

Screening of Key Biomarkers and Molecular Mechanisms of Major Depressive Disorder Based on Multi-Cohort Transcriptomic Data

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Abstract. Purpose: Major depressive disorder (MDD) is a highly heterogeneous psychiatric disorder with a complex etiology. Its molecular pathological mechanisms are not fully understood. To identify stable biomarkers with potential clinical value and explore their associated molecular pathways, we performed a systematic bioinformatic analysis of three publicly available transcriptomic datasets. Methods: Three expression profile datasets related to major depressive disorder (MDD)—GSE54562, GSE54572, and GSE54568—were retrieved from the Gene Expression Omnibus (GEO) database. After normalization, we performed a differential expression analysis on each dataset and visualized the results using box plots, principal component analysis (PCA), and heat maps. The first dataset underwent further analysis using GO, KEGG, and GSEA enrichment. Then, a protein-protein interaction (PPI) network was constructed using the STRING database. The second and third datasets were then used to validate the candidate features independently. Results: In the first dataset, the major depressive disorder (MDD) and control groups exhibited distinct overall expression patterns, and normalization was effective. Differential analysis identified several markedly dysregulated genes. Among them, SPP1, GLDN, and MEIS1 were upregulated in the MDD group, while MORN4, PCBP3, and SORCS1 were downregulated. Gene ontology (GO) enrichment analysis revealed that the differentially expressed genes were primarily associated with the myelin sheath, compact myelin, and gap junctions. KEGG analysis revealed significant enrichment of the phospholipase D (PLD) signaling pathway and several amino acid metabolism pathways. GSEA also indicated aberrant activation of oxidative phosphorylation, processes related to reactive oxygen species, the phagosome, antigen processing and presentation, ferroptosis, and multiple immune-inflammatory pathways. The PPI network revealed interaction modules centered on myelin structural and membrane transport molecules. In the second dataset (GSE54572), the two groups exhibited consistent but partially overlapping separation. All six top probes differed significantly between the groups. 235779_at showed the most pronounced difference. The third dataset (GSE54568) also displayed a clear case-control separation. All six top probes reached statistical significance, and 232769_at showed the most prominent difference. Conclusion: The onset and progression of MDD may be closely associated with myelin structural damage, membrane lipid metabolic disturbance, neuroinflammation, oxidative stress, and energy metabolic dysregulation. SPP1, GLDN, MEIS1, MORN4, PCBP3, and SORCS1 may be key molecular markers with diagnostic potential. Multi-cohort validation supports the robustness and reproducibility of these candidate molecules, providing a new basis for early MDD diagnosis and molecular subtyping.

Keywords: Major depressive disorder; biomarker; transcriptome; myelin; phospholipase D signaling pathway; multi-cohort validation.

1. Introduction

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders worldwide. Characterized by high prevalence, high recurrence, and a heavy disability burden, it has become a major condition that severely affects public health and social functioning. The World Health Organization has noted that MDD imposes a substantial global disease burden, and that current treatments are limited in efficacy and unevenly accessible [1]. Although several classes of antidepressants are available, their overall efficacy is modest and treatment responses vary considerably among patients. Traditional research has primarily focused on the monoamine neurotransmitter hypothesis. However, a growing body of evidence suggests that MDD is not likely

driven by a single pathway. Instead, MDD appears to be a complex, multidimensional disorder involving neurotransmitters, immune inflammation, neuroplasticity, energy metabolism, and myelin function [2, 3].

In recent years, ferroptosis, an iron-dependent form of programmed cell death, has attracted increasing attention, and its association with MDD has gradually been established. Reviews have suggested that oxidative stress, lipid peroxidation, and an imbalance in iron homeostasis may play critical roles in the development of MDD [4,5]. In parallel, peripheral and central white matter/myelin abnormalities are also considered to be closely linked to MDD. Magnetic resonance spectroscopy studies have reported marked alterations in choline-related metabolites in the prefrontal white matter of patients with depression, reflecting glial and myelin dysfunction [6,7].

MDD research is also progressively expanding from the classical monoamine framework toward rapid-acting antidepressants, the glutamate system, inflammatory networks, and neuroplasticity modulation [8-10]. Multi-cohort transcriptomic analysis based on public databases and high-throughput technologies can partly mitigate the sample bias inherent in any single dataset, thereby improving the robustness and reliability of candidate biomarkers. In this study, therefore, we used three independent MDD transcriptomic datasets. We first performed differential expression screening, functional enrichment, and network analysis in the first dataset, and subsequently used the second and third datasets for independent validation of the candidate features. The aim was to characterize key biomarkers of MDD and their potential molecular mechanisms from multiple perspectives, providing a basis for subsequent experimental validation and clinical translation.

2. Materials and Methods

2.1. Data Source

Three expression profile datasets related to MDD—GSE54562, GSE54572, and GSE54568—were downloaded from the GEO database. Each dataset included samples from patients with MDD and healthy controls. These samples were used for differential expression analysis and between-group comparisons.

2.2. Data Preprocessing and Normalization

The raw expression matrices were subjected to background correction, normalization, and probe annotation. Box plots were then used to evaluate the consistency of expression distributions across samples. After that, principal component analysis (PCA) was used to assess sample clustering and group separation. Overall, these actions were taken to confirm the quality of the data and ensure its suitability for the subsequent analysis.

2.3. Differential Expression Analysis

Differential expression between cases and controls was assessed using the relevant R packages. Candidate differentially expressed features were selected on the basis of between-group expression levels and statistical results, and the changes were visualized using volcano plots, heatmaps, and box plots of the top-ranked features. The candidate genes from the first dataset were retained for subsequent mechanistic analysis, whereas the second and third datasets were used mainly to validate the expression patterns.

2.4. GO, KEGG, and GSEA Analyses

The differentially expressed genes from the first dataset were subjected to GO enrichment analysis covering biological processes, cellular components, and molecular functions, as well as KEGG pathway analysis to identify significantly perturbed signaling pathways. GSEA was additionally performed on the genome-wide ranked gene list to identify the core biological processes associated with MDD at a global level.

2.5. PPI Network Construction

The differentially expressed genes from the first dataset were imported into the STRING database to construct a PPI network. Core nodes and modules were identified from the network topology to screen for potential key regulatory molecules.

3. Results

3.1. Quality Control and Differential Expression in the First Dataset (GSE54562)

Box plots for GSE54562 are shown in Figure 1. Consistent expression distributions were observed across samples, indicating that normalization was effective and the data quality was reliable. PCA disclosed a clear separation of the MDD and control groups in a two-dimensional space, showing that the two groups could be distinguished by their global transcriptional patterns. The volcano plot showed that most genes were less changed, but a few significantly changed molecules were found (Figure 2). The heatmap also showed that the top DEGs could efficiently separate cases from controls, implying the potential usefulness of these DEGs for disease discrimination.

3.1.1. Expression Characteristics of the Top Differentially Expressed Genes

Figure 3 shows box plots of top genes, which revealed that SPP1, GLDN and MEIS1 were significantly increased and MORN4, PCBP3 and SORCS1 were significantly decreased in the MDD group. SPP1 is upregulated in patients and may play a role in inflammation and tissue remodeling. GLDN is also upregulated and may be associated with neural connectivity and myelin-related processes. MEIS1 is likewise upregulated and might be involved in transcriptional regulation and neural development. Within the down-regulated genes, MORN4 may suggest impaired membrane-associated functions, PCBP3 may indicate disrupted RNA binding and post-transcriptional regulation, and SORCS1 may affect receptor trafficking and neural signal modulation. In contrast, no significant differences between groups were observed for EEF1A1, GAPDH and SLC35E2A, suggesting a relatively stable expression under these conditions. This finding further supports the specificity of the differential analysis.

3.1.2. GO Enrichment Implicates Myelin and Gap Junction Abnormalities

GO enrichment analysis of differentially expressed genes in the first dataset found significant terms related to the myelin sheath, compact myelin and gap junctions (Figure 4). These results indicate that oligodendrocyte dysfunction, abnormal myelination and disturbed intercellular communication may be involved in MDD. Myelin is essential for fast transmission of nerve impulses and for the stability of neural networks. Hence, abnormalities in myelin-related molecules usually point to compromised integrity of white matter. Gap junctions mediate the exchange of metabolites and signals between neurons and glial cells. Defects in these junctions can lead to further impairment of neural circuit coordination and local homeostasis. In sum these findings suggest that MDD is not only a neurotransmitter disorder but also involves substantial remodeling of neural structures.

3.1.3. KEGG Analysis Implicates the PLD Signaling Pathway and Amino Acid Metabolism

KEGG enrichment showed that the differentially expressed genes in the first dataset were significantly enriched in the phospholipase D (PLD) signaling pathway. Several metabolic pathways, including β -alanine metabolism, histidine metabolism, and arginine and proline metabolism, were also affected (Figure 5).

The PLD signaling pathway plays a key role in membrane lipid remodeling, vesicular trafficking, cytoskeletal regulation, and receptor signal transduction. Disruption of this pathway may affect synaptic release, membrane receptor localization, and neuron–glia communication, thereby contributing to the development of MDD. The involvement of amino acid metabolic pathways further suggests that the supply of neurotransmitter precursors, cellular energy metabolism, and the synthesis of local neuroactive substances may be impaired.

3.1.4. GSEA Reveals Abnormalities in Oxidative Stress, Immune Inflammation, and Energy Metabolism

GSEA further characterized the global pathological features of the first dataset. Multiple pathways were significantly enriched, including oxidative phosphorylation, chemical carcinogenesis–reactive oxygen species, phagosome, antigen processing and presentation, ferroptosis, prion disease, Parkinson disease, and systemic lupus erythematosus, among others (Figure 6).

These results indicate that MDD-associated transcriptional alterations are not confined to the nervous system but also involve impaired mitochondrial oxidative phosphorylation, reactive oxygen species accumulation, altered phagocytic function, aberrant antigen presentation, and immune activation. In particular, the enrichment of oxidative phosphorylation– and ferroptosis-related pathways suggests that energy metabolic imbalance and lipid peroxidation may jointly contribute to the disease process of MDD.

3.1.5. PPI Network Highlights Core Myelin and Membrane Modules

The PPI network constructed using STRING showed that the differentially expressed genes in the first dataset formed several biologically meaningful interaction modules (Figure 7). Although the overall network was relatively sparse, with a limited number of edges, distinct functional core clusters could still be identified. Nodes such as PMP22, CLDN11, GJC2, ZDHHC9, and PLLP were densely interconnected within regions related to myelin and membrane connections, suggesting that oligodendrocyte and myelin abnormalities may constitute an important molecular basis of MDD. In addition, the inflammation-related molecule SPP1 showed a strong disease association, indicating that neuroinflammation may act synergistically with structural changes in the development of MDD.

3.2. Transcriptomic Features and Differential Expression in the Second Dataset (GSE54572)

The raw expression matrix of GSE54572 was first normalized. The box plots showed highly consistent expression distributions across samples, with small differences in median and interquartile range, indicating good comparability after normalization and well-controlled technical bias—a reliable basis for subsequent analysis. PCA further showed a degree of separation between the MDD and control groups in two-dimensional space; Dim1 and Dim2 explained 17.2% and 9.2% of the variance, respectively. This indicates a clear overall expression difference between groups, although some overlap remained, reflecting a degree of heterogeneity in MDD-related transcriptional changes. This pattern of partial rather than complete separation is consistent with the typical features of complex psychiatric disorders at the peripheral transcriptomic level. The heatmap showed that the top differential features clustered clearly across samples and distinguished the MDD group from controls, indicating discriminative potential. The volcano plot showed that most genes exhibited limited changes, with only a few reaching significance, suggesting that the MDD signal in GSE54572 is relatively concentrated and that these differentially expressed genes may be of considerable biological relevance (Figure 8).

3.2.1. Expression Patterns of the Top Differential Probes

Six significant differential probes were identified in this dataset: 1559701_s_at, 1565495_at, 214396_s_at, 214816_x_at, 235779_at, and 236972_at, all with statistically significant between-group differences (Figure 9). The dataset showed a pattern of transcriptional remodeling with some probes up- and others downregulated instead of one direction of global up- or downregulation. This indicates that MDD-associated molecular alterations are not necessarily a net upregulation or downregulation but instead a coordinated dysregulation of multiple molecular networks. Notably, 235779_at showed the lowest P value, indicating that its corresponding transcriptional feature was the most significantly different between groups and may be among the most valuable candidate markers in this dataset. Although this dataset was not subjected to GO/KEGG enrichment, the direction and magnitude of its differential features already showed marked disease specificity, making it an important source of evidence for subsequent cross-validation.

3.2.2. Summary

Overall, GSE54572 confirmed stable expression differences between MDD patients and healthy controls. Normalization was reliable, PCA indicated overall between-group separation, and the heatmap and box plots further confirmed the significant differences in the top probes. These results indicate that the second dataset not only reproduced MDD-related transcriptional abnormalities but also, together with the first dataset, supports the view that MDD has a distinct yet heterogeneous molecular pathological basis.

3.3. Transcriptomic Features and Differential Expression in the Third Dataset (GSE54568)

GSE54568 was likewise normalized prior to analysis. The box plots showed well-balanced expression distributions across samples, with small differences in median values, indicating effective preprocessing and suitability for differential analysis. PCA showed a relatively clear separation between the MDD and control groups in principal component space, with Dim1 and Dim2 explaining 15.3% and 12.9% of the variance, respectively, indicating that this dataset could also distinguish cases from controls at the overall expression level. The case-control separation was more pronounced here compared with the second dataset, indicating a stronger signal of transcriptional differences. However, some overlap still existed, reflecting the biological heterogeneity and population complexity of MDD samples [8-10]. The heatmap also showed that the top differential features could effectively distinguish the MDD and control groups, indicating that these features not only had statistical significance but also had strong discriminative power. Again the volcano plot showed that the majority of genes were changed to a small degree with only a few transcripts deviating significantly, indicating that the molecular abnormalities of MDD are focal and not diffuse, consistent with the molecular pathology of complex neuropsychiatric disorders (Figure 10).

3.3.1 Expression Patterns of the Top Differential Probes

Six major differential probes were picked in the third data set: 1565838_at, 201452_at, 216527_at, 232769_at, 240974_at, and 242608_x_at. All of these probes showed statistically significant group differences (Figure 10). Again, the third dataset showed a distinct bidirectional pattern with some probes increased and others decreased in the MDD group. This indicates that transcriptional changes in MDD are not driven by activation or repression of a single class of genes, but rather reflect dysregulation of multiple regulatory modules. Of these probes, 232769_at exhibited the greatest significance, suggesting that its corresponding molecular feature differed most significantly between the MDD and control groups and may be highly relevant to the disease.

3.3.2 Summary

Overall, GSE54568 showed relatively consistent MDD-related expression abnormalities across normalization, PCA, heatmap, and top-probe analyses. A clear, though not absolute, separation existed between cases and controls, indicating that this cohort likewise supports a stable basis of transcriptional abnormalities in MDD. When corroborated by the first and second datasets, these findings suggest that MDD-related molecular alterations possess cross-cohort reproducibility, and the top differential probes in the third dataset further strengthen the credibility of the candidate biomarkers.

3.4. Integrated Features Across the Three Cohorts

Integrating the results from the three datasets, the MDD and control groups showed stable expression differences across all three independent cohorts. The first dataset provided mechanistic enrichment evidence, suggesting that myelin structural damage, aberrant PLD signaling, oxidative stress, and immune inflammation may be important molecular bases of MDD; the second and third datasets reproduced significantly different expression patterns between cases and controls in independent samples and further confirmed the stability of these differences through top-feature box plots, PCA, and heatmaps.

The three datasets together suggest the following: First, transcriptional abnormalities associated with MDD are replicable across cohorts. Second, these abnormalities are not simple unidirectional changes, but rather complex bidirectional remodeling. Third, the candidate molecules identified here may serve as potential biomarkers for the early diagnosis or molecular subtyping of MDD.

4. Discussion

Here we systematically screened and validated candidates of MDD biomarkers using three independent transcriptomic datasets. The results suggest that MDD is a disorder with multiple pathological processes including myelin injury, membrane lipid metabolism disturbance, neuroinflammation, oxidative stress, and energy metabolism dysregulation, rather than a simple disorder of neurotransmitters.

Particularly interesting are the results of GO enrichment for the myelin sheath, compact myelin and gap junctions. Myelin is an insulator for the efficient conduction of nerve impulses. Damage to myelin could reduce synchrony of neural networks, affecting information transmission, emotion regulation and cognitive function. Impaired white matter integrity and oligodendrocyte dysfunction have been increasingly reported in MDD patients, and our enrichment results further confirm this view at the transcriptomic level [6, 7].

KEGG analysis showed that the PLD signaling pathway was significantly perturbed. PLD participates in phospholipid metabolism generating phosphatidic acid and is an important point of convergence between membrane remodeling and signal transduction. The PLD signaling pathway is involved in vesicle cycling, membrane receptor trafficking, cell migration and axon growth in the nervous system. Disruption of this pathway may contribute to loss of synaptic plasticity and abnormal neurotransmitter release. Together, these results indicate that a dysregulation of membrane lipid metabolism and signal integration might be an important molecular basis of MDD.

GSEA analysis showed abnormal enrichment of oxidative phosphorylation, reactive oxygen species, phagosome, antigen processing and presentation, and ferroptosis pathways in MDD. Impaired oxidative phosphorylation indicates that the mitochondrial energy supply is inadequate. The accumulation of reactive oxygen species results in increased lipid peroxidation and aggravated cell damage. In recent years, neuropsychiatric research has increasingly focused on ferroptosis, a newly identified form of cell death that is closely associated with lipid peroxidation [4,5]. Together with our enrichment findings, these observations suggest that impaired energy metabolism and oxidative damage may form a mutually reinforcing loop in MDD.

Among the candidate genes, SPP1 is the most notable. Also known as osteopontin, SPP1 is involved in immune regulation, inflammatory responses, cell adhesion, and tissue repair. Its up-regulation in MDD suggests that inflammatory activation and glial responses may be involved in disease progression. GLDN, a component of axonal and nodal structures, may be implicated in the stability of neural connections; MEIS1, a transcriptional regulator, may be implicated in MDD via its effect on neural development and cell fate. MORN4 is linked to membrane protein function, PCBP3 to RNA binding regulation and SORCS1 to receptor trafficking and neural signal modulation. These genes jointly constituted a molecular network closely related to neural structure, membrane function and immune inflammation.

Importantly, the 2nd and 3rd data sets reproduced the between-group differences in principal component analysis (PCA), heatmaps, and top features. They also preserved the bidirectional remodelling pattern observed in the first dataset. This demonstrates the reproducibility of the pathological signals found in the first dataset in the cohorts. Cross-cohort consistency is more clinically relevant than statistical significance in a single cohort in biomarker studies.

There are some limitations of this study. First, the second and third datasets currently only give results at the probe level. Uniform probe-to-gene annotation would improve the biological clarity of the findings in future work. Second, transcriptomic data reflect changes only at the mRNA level, and further validation at the protein level and by functional experiments is still necessary. Third, MDD is

highly heterogeneous and the expression profiles may be affected by differences in tissue source, clinical subtype and treatment status. Therefore, the candidate molecules identified here are worth further validation in larger, multicenter cohorts.

5. Conclusion

In this study, we systematically screened and validated candidate biomarkers of major depressive disorder (MDD) based on three independent public transcriptomic datasets. The results imply that MDD is associated with structural injury of myelin, disturbance of membrane lipid metabolism, neuroinflammation, oxidative stress and dysregulation in energy metabolism. SPP1, GLDN, MEIS1, MORN4, PCBP3, and SORCS1 emerged as potential MDD biomarkers. Multi-cohort validation further enhances the robustness and reliability of these candidate molecules, providing a new basis for the early diagnosis, molecular subtyping, and targeted treatment of MDD.

6. Figures

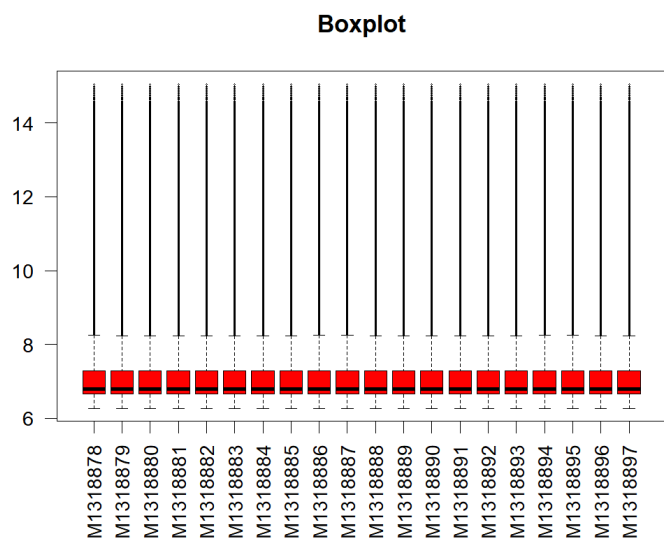


Figure 1. Boxplot of normalized expression in GSE54562. Distribution of expression values across all samples after normalization with largely consistent medians and interquartile ranges confirming reliable data quality for downstream analysis.

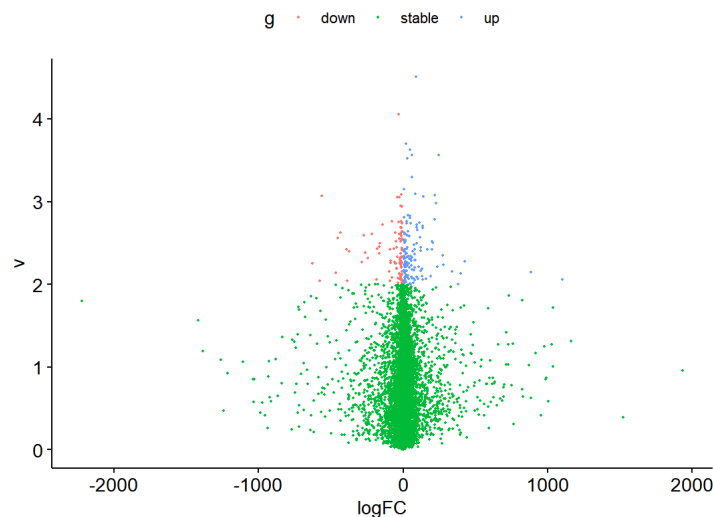


Figure 2. Each point is a gene and those that were significantly upregulated and downregulated in the MDD group compared to controls are highlighted. Most genes show little change.

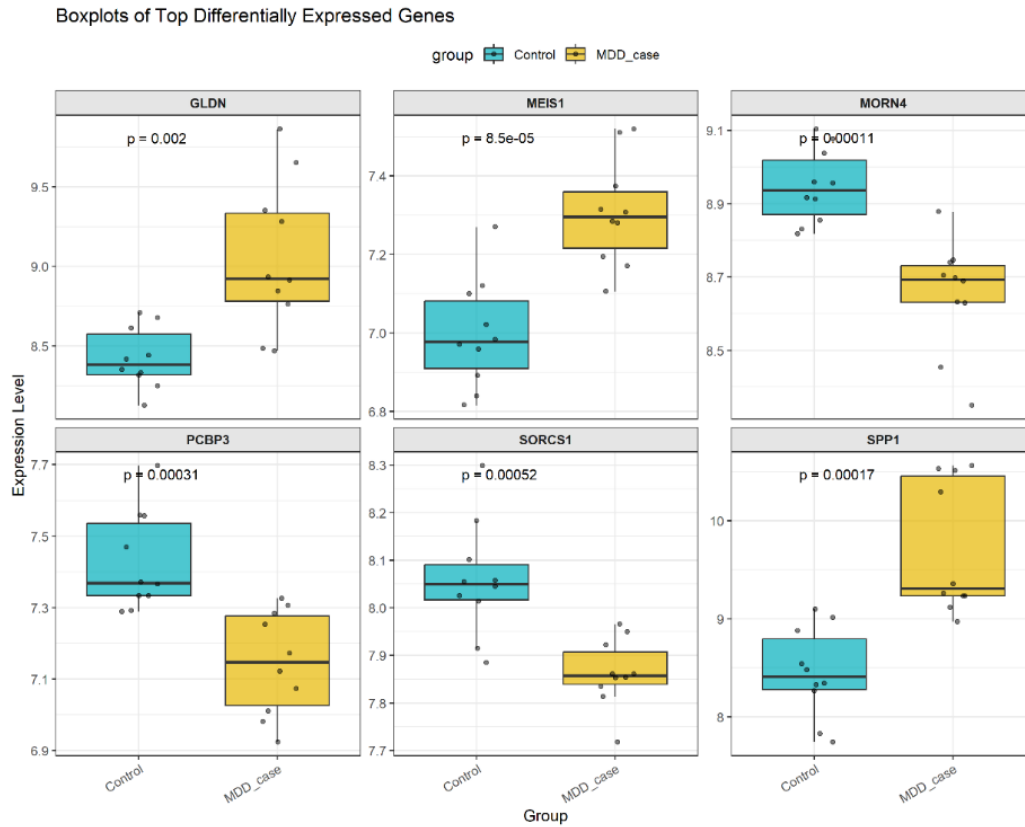


Figure 3. Box plots of the top differentially expressed genes in GSE54562. Expression levels of candidate genes between the MDD and control groups. SPP1, GLDN, and MEIS1 are significantly upregulated and MORN4, PCBP3, and SORCS1 are significantly downregulated in MDD, whereas *EEF1A1*, *GAPDH*, and *SLC35E2A* show no significant between-group difference.

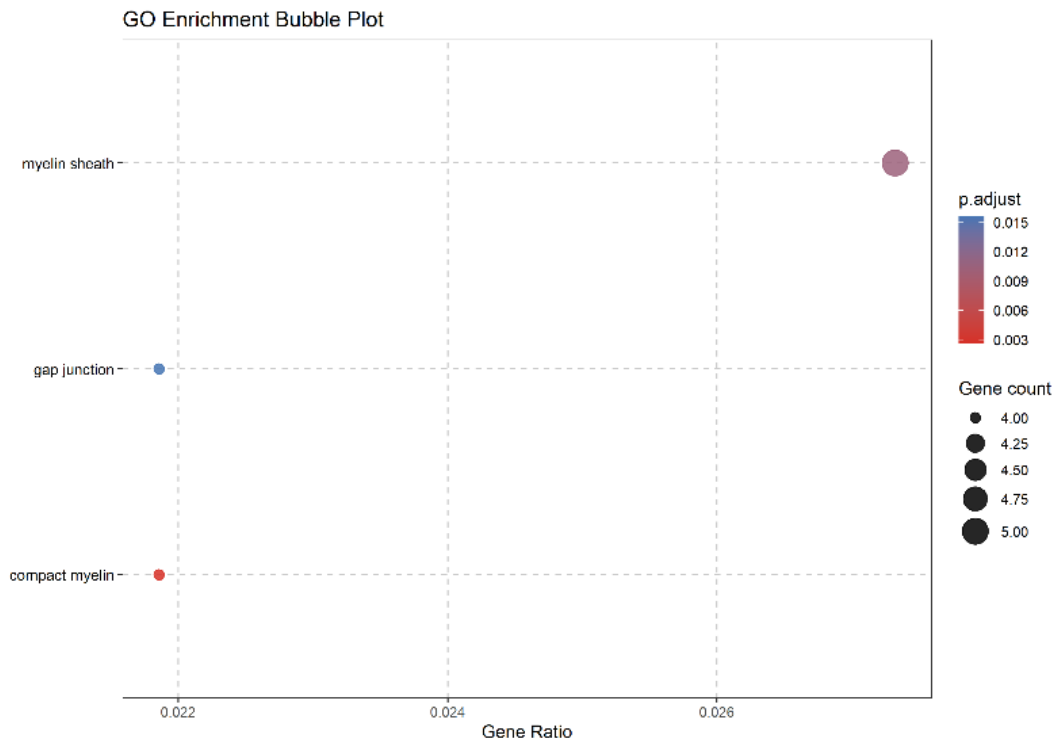


Figure 4. GO enrichment bubble plot for GSE54562. Significantly enriched GO terms for the differentially expressed genes, with terms concentrated in the myelin sheath, compact myelin, and gap junction. Bubble size and color denote gene count and enrichment significance, respectively.

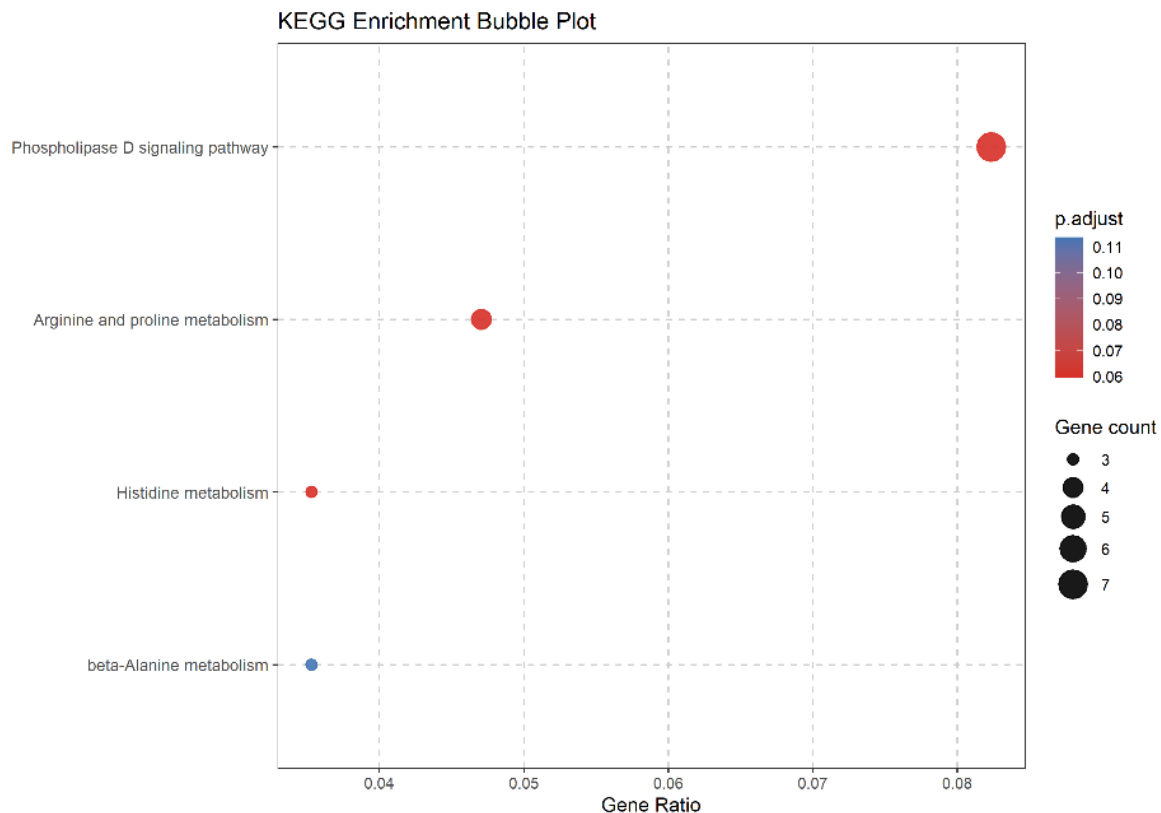


Figure 5. KEGG enrichment bubble plot for GSE54562. Significantly enriched KEGG pathways, including the phospholipase D (PLD) signaling pathway and several amino acid metabolism pathways. Bubble size and color denote gene count and enrichment significance, respectively.

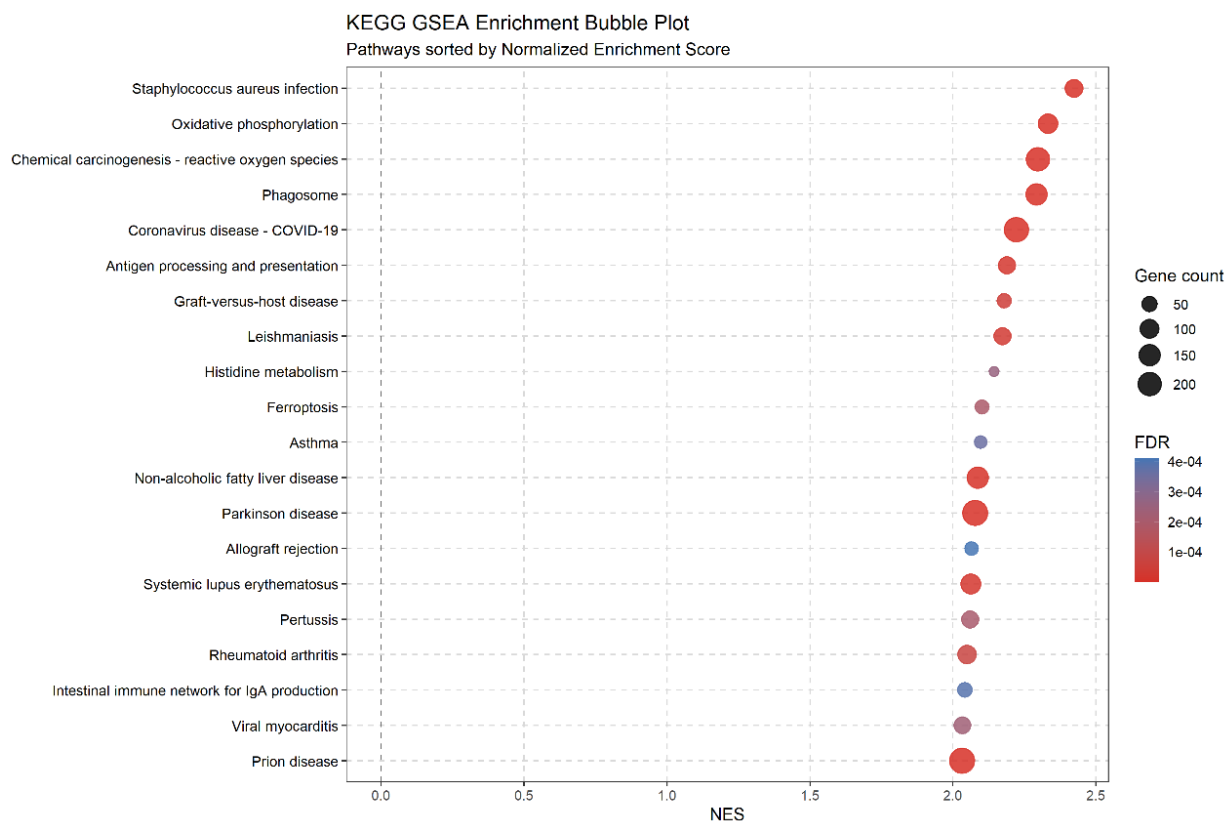


Figure 6. GSEA bubble plot for GSE54562. Pathways significantly enriched by genome-wide GSEA, including oxidative phosphorylation, reactive oxygen species, phagosome, antigen processing and presentation, and ferroptosis.

Protein-Protein Interaction Network
STRINGdb | Nodes: 93 | Edges: 8

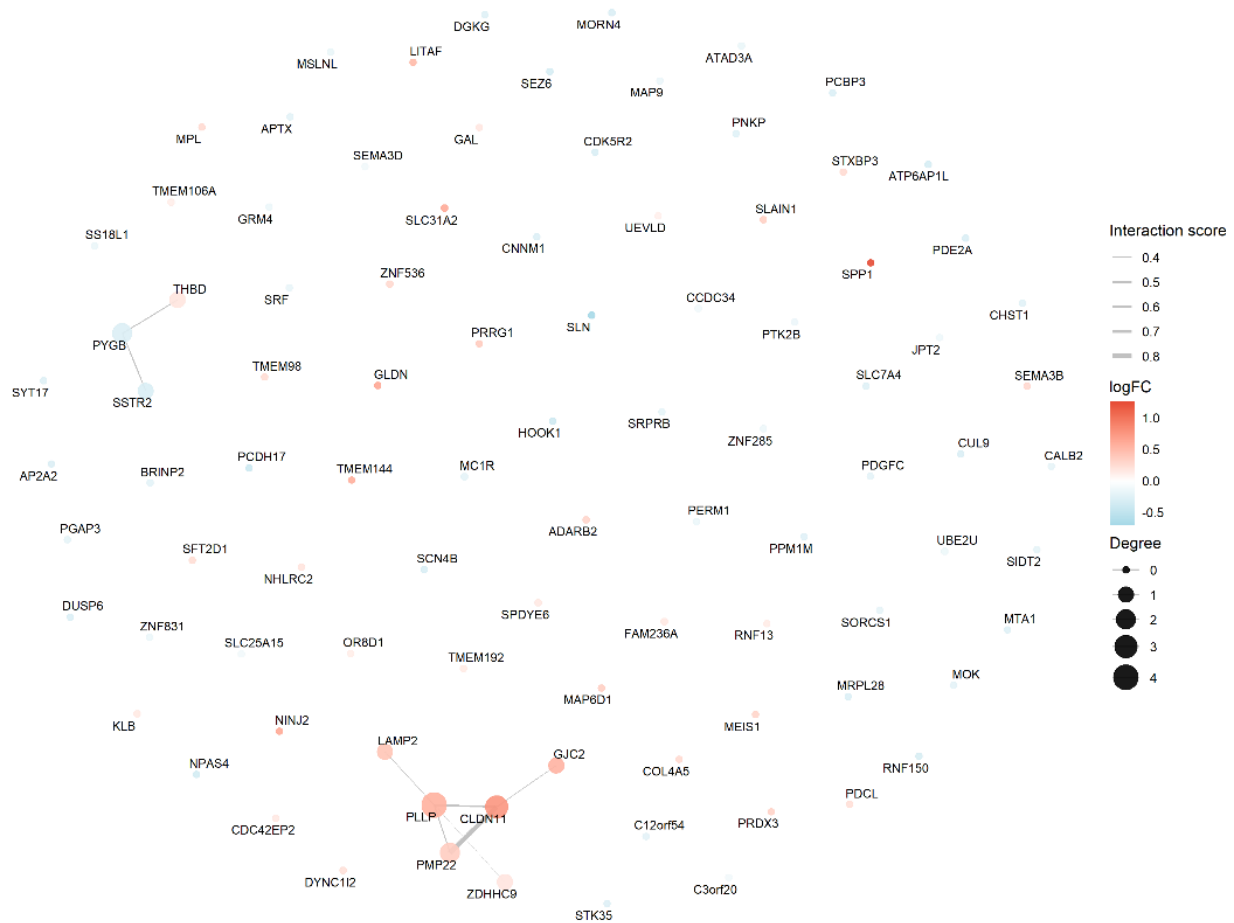
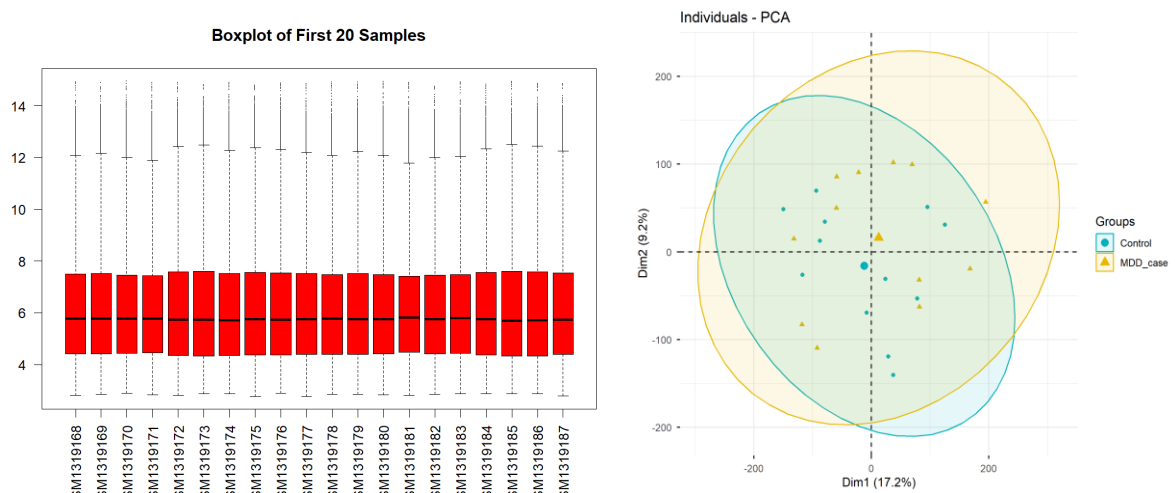


Figure 7. PPI network of differentially expressed genes in GSE54562. Protein-protein interaction network constructed using the STRING database. A core cluster of myelin- and membrane-related nodes (PMP22, CLDN11, GJC2, ZDHHC9, PLLP) and the inflammation-related molecule SPP1 are highlighted.



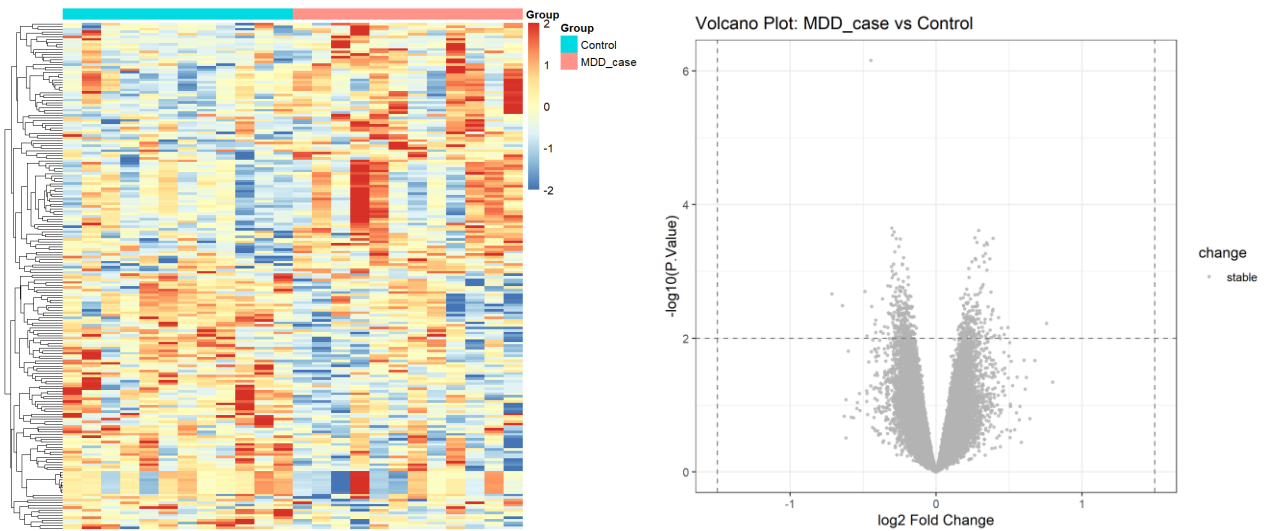


Figure 8. Quality control and differential expression in GSE54572. Box plot (normalized expression distribution across samples), PCA (separation between the MDD and control groups; Dim1 = 17.2%, Dim2 = 9.2%), heatmap (clustering of the top differential features), and volcano plot (differentially expressed probes between groups).

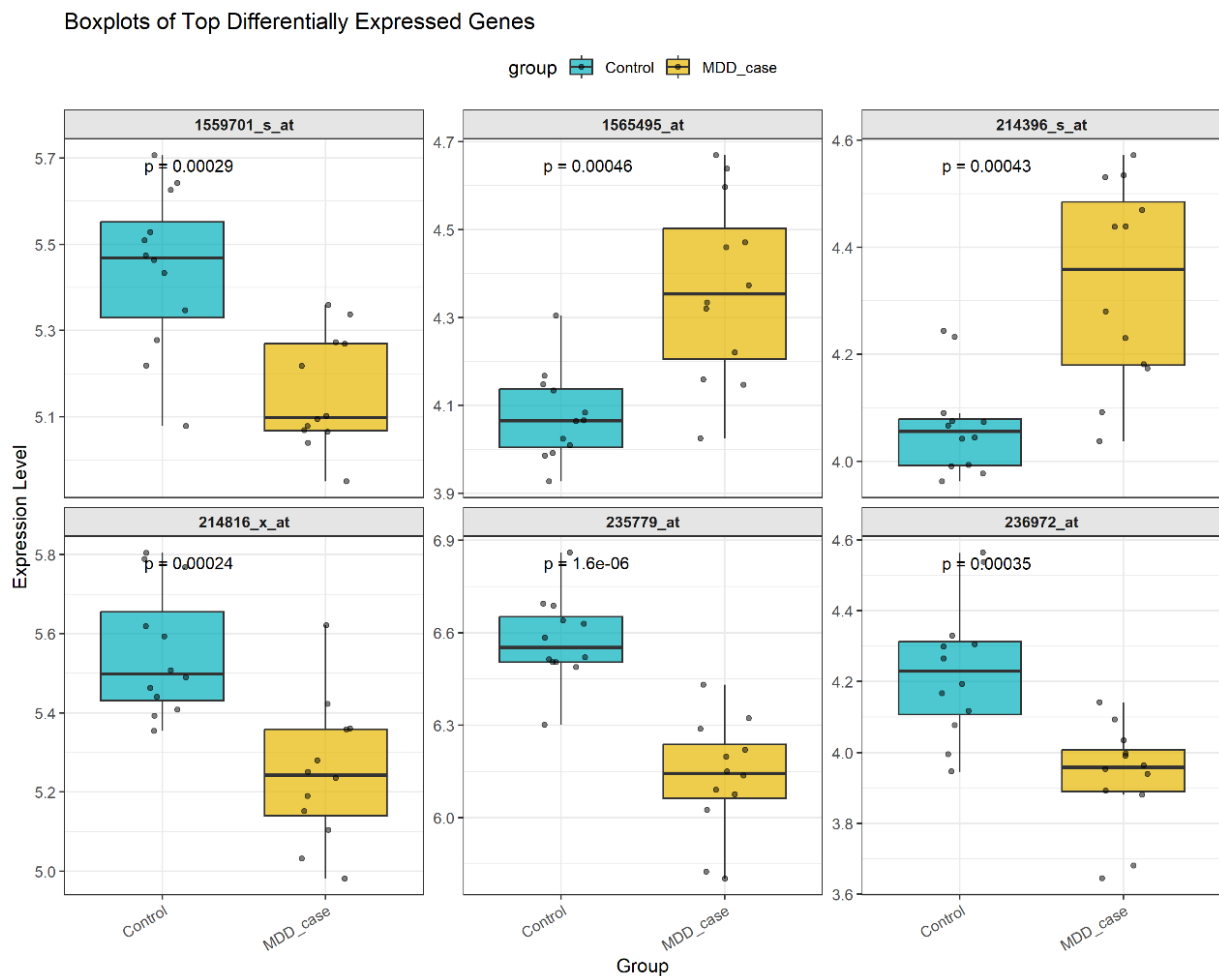


Figure 9. Box plots of the top differential probes in GSE54572. Expression of the six significant probes (1559701_s_at, 1565495_at, 214396_s_at, 214816_x_at, 235779_at, and 236972_at) between the MDD and control groups, showing a bidirectional pattern of up- and downregulation; 235779_at has the lowest P value.

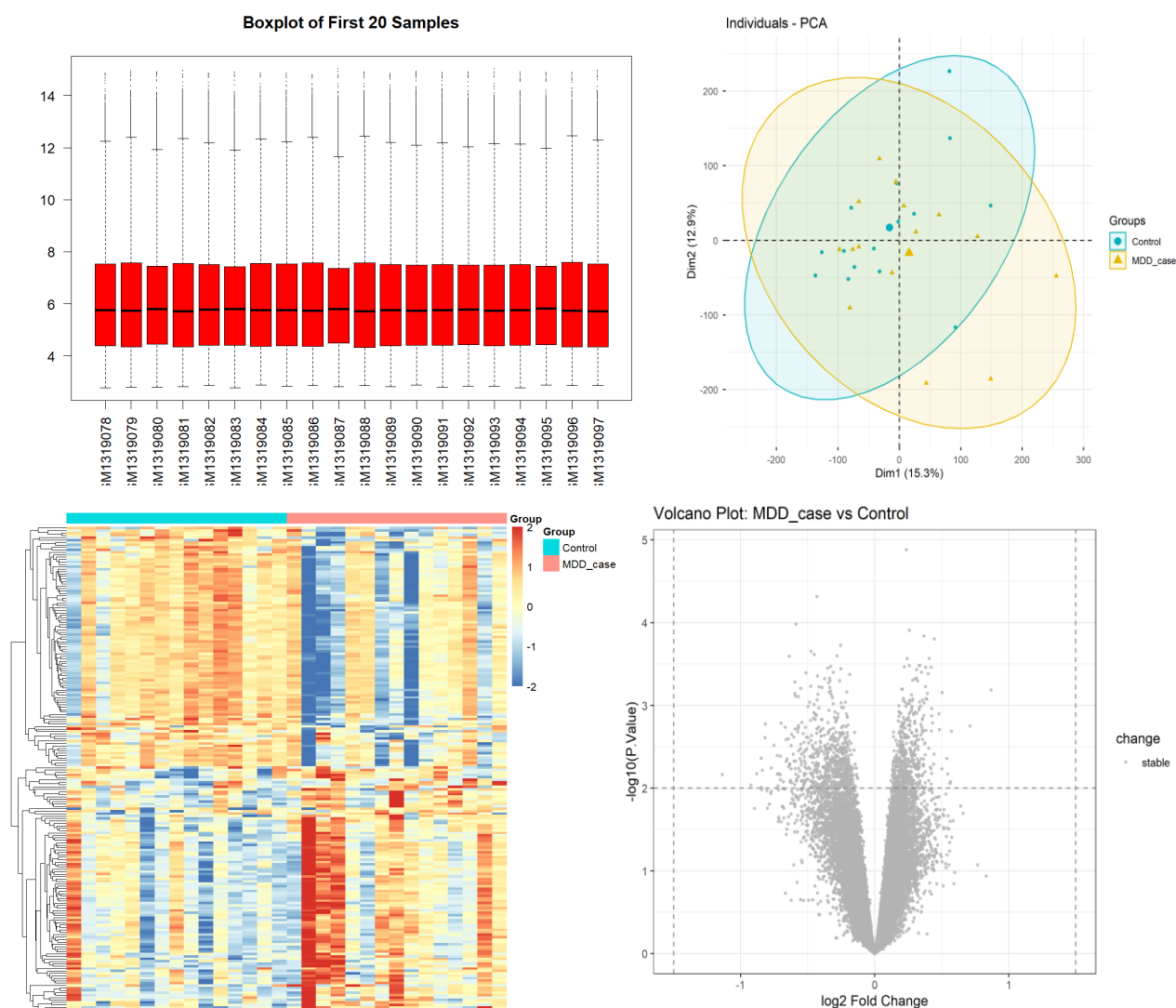


Figure 10. Quality control and differential expression in GSE54568. Box plot (normalized expression distribution across samples), PCA (separation between the MDD and control groups; Dim1 = 15.3%, Dim2 = 12.9%), heatmap (clustering of the top differential features), and volcano plot (differentially expressed probes between groups). The six significant probes were 1565838_at, 201452_at, 216527_at, 232769_at, 240974_at, and 242608_x_at, with 232769_at showing the strongest significance

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