravir	-0.31	Antiretroviral, integrase strand inhibitor			
Temoporfin	-0.309	Photodynamic therapy cytotoxic agent			

Table VI. Discordant Drugs for Females Diagnosed with Schizophrenia

Top 10 FDA approved compounds identified through iLINCS perturbagen analysis that exhibit the most discordant transcriptional signatures relative to those observed in females diagnosed with schizophrenia. The table also provides information regarding investigations of each compound in the context of schizophrenia, including evidence from preclinical studies conducted in animal models and the clinical evaluation in human subjects.

