

Decoding Shared Genetics: Unveiling the Link Between Major Depressive Disorder and Glioblastoma Multiforme

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Abstract: Major depressive disorder (MDD) is a common psychiatric disorder, and glioblastoma multiforme (GBM) is the most common primary central nervous system tumor. Patients with GBM have been shown to have a high incidence of MDD, but the pathogenesis of these two diseases remains unclear. This study utilized a high-throughput omics approach to explore the genetic link between MDD and GBM. First, five shared genes between MDD and GBM were identified using differential expression analysis, including EN1 and UBE2C. The result showed that the shared genes EN1 and UBE2C were both differentially expressed in the two diseases, respectively, and related to the development of glioma, dopamine regulation and Alzheimer's disease. Subsequently, weighted gene co-expression network analysis (WGCNA) revealed different functional enrichments in neural activity for GBM and MDD, respectively. The co-expression network results highlighted the common molecular mechanisms between MDD and GBM gene modules, emphasizing neural-related activities and gene expression regulation. Our study reveals a compelling genetic link between MDD and GBM, revealing potential co-pathogenesis. And EN1 and UBE2C emerged as key genes, indicating common signaling pathways and potential therapeutic targets. Further exploration of these genes and pathways could provide avenues for targeted therapeutic intervention in these devastating diseases.

1. Introduction

Major Depressive Disorder (MDD) is a prevalent mood disorder characterized by persistent sadness, lack of interest or pleasure, and a range of cognitive and physical symptoms that pose a significant global health burden. According to the World Health Organization (WHO), MDD is a leading cause of disability worldwide, affecting over 264 million individuals as of 2020 [1].

So far, the cause of MDD is still an essential topic in the health field. What is sure is that MDD has no single cause, and the significant factors include biological, genetic, environmental, and psychosocial factors [2]. MDD was once thought to be primarily induced by abnormalities in neurotransmitters such as serotonin, norepinephrine, and dopamine [3]. However, new research suggests that MDD may be a secondary disorder of the neurotransmitter system caused by more complex neuromodulator system factors [4]. In addition, MDD has been shown to have a significant genetic component. Twin study data indicate that the heritability of major depression may range from 31% to 42%. Children of depressed parents are 2 to 3 times more likely to suffer from depression [5]. These estimates rise to 70% when severity of onset, recurrence rate, and age at onset are also considered [6].

Glioblastoma multiforme (GBM) is the most common primary central nervous system tumor [7] accounting for approximately 80% of all malignant primary brain tumors

[8, 9]. Compared with other malignancies, the patients with glioblastoma have only 6.7% of 2-year survival rate and have no significant improvement in prognosis in recent decades, with the median survival of patients being only 14 months [10]. GBM is believed to originate from astrocytes, oligodendrocyte progenitor cells, and neural stem cells [11]. The cause of most of these cases is unknown [12], but research shows that about 5% of cases are related to genetic diseases [13]. It is well-known that depression has become one of the most common complications of brain tumors [14]. The concomitant development of depression can affect or even worsen the condition of cancer patients. Also, compared with other cancers, GBM patients are more susceptible to depression [15, 16].

Some researchers attribute the high correlation between GBM and MDD to the poor prognosis of GBM patients and the potential side effects of cancer treatment drugs [17]. However, as two diseases whose pathogenesis is not yet clear and are highly related to gene mutations and polymorphisms [8, 18], there are few studies on the relationship between GBM and MDD in gene expression. Yet previous studies have demonstrated that MDD and GBM share transcriptomic gene expression pathways, but no detailed genomic relationship has yet been established [19].

With the development of human science, people have been able to explore the information of molecules inside cells, such as DNA, RNA and proteins. The research that uses high-throughput methods to measure biomolecular

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information is called omics. Omics can be roughly divided into genomics, transcriptomics, and proteomics, etc. Among them, genomics sequencing methods were first developed in the 1970s, including Maxam–Gilbert sequencing and Sanger sequencing. However, new technologies have made it possible to sequence larger amounts of DNA quickly with a lower cost than before. These new technologies, often referred to as next-generation, massively parallel or high-speed sequencing [20]. In contrast, transcriptomics examines the sequence of cellular RNA to obtain information about intracellular transcription products. Test objects include messenger RNA (mRNA), non-coding RNA and microRNA. Currently, RNA sequencing (RNA-Seq) commonly uses high-throughput sequencing methods, which provides higher coverage and more detailed and quantitative transcriptome information [21]. The development of these sequencing technologies has greatly advanced people’s

understanding of biology and helped reveal the pathology and genetics beneath various diseases. Hence it is completely feasible to use omics to establish the relationship between MDD and GBM, which has a huge therapeutic potential.

Therefore, this study would explore the similarities and differences in gene expression between MDD as an affective disorder and GBM as a brain tumor. The study designs a set of omics analysis in two directions to study the common genes and pathways of the two diseases, with the flowchart shown in Fig.1. By leveraging cutting-edge technology and analyzing large-scale expression data sets, we sought to find shared molecular pathways or genetic factors between the two diseases to explore the underlying pathogenesis. We also aim to uncover hidden patterns and regulatory networks that hold the key to better diagnosis, prognosis, and targeted treatment of these devastating diseases.

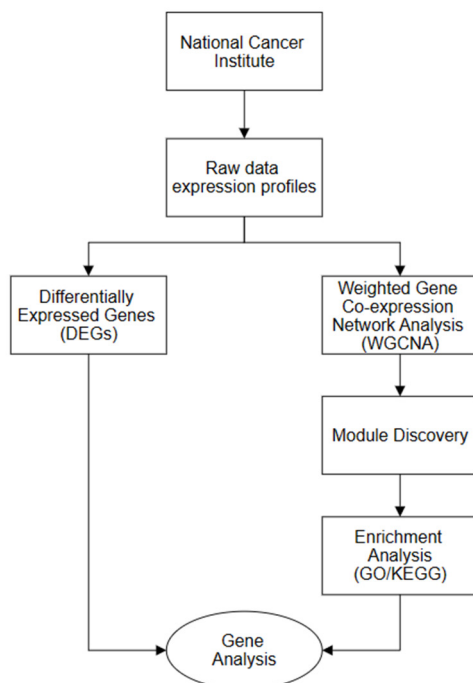


Figure 1. The flowchart of the study. Rectangle: analysis process, circle: gene analysis results

2. Results

2.1. Differentially expression analysis identified a set of shared genes between MDD and GBM

Due to MDD and GBM are both brain-related diseases, we hypothesized that there would be a set of genes shared between two disorders. To investigate this, we first applied the differential expression analysis to identify the

differentially expressed genes in MDD and GBM separately. Through the edgeR package of R software, the Differentially Expressed Genes of MDD and GBM in the human brain were screened out ($q\text{-value} < 0.001$, $\text{Fold Change} > 2.5$) (**Methods and Materials**). Among them, nine DEGs were significantly related to MDD, while 4053 DEGs were significantly related to GBM. Using the DEGs of MDD as a reference, we found five genes that were co-expressed in MDD and GBM and all were significantly differentially expressed.

Table 1. The DNA expression fold change (FC) of the 5 co-expressed and differentially expressed genes in brain tissues from MDD and GBM patients.

Gene Symbol	MDD vs Control		GBM vs Control	
	edgeR.logFC	edgeR.FDR	edgeR.logFC	edgeR.FDR
MTND1P23	-4.65	9.27×10^{-7}	-2.91	2.23×10^{-4}
MTCO1P53	-3.58	6.05×10^{-5}	-2.71	4.93×10^{-15}

MTATP8P1	-3.95	6.05×10^{-5}	3.01	2.49×10^{-5}
EN1	-3.99	6.33×10^{-3}	8.42	1.99×10^{-9}
UBE2C	-2.58	2.91×10^{-2}	7.37	5.62×10^{-19}

* logFC: The value of Fold Change in log base 10

It can be found that three of the five highly differentially expressed shared genes are pseudogenes and do not encode any proteins. Interestingly, gene Engrailed Homeobox 1 (EN1) was significantly differentially expressed in the brain tissues of both MDD patients (p-value = 6.33×10^{-3}) and GBM patients (p-value = 1.99×10^{-9}). Studies have shown that EN1 is highly expressed in glioma cells and glioma tissues, and plays a role in cancer cell proliferation, colony formation, and radiotherapy resistance. At the same time, EN1 also promotes tumor growth in the body and may play an oncogene role in glioma. At the same time, patients with high EN1 expression also have significantly worse survival outcomes [22].

EN1 also plays a role in neurological diseases. Dopamine (DA) is a neurotransmitter responsible for the behavioral and cognitive regulation of organisms, including voluntary movement; motivation; punishment and reward, mood, etc. [23]. In the brain, the mdDA neurons are the major source of dopamine in the mammalian central nervous system (CNS). Studies have shown that En1 is highly expressed by all mdDA neurons and is involved in the development of mdDA neurons. At the same time, En1-deficient heterozygous adult mice have significantly reduced DA levels and exhibit motor defects, anhedonia, reduced social interaction, and depressive-like behaviors, which have been proven to be related to Parkinson's disease [24, 25]

Ubiquitin-conjugating enzyme E2C (UBE2C) is a key regulator of cell cycle progression and a member of the structurally related protein family that mediates ubiquitin-dependent proteolysis, including cell cycle progression, signal transduction, differentiation, and other cellular processes [26, 27]. Studies have shown that UBE2C is involved in the occurrence of various brain tumors and is also an important factor in the malignant progression of astrocyte tumors [28, 29]. At the same time, UBE2C is

overexpressed in malignant glioma and is closely related to the invasive progression of brain cancer cells and poor prognosis of patients [30].

At the same time, UBE2C is also highly expressed in the hippocampus of patients with Alzheimer's disease, which is closely related to patients' cognitive decline, memory decline, and psychological and behavioral abnormalities [31]. At the same time, related genomic studies have proven that the UBE2C gene locus is also highly related to mental diseases [32]. Therefore, high expression of UBE2C may also be one of the potential causes of MDD (shown as in Table 1).

2.2. Weighted Gene Co-expression Network analysis (WGCNA) identified shared and unique biological mechanisms between MDD and GBM

To further explore the underlying biological connection between MDD and GBM diseases, we applied WGCNA method (**Methods and Materials**) to conduct co-expression network analysis to compare the co-expression modules between two diseases.

WGCNA analyze groups genes into modules or clusters based on their co-expression patterns. Each module consists of genes that exhibit similar expression patterns across samples. These modules are usually represented by distinct colors and assigned arbitrary identifiers. In this study, GBM and MDD gene expressions was classified and merged into modules.

The GBM gene modules were merged with a module merging threshold of 0.25, a soft threshold of 4, resulting in 164 different gene modules (Fig. 2A). The MDD gene modules were merged with a module merging threshold of 0.25, a soft threshold of 6, resulting in 67 different gene modules (Fig. 2B).

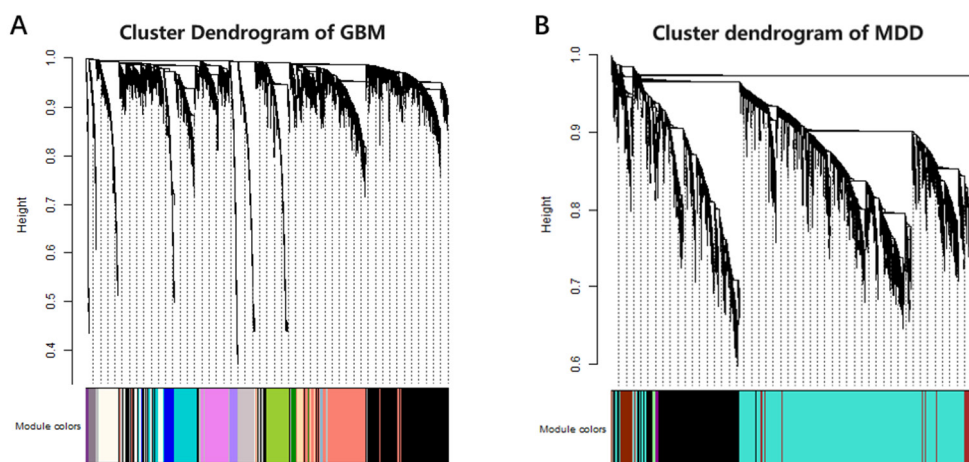


Figure 2. Construction of DNA co-expression network. (A) Cluster Dendrogram of GBM. The different colors on the bottom represents the different co-expression gene modules. The branches on top represents different genes. Total of 164 modules were obtained. (B) Cluster Dendrogram of MDD. The different colors on the bottom represents the different co-expression gene modules. The branches on top represents different genes. Total of 67 modules were obtained.

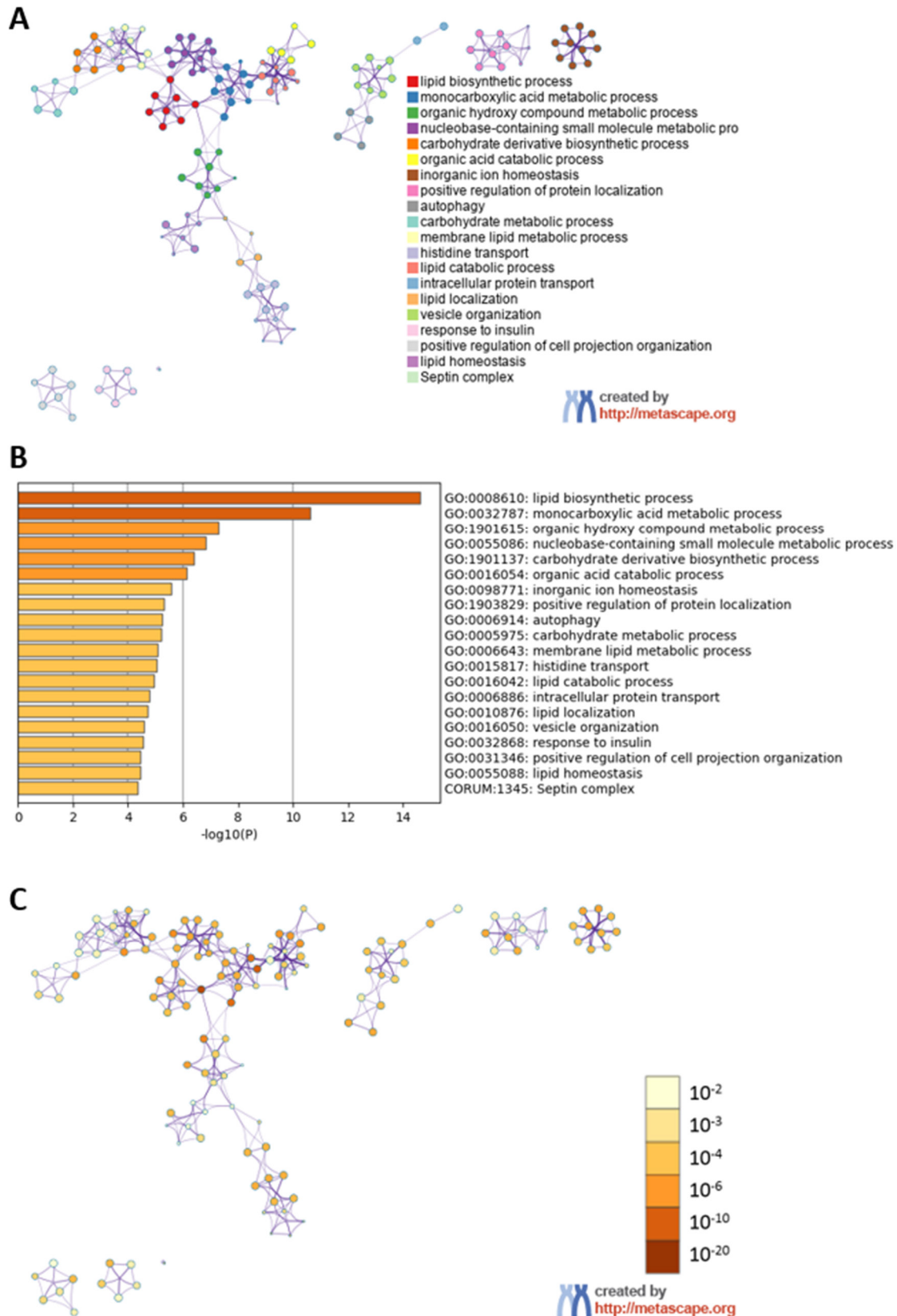


Figure 3. WGCNA analysis of the grey module from GBM (A) Network of 20 highly connected clusters from the grey module of GBM. (B) Heat map of the 20 clusters from the grey module of the GBM in network form. The gene with the most significant P-value was ranked on the top, the gene with the least significant P-value was ranked at the bottom. (C) Heat map of the 20 clusters from the grey module of the GBM. The genes were shown in the network connections, colored by the P-values. The darker color represents the higher significance.

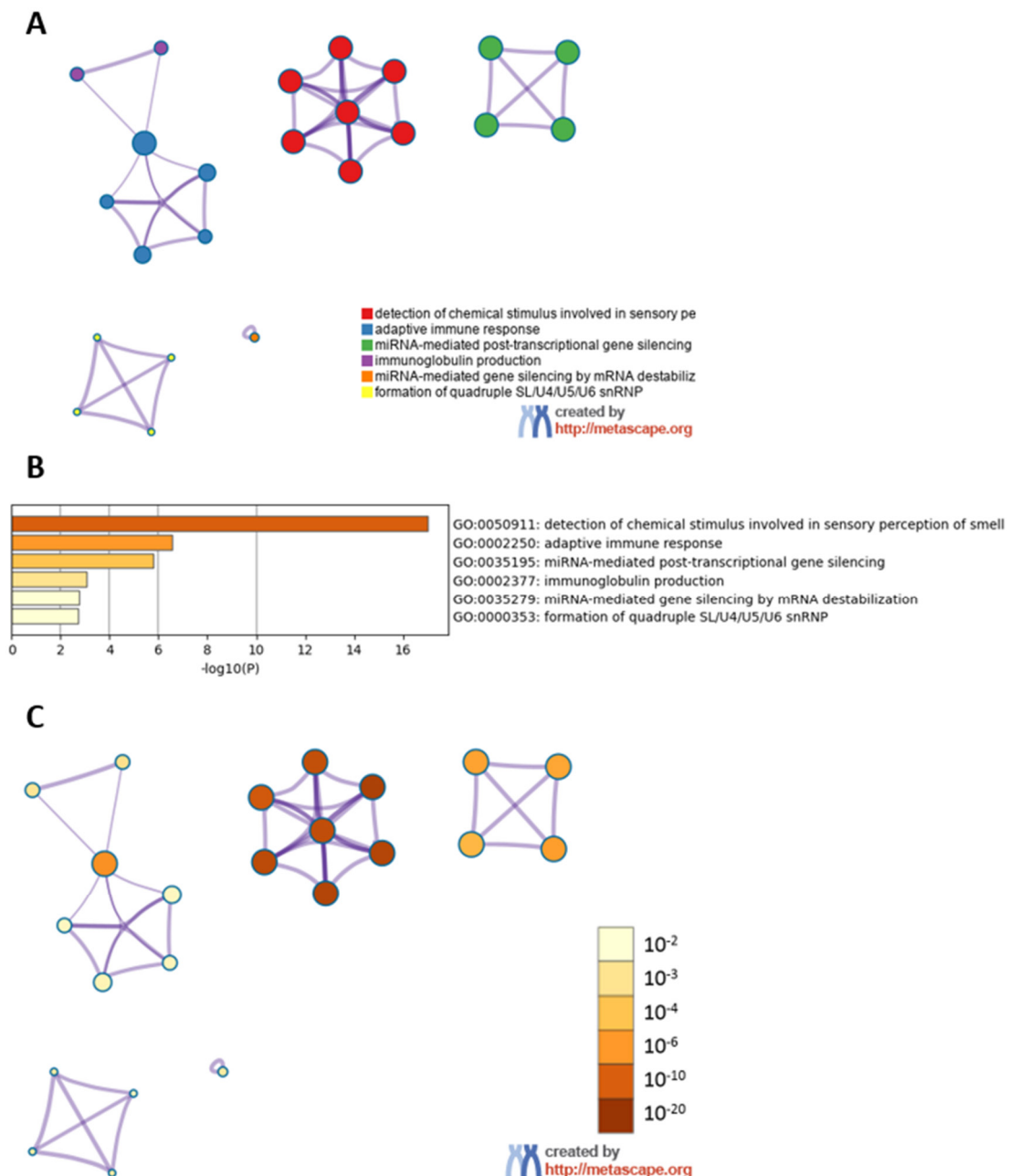


Figure 4. WGCNA analysis of the selected modules (A) Network of six highly connected clusters from the green module of MDD. (B) Heat map of the six clusters from the green module of the MDD in network form. The gene with the most significant P-value was ranked on the top, the gene with the least significant P-value was ranked at the bottom. (C) Heat map of the six clusters from the green module of the MDD. The genes were shown in the network connections, colored by the P-values. The darker color represents the higher significance.

Subsequently, to explore the function of the gene clusters in human body which include the EN1 and UBE2C genes, the recorded gene module information was subjected to GO functional enrichment analysis by the Metascape to carry out the GO Biological Processes. Functional enrichment analysis can link genes with corresponding biological pathways to construct a functional network of genes. Taking the grey module of GBM cluster dendrogram as an example, 20 clusters that are highly correlated with p-values exceeding the threshold of 0.01 are identified and displayed based on cluster ID (Fig. 3A), including lipid biosynthetic process, monocarboxylic acid metabolic process and organic

hydroxyl compound metabolic process. The MDD network was generated with the green module, six clusters that are highly correlated with p-values exceeding the threshold of 0.01 are identified and displayed based on cluster ID (Fig. 4A), including detection of chemical stimulus, adaptive immune response, and miRNA-mediated post-transcriptional gene silencing.

Furthermore, to explore the relationships between the different genes, the heat maps were also generated by Metascape based on p-values (Fig. 3B-C, 4B-C). Among them, the biological processes with the highest p-value were ranked on the top, with a darker color representation. For the GBM, the lipid biosynthetic process and

monocarboxylic acid metabolic process have the highest significance, while in the case of MDD, the detection of chemical stimulus have the highest significance. At the same time, the number and proportion of each term in the summarized enrichment analysis of gene modules of

MDD and GBM are shown (Table 2 & 3), with the lipid biosynthetic process, detection of chemical stimulus occupied the most percentages in GBM and MDD, respectively.

Table 2. Pathway and process enrichment Analysis in grey module from GBM with their representative enriched terms.

GO	Category	Description	Count	%	Log10(P)	Log10(q)
GO:0008610	GO Biological Processes	lipid biosynthetic process	84	5.02	-14.63	-10.29
GO:0032787	GO Biological Processes	monocarboxylic acid metabolic process	68	4.06	-10.62	-6.58
R-HSA-382551	Reactome Gene Sets	Transport of small molecules	78	4.66	-7.74	-4.18
WP5329	WikiPathways	Cholesterol biosynthesis pathway in hepatocytes	23	1.37	-7.47	-3.97
GO:1901615	GO Biological Processes	organic hydroxy compound metabolic process	57	3.41	-7.28	-3.89
GO:0055086	GO Biological Processes	nucleobase-containing small molecule metabolic process	62	3.71	-6.84	-3.49
WP4723	WikiPathways	Omega-3 / omega-6 fatty acid synthesis	8	0.48	-6.41	-3.15
GO:1901137	GO Biological Processes	carbohydrate derivative biosynthetic process	62	3.71	-6.38	-3.15
GO:0016054	GO Biological Processes	organic acid catabolic process	33	1.97	-6.13	-2.96
hsa01212	KEGG Pathway	Fatty acid metabolism	14	0.84	-5.72	-2.63
R-HSA-166520	Reactome Gene Sets	Signaling by NTRKs	22	1.32	-5.37	-2.35
WP2882	WikiPathways	Nuclear receptors meta-pathway	38	2.27	-5.29	-2.34
GO:1903829	GO Biological Processes	positive regulation of protein localization	51	3.05	-5.29	-2.34
GO:0006914	GO Biological Processes	autophagy	38	2.27	-5.23	-2.33
GO:0005975	GO Biological Processes	carbohydrate metabolic process	48	2.87	-5.20	-2.33
GO:0006643	GO Biological Processes	membrane lipid metabolic process	28	1.67	-5.08	-2.29
GO:0015817	GO Biological Processes	histidine transport	4	0.24	-5.03	-2.29
GO:0016042	GO Biological Processes	lipid catabolic process	35	2.09	-4.93	-2.25
GO:0006886	GO Biological Processes	intracellular protein transport	66	3.95	-4.76	-2.14
GO:0010876	GO Biological Processes	lipid localization	42	2.51	-4.71	-2.11

* "Count" is the number of genes in the selected gene modules with membership in the given ontology term. "%" is the percentage of all the genes that are found in the given ontology term. "Log10(P)" is the p-value in log base 10. "Log10(q)" is the multi-test adjusted p-value in log base 10.

Table 3. Pathway and process enrichment Analysis in green module from MDD with their representative enriched terms.

GO	Category	Description	Count	%	Log10(P)	Log10(q)
GO:0050911	GO Biological Processes	detection of chemical stimulus involved in sensory perception of smell	49	6.13	-17.03	-12.68
R-HSA-6805567	Reactome Gene Sets	Keratinization	22	2.75	-7.16	-3.89
GO:0002250	GO Biological Processes	adaptive immune response	41	5.13	-6.56	-3.33
GO:0035195	GO Biological Processes	miRNA-mediated post-transcriptional gene silencing	37	4.63	-5.79	-2.59
GO:0002377	GO Biological Processes	immunoglobulin production	11	1.38	-3.06	0.00

GO:0035279	GO Biological Processes	miRNA-mediated gene silencing by mRNA destabilization	7	0.88	-2.76	0.00
GO:0000353	GO Biological Processes	formation of quadruple SL/U4/U5/U6 snRNP	3	0.38	-2.72	0.00
R-HSA-1433617	Reactome Gene Sets	Regulation of signaling by NODAL	3	0.38	-2.59	0.00

* "Count" is the number of genes in the selected gene modules with membership in the given ontology term. "%" is the percentage of all the genes that are found in the given ontology term. "Log10(P)" is the p-value in log base 10. "Log10(q)" is the multi-test adjusted p-value in log base 10.

3. Discussion

GBM and MDD are two highly related and associated diseases, however, their pathogenesis is still unknown. The findings of this study reveal a compelling genetic link between MDD and GBM, shedding light on potential shared pathogenesis and pathways between these seemingly disparate diseases. The edgeR of R software was used to compare the gene expression of the brain tissue of MDD patients and GBM patients with normal people. At the same time, WGCNA was used to analyze the gene expression connection between MDD and GBM.

The investigation into the gene expression patterns of both disorders, identified five differentially expressed genes that were common to both MDD and GBM: MTND1P23, MTCO1P53, MTATP8P1, EN1 and UBE2C. Among them, three genes are pseudogenes, except for EN1 and UBE2C. EN1, known for its involvement in glioma cells and tissues, has been associated with cancer cell proliferation, colony formation, and radiotherapy resistance. Furthermore, high expression of EN1 has been linked to worse survival outcomes in GBM patients [22]. Interestingly, EN1 also plays a role in neuropsychiatric diseases, particularly in dopamine regulation. Studies have demonstrated its significance in the development of midbrain dopamine (mdDA) neurons, with En1-deficient mice exhibiting reduced dopamine levels and depressive-like behaviors, indicating a potential link between EN1 and the development of depressive disorders such as MDD [24, 25]. The poor prognosis of GBM patients with high EN1 expression also means that they are more susceptible to depression, thus strengthening the connection between the two diseases. Similarly, UBE2C, a key regulator of cell cycle progression, has been implicated in various brain tumors, including astrocyte tumors and malignant gliomas. Notably, UBE2C's high expression in the hippocampus of Alzheimer's patients, along with its genetic association with mental diseases [30, 31, 32], suggests its potential role in the development of MDD. Therefore, the differential expression of EN1 and UBE2C genes may be an important reason for the connection between MDD and GBM. However, the specific interaction between EN1 and UBE2C proteins and the underlying molecular mechanisms contributing to disease development remain unclear. Further biochemical and molecular studies are needed to elucidate the intricate relationships and pathways involving EN1 and UBE2C, providing insights into potential therapeutic targets for both disorders.

The results of WGCNA provided additional depth to

the understanding of the genetic associations between MDD and GBM. In GBM, grey gene modules were selected as modules of interest, while in MDD, green gene modules were selected, both include the EN1 and UBE2C genes respectively. Enrichment analysis of these two modules shows that the gene modules from GBM are mainly responsible for the metabolism, such as lipid biosynthetic process, monocarboxylic acid metabolic process and organic hydroxyl compound metabolic process; while the gene modules from MDD are mainly focused on the neural activities and gene regulations, such as detection of chemical stimulus, adaptive immune response, and miRNA-mediated post-transcriptional gene silencing. These differences in functional enrichment indicate that, despite the overlap in gene expression, MDD and GBM have unique and independent pathogenic mechanisms. It is worth noting that the genetic modules of both GBM and MDD diseases have neural-related activities. In the GBM module, some genes are responsible for histidine transport, affecting neurotransmission and the immune system [33], while in the MDD module, some genes are responsible for detecting chemical stimuli. At the same time, the two gene modules are also responsible for gene expression regulation. For example, the GBM module has genes responsible for protein translocation, while the MDD module has genes responsible for miRNA-mediated gene silencing. These related GO pathways may indicate the underlying differential co-expression and common signaling pathways of EN1 and UBE2C genes.

This study innovatively utilized WGCNA to identify co-expressed gene modules from GBM and MDD and compared between them to explore the shared and different molecular mechanism between MDD and GBM. The multi-step analysis provided a comprehensive overview of the shared genetic landscape. The identification of common differentially expressed genes, particularly EN1 and UBE2C, added novel insights to the understanding of the link between MDD and GBM. These findings offer potential avenues for further research and the development of targeted interventions.

While this study provides valuable insights into the genetic link between MDD and GBM, several limitations must be acknowledged that may affect the interpretation of the findings. First, the analysis relies on large-scale expression datasets, and the different sources of these datasets may lead to different analysis results, thus introducing biases. Furthermore, this study mainly focused on gene expression patterns and did not delve into other potential influencing factors, such as epigenetic modifications or post-translational modifications, which

may play a key role in the pathogenesis of MDD and GBM. At the same time, this study does not cover the entire molecular process involved in these complex diseases, such as the specific role signaling pathways of genes EN1 and UBE2C in the context of MDD and GBM.

In conclusion, this study contributes valuable insights into the shared genetic landscape of MDD and GBM. The identified DEGs, particularly EN1 and UBE2C, warrant further exploration to unravel the complex molecular interactions and mechanisms underlying the link between these two diseases. The distinct functional enrichments observed in WGCNA underscore the need for a nuanced understanding of the individual pathogenesis of MDD and GBM, offering potential avenues for targeted therapeutic interventions.

4. Materials & Methods

4.1. Data Acquisition and Preprocessing

Gene expression data for MDD and GBM were retrieved from publicly available datasets of Genomic Data Commons Data Portal (National Cancer Institute). The MDD expression data was obtained from the cells from prefrontal cortex, while the GBM dataset was also obtained from brain with a project ID of TCGA-GBM. Website: <https://portal.gdc.cancer.gov/repository>

Raw gene expression data were preprocessed to ensure data quality and comparability. Data preprocessing included the normalization and filtering of low-quality data points. The R package "DESeq2" was employed for normalization and quality control.

4.2. Differential Expression Analysis with edgeR

The edgeR package (version 3.42.4) was employed for differential expression analysis. Negative binomial modeling and common dispersion estimation were used to identify DEGs. A significance level of 0.05 was applied to select DEGs.

4.3. Weighted Gene Co-expression Network Analysis (WGCNA)

A co-expression network analysis was conducted using the WGCNA R package (version 1.72-1). Initially, a soft thresholding power of 4 was determined to ensure a scale-free network. Co-expression modules were identified using the `blockwiseModules` function with a minimum module size of 30 genes and a `mergeCutHeight` of 0.25 to merge closely related modules. The module eigengene was calculated for each identified module, and modules significantly associated with MDD or GBM were selected for further analysis. Additionally, gene significance values were calculated to correlate modules with clinical traits, such as disease status.

4.4. Comparison between MDD and GBM

The lists of DEGs generated by DESeq2, limma, and

edgeR were compared to identify common genes that were consistently differentially expressed between MDD and GBM. Pathway analysis and functional annotation were performed on these common DEGs to gain insights into the shared biological mechanisms.

4.5. Multiple Testing Correction

To control for multiple testing, the Benjamini-Hochberg procedure was applied to adjust p-values for false discovery rate (FDR) in all differential expression analyses.

4.6. Software and Packages

The analysis was conducted using R (version 4.3.1) and the following R packages: DESeq2, limma, edgeR, and Bioconductor. The versions mentioned earlier were used.

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