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Exploring Key Genes and Pathways in Brain Tumor Isolates through Bioinformatics; Comparative analysis of GEO and GTEx-based data

XU HAN[1] A15336592080@163.COM, KAIBO GUO[2] GUOKAIBO@ZCMU.EDU.CN

[1]The First School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou 310053, China

[2]Department of Oncology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, 310006, China

Corresponding author:

Abstract

Background

Brain tumours are a diverse and complex category of disorders that can occur in many cell types within the brain. Genomic technology has identified important genetic abnormalities and biological mechanisms that cause brain tumour subtypes, enabling more accurate diagnosis and focused treatments. Using bioinformatic analysis, this study establishes predictive gene targets of expression changes in brain tumours compared to normal samples.

Methods and results

Datasets GSE213269 (n=20) and GSE212377 (n= 102) brain tumor were downloaded from GEO and data as a healthy control dataset was downloaded from GTEx. The datasets were integrated using ComBat-Seq. The differential expression analysis was performed using edgeR evaluating differences between tumor samples and healthy samples. The set criteria to identify was of FDR < 0.01 and |logFC| >1. We found that a total of 4789 genes were differentially expressed. There were 1925 genes upregulated while 2864 genes were downregulated. The most significant upregulated genes were CT47A10, TTTY13, TTTY8, OR1I1, SNORD115-32, KRTAP19-3, SNORD7. The most significant downregulated genes were OPALIN, MOBP, SCN2B, MAG, BCAS1. Besides the GSEA, KEGG pathway and several transcription factors were identified related to the brain tumor.

Conclusion

Finding the risk hub genes and prognostic indicators of brain tumours can be accomplished through the use of an effective method that involves the analysis of different datasets in conjunction with information regarding global networks.

Keywords: *Brain tumor, GEO, publicly available database, Bioinformatics, GSEA, DEGs*

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Introduction

Brain tumors represent a complex and heterogeneous group of diseases that can arise from different cell types within the brain. Advancements in genomic technology have enabled an unprecedented level of understanding regarding the molecular and genetic drivers of brain tumors [3]. These advancements have led to the identification of key genetic alterations and molecular pathways underlying various brain tumor subtypes, allowing for more precise diagnoses and targeted therapies [4]. These advancements have led to the identification of key genetic alterations and molecular pathways underlying various brain tumor subtypes, allowing for more precise diagnoses and targeted therapies. For instance, glioblastoma multiforme (GBM), the most common and aggressive type of brain tumor, is characterized by mutations in genes such as TP53, PTEN, and EGFR [5, 6].

In 2018, brain cancer, the primary cause of death in both children and adults, was diagnosed in approximately 300,000 new cases and was responsible for 241,000 deaths worldwide [7]. More recently, statistics on mortality from brain and other nervous system malignancies in the US predicted that there would be 23,890 deaths from these diseases in 2020. (12,590 males and 10,300 females) [8]. Unchecked cell proliferation in brain cancer is a diverse disease with complicated molecular pathways that may be brought on by promoter methylation, dysregulated gene expression, genetically altered tumor-suppressor genes, and/or oncogenes [9]. There are 6166 instances that cover a thorough multi-omics data of genetic changes and deregulated expression, according to the most recent data summary in the cancer genomics data portal cBioPortal. The literature-based genetic distinctions of various brain cancers are still mostly unknown, despite the fact that their genomic profilings have a significant impact on how the genetics and transcriptome of brain tumors are shaped. With rare exceptions, the median survival time for patients with GBM is typically 14 to 17 months [10, 11]. Gene expression profiling analysis is a useful method with broad clinical application for identifying tumor-related genes in various types of cancer, from molecular diagnosis to pathological classification, from therapeutic evaluation to prognosis prediction, and from drug sensitivity to neoplasm recurrence [12-14].

GEO database has been instrumental in providing researchers with access to vast amounts of genomic data, enabling them to identify new targets for treatment and improve patient outcomes

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[15]. With the help of GEO database, researchers are able to analyze large-scale genomic data sets from brain tumor patients and compare them with normal counterparts. Similarly, GTEx database has also been useful in understanding the normal gene expression patterns of different tissues, including the brain. Through the utilization of these genomic databases, researchers have been able to identify potential therapeutic targets for brain tumors and develop personalized treatment strategies based on a patient's unique genomic profile.

Materials and methods

Datasets and pre-processing

The datasets GSE213269 (n=20) and GSE212377 (n= 102) brain tumor were downloaded from GEO [16] and data as a healthy control dataset was downloaded from GTEx [17]. The datasets were integrated using ComBat-Seq [18] to adjust as many batch effects as possible to minimize the loss of biological information.

Differential expression analysis

The differential expression analysis was performed using edgeR [19] and Quasi-likelihood function [20] evaluating differences between tumor samples and healthy samples. Further the results were filtered out with commonly used filters of FDR < 0.01 and |logFC| > 1.

Gene set enrichment analysis

The differential expression results were proceeded to GSEA pre-ranked analysis using the MSigDB c2, c5 (GO:BP) [21] and Hallmark datasets (version 2023 Homo sapiens 1). Further we filtered the results for FDR<0.25 to identify significant enrichment of pathways.

Network analysis

To create the network we used hgnc_symbols [22] of the filtered list from differential expression analysis as input to Cytoscape stringApp plugin [23]. The criteria was set to 0.5 confidence level to get more confident results. The plugin cytoHubba [24] was used to analyze the network.

Network analysis in R

The network from Cytoscape [25] was extracted and the statistics were calculated in R using the igraph package. We have filtered the interactions for only experimentally validated interactions

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using the information provided by stringDB. The network degrees and betweenness of the proteins was calculated.

Results

Differential expression analysis

The differential gene expression analysis was performed using edgeR and Quasi-likelihood function to find the upregulated and downregulated genes between tumor samples and healthy samples. Our set criteria was commonly used filters of FDR < 0.01 and |logFC| > 1. Following this criterion, we found that a total of 4789 genes were differentially expressed. The processing flow is shown in Figure 1. A volcano map is provided in Figure 2. There were 1925 genes upregulated while 2864 genes were downregulated. The most significant upregulated genes were CT47A10 with logFC 18, TTTY13 with logFC 17.9. A list of top fifteen up and downregulated genes is provided in table 1. Detailed description of all the DEGs is provided in Supplementary file S1.

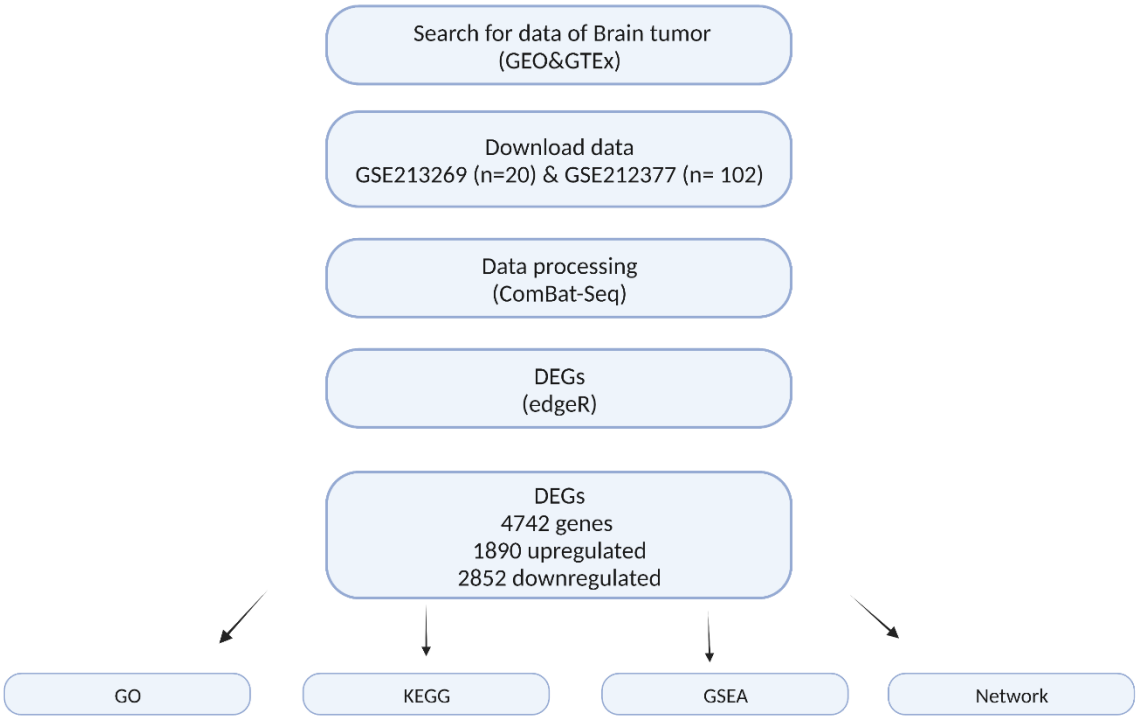

Figure 1. Data collection, preparation, analysis, and validation are shown in the analysis process flow diagram.

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Table 1. Top fifteen up and downregulated genes.

hgnc_symbol	Log_FC	Log_CPM	FDR	Description
CT47A10	18.00084593	8.807185243	5.8E-72	cancer/testis antigen family 47, member A10
TTTY13	17.97956489	8.864125207	1.9E-227	testis-specific transcript, Y-linked 13 (non-protein coding)
TTTY8	17.77899869	8.585363392	2.71E-64	testis-specific transcript, Y-linked 8 (non-protein coding)
OR1I1	17.56814424	9.363737389	6E-210	olfactory receptor, family 1, subfamily I, member 1
SNORD115-32	16.94160926	7.819359868	2.7E-230	small nucleolar RNA, C/D box 115-32
KRTAP19-3	16.82248184	8.183067898	5.5E-212	keratin associated protein 19-3
SNORD7	16.74581821	7.552368369	2.86E-71	small nucleolar RNA, C/D box 7
LINC01056	16.72564816	9.08973423	3.7E-200	long intergenic non-protein coding RNA 1056
SPZ1	16.69319301	9.497988251	1.5E-187	spermatogenic leucine zipper 1
MIR758	16.65255878	7.575559808	4E-225	microRNA 758
TTTY19	16.45482457	7.915329958	3.6E-209	testis-specific transcript, Y-linked 19 (non-protein coding)
SNORD115-44	16.40355825	7.2869194	9.6E-230	small nucleolar RNA, C/D box 115-44
RNASE9	16.38964971	8.389103204	7E-202	ribonuclease, RNase A family, 9 (non-active)
KRTAP20-3	16.34341778	7.189697331	1.2E-235	keratin associated protein 20-3
SNORD115-27	16.29801629	7.249008393	8.5E-198	small nucleolar RNA, C/D box 115-27
Downregulated genes (Top fifteen)				
hgnc_symbol	Log_FC	Log_CPM	FDR	Description
OPALIN	-15.05442357	7.432602225	1.6E-186	oligodendrocytic myelin paranodal and inner loop protein
MOBP	-14.3924817	9.35472389	4.4E-135	myelin-associated oligodendrocyte basic protein
SCN2B	-14.16700372	7.710019009	2.5E-230	sodium channel, voltage gated, type II beta subunit
MAG	-13.75002348	7.234847989	5.7E-158	myelin associated glycoprotein
BCAS1	-13.27902691	9.216749727	1.4E-131	breast carcinoma amplified sequence 1
ETNPPL	-13.05737858	8.086251381	1.7E-164	ethanolamine-phosphate phospho-lyase
PIK3R2	-13.02908698	7.534851101	2.4E-225	phosphoinositide-3-kinase, regulatory subunit 2 (beta)

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CNDP1	-12.99330478	6.388890115	2E-174	carnosine dipeptidase 1 (metallopeptidase M20 family)
TCEAL2	-12.97280231	7.715901772	1.3E-219	transcription elongation factor A (SII)-like 2
UPK3BL	-12.91425361	4.886501467	1E-186	uroplakin 3B-like
CTNNA2	-11.99784488	8.256141865	7.4E-162	catenin (cadherin-associated protein), alpha 2
SLC6A12	-11.91290052	6.206503834	8.8E-198	solute carrier family 6 (neurotransmitter transporter), member 12
PART1	-11.54731444	5.729097582	2.6E-176	prostate androgen-regulated transcript 1 (non-protein coding)
PMP2	-11.51125936	8.768261127	1.1E-119	peripheral myelin protein 2
KCNJ16	-11.26663791	4.261881195	6E-173	potassium channel, inwardly rectifying subfamily J, member 16

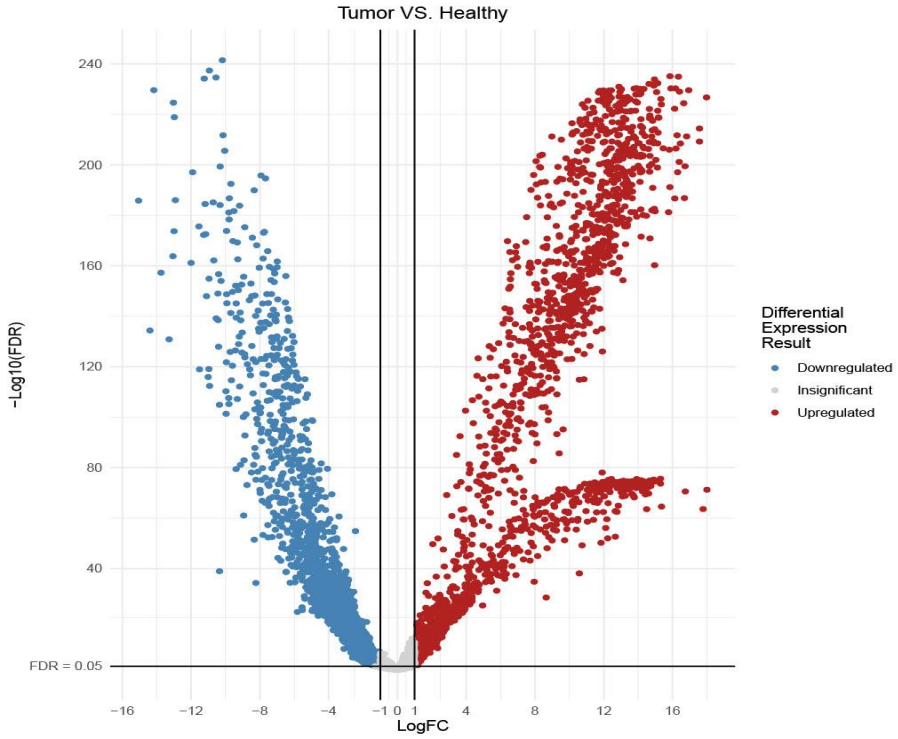

Figure 2. The Volcano graph of the differentially expressed genes between the tumor samples and the control sample. The blue dots represent the downregulated genes while the red dots represent the upregulated genes. The nonsignificant genes are represented by grey color dots.

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Gene set enrichment analysis

GSEA is a powerful tool for analyzing high-throughput gene expression data, such as microarray or RNA sequencing data, and is widely used in systems biology and functional genomics research. It can help identify biologically relevant gene sets and pathways that are differentially regulated between two conditions, providing insights into the underlying molecular mechanisms of disease or biological processes.

The differential expression results were proceeded to GSEA pre-ranked analysis using the MSigDB c2, c5 (GO:BP) and Hallmark datasets (version 2023 Homo sapiens 1). Further we filtered the results for FDR<0.25 to identify significant enrichment of pathways. The most significantly enriched terms of tumor vs normal samples are provided in the table 2.

Table 2. The most significantly enriched GSEA pathways between tumor and normal tissues.

Name	SIZE	ES	NES	Source
Reactome_Olfactory_Signaling_Pathway	222	0.9414493	1.3146309	C2
Gobp_Detection_Of_Chemical_Stimulus	274	0.936134	1.3111466	C5GOBP
Gobp_Sensory_Perception_Of_Smell	236	0.94072485	1.3109825	C5GOBP
Gobp_Sensory_Perception_Of_Chemical_Stimulus	288	0.93585694	1.3084416	C5GOBP
Kegg_Olfactory_Transduction	232	0.94033146	1.3079274	C2
Gobp_Autonomic_Nervous_System_Development	41	0.9904405	1.2981668	C5GOBP
Gobp_Detection_Of_Stimulus_Involved_In_Sensory_Perception	307	0.9288295	1.2860136	C5GOBP
Gobp_Detection_Of_Stimulus	421	0.91836226	1.2769622	C5GOBP
Reactome_Drug_Adme	88	0.92703927	1.2759207	C2
Hofmann_Cell_Lymphoma_Up	46	0.9636233	1.2749581	C2
Reactome_Phase_Ii_Conjugation_Of_Compounds	86	0.9337352	1.2737823	C2
Gobp_Defense_Response_To_Gram_Positive_Bacterium	94	0.9250359	1.2721776	C5GOBP
Reactome_Sensory_Perception	420	0.906959	1.2676595	C2
Wp_Neurogenesis_Regulation_In_The_Olfactory_Epithelium	53	0.94201386	1.266694	C2
Seitz_Neoplastic_Transformation_By_8p_Deletion_Up	72	0.92408925	1.2651991	C2
Reactome_Translation	283	-0.8576527	-2.035354	C2
Gobp_Sodium_Ion_Transport	233	-0.9037003	-2.0275338	C5GOBP
Browne_Hcmv_Infection_16hr_Up	210	-0.86743903	-2.019824	C2

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Gobp_Regulation_Of_Neurotransmitter_Levels	198	-0.89416337	-2.004378	C5GOBP
Gobp_Developmental_Growth_Involved_In_Morphogenesis	222	-0.8597496	-1.9960461	C5GOBP
Kaab_Heart_Atrium_Vs_Ventricle_Up	237	-0.89467764	-1.9877949	C2
Hallmark_Oxidative_Phosphorylation	194	-0.86485475	-1.9875525	HALLMARK
Hsiao_Housekeeping_Genes	368	-0.84722936	-1.9803252	C2
Cairo_Hepatoblastoma_Up	198	-0.86507136	-1.9762344	C2
Coldren_Gefitinib_Resistance_Dn	211	-0.90749794	-1.9717392	C2
Gobp_Regulation_Of_Chromosome_Organization	236	-0.8260891	-1.9631209	C5GOBP
Pasqualucci_Lymphoma_By_Gc_Stage_Up	268	-0.85848224	-1.9608805	C2
Oswald_Hematopoietic_Stem_Cell_In_Collagen_Gel_Dn	256	-0.84913975	-1.9492453	C2
Miyagawa_Targets_Of_Ewsr1_Ets_Fusions_Dn	215	-0.8470412	-1.9451728	C2
Horiuchi_Wtap_Targets_Up	291	-0.86113447	-1.9446048	C2

KEGG pathway

KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways are a collection of manually curated and annotated biological pathways that represent molecular interactions and reactions within cells, organisms, and ecosystems. These pathways provide a comprehensive view of the relationships between genes, proteins, and other molecules involved in various biological processes such as metabolism, signaling, and disease. KEGG pathways are widely used in bioinformatics and systems biology research to help understand the complex biological processes that underlie normal physiology and disease.

The significantly enriched DEGs were assigned to the KEGG pathway analysis. We found that Reactome translation was on the top among others. The top fifteen pathways are provided in table 3. A detailed description is provided in Supplementary file S2.

Table 3. Top fifteen enriched KEGG pathways.

Name	SIZE	NES	source
Reactome_translation	283	-2.035354	C2
Gobp_sodium_ion_transport	233	-2.0275338	C5GOBP
Browne_hcmv_infection_16hr_up	210	-2.019824	C2

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Gobp_regulation_of_neurotransmitter_levels	198	-2.004378	C5GOBP
Gobp_developmental_growth	222	-1.9960461	C5GOBP
Kaab_heart_atrium_vs_ventricle_up	237	-1.9877949	C2
Hallmark_oxidative_phosphorylation	194	-1.9875525	HALLMARK
Hsiao_housekeeping_genes	368	-1.9803252	C2
Cairo_hepatoblastoma_up	198	-1.9762344	C2
Coldren_gefitinib_resistance_dn	211	-1.9717392	C2
Gobp_regulation_of_chromosome_organization	236	-1.9631209	C5GOBP
Pasqualucci_lymphoma_by_gc_stage_up	268	-1.9608805	C2
Oswald_hematopoietic_stem_cell_in_collagen_gel_dn	256	-1.9492453	C2
Miyagawa_targets_of_ewsr1_ets_fusions_dn	215	-1.9451728	C2
Horiuchi_wtap_targets_up	291	-1.9446048	C2

Transcription factor genes

Transcription factor genes are genes that encode proteins that bind to DNA and control the transcription of genes into RNA. They are a class of regulatory genes that play a key role in the regulation of gene expression by controlling the rate at which specific genes are transcribed into mRNA.

These proteins, known as transcription factors, recognize specific DNA sequences and bind to them, either activating or repressing the transcription of target genes. This binding event can occur in the promoter region of a gene, where it can affect the rate of transcription initiation, or at enhancer or silencer elements, where it can modulate the activity of the promoter.

Transcription factor genes themselves are regulated by a variety of signals, including other transcription factors, signaling pathways, and environmental stimuli. Dysregulation of transcription factor genes can lead to a wide range of diseases, including cancer, developmental disorders, and autoimmune diseases.

In this study we have identified basic transcription factors that play a key role in brain tumors. A brief description is provided in table 4.

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Discussion

Although modern clinical diagnosis and treatment procedures show encouraging improvements, early detection and the associated improvement in the prognosis for individuals with brain tumors are difficult to achieve. Brain tumors are a diverse and complex category of disorders that can develop from several types of brain cells. Unprecedented insight into the molecular and genetic causes of brain cancers has been made possible by advances in genomic technology [3]. These developments have enabled the identification of important genetic changes and molecular processes underlying different subtypes of brain tumors, enabling more accurate diagnosis and tailored treatments [4]. In this study we have used GEO database to retrieve the genomic data sets from brain tumor patients and compared them with normal counterparts from the GTEx database. We investigated important brain tumor-related genes and signaling pathways that may deepen our understanding of potential molecular mechanisms and their advantages for disease detection, therapy, and prognosis. The differential expression analysis was performed using edgeR. We set the criterion for the differential analysis as FDR < 0.01 and |logFC| > 1. We found that a total of 4742 genes were differentially expressed (Figure 2). There were 1890 genes upregulated while 2852 genes were downregulated. The most significant upregulated gene was Cancer/testis antigen family 47 member A10 (CT47A10) with logFC 18. A research team conducted a study based on underlying ganglioneuroma (GN), ganglioneuroblastoma (GNB), and neuroblastoma (NB). Based on exome sequencing, they have found that the missense mutation of CT47A10 is involved in GNB. This mutation was predicted to be c.344C>T [26]. Another study predicted the involvement of this gene across human tumors [27]. The second most significant upregulated gene was Testis-specific transcript Y-linked 13 (TTTY13), with logFC 17.9. This gene, which is present in the male-specific region of the Y chromosome, has been linked to the prognosis of several malignancies, including gastric cancer and laryngeal squamous cell carcinoma [28, 29]. Similarly, this gene was also studied by another group of researchers in the LNCaP and PC3 prostate cancer cell lines [30]. Olfactory receptor family 1 subfamily I member 1 (OR1I1) was identified with logFC 17.5. This is member of a large family of G-protein-coupled receptors (GPCR) originating from genes containing only one coding exon. Olfactory receptors, which share a 7-transmembrane domain structure with various neurotransmitter and hormone receptors, detect and transduce odorant signals via G protein-

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mediated signaling. Similarly; among downregulated genes, Oligodendrocytic myelin paranodal and inner loop protein (OPALIN) with logFC -15.05 was the most significant. This is a transmembrane sialylglycoprotein and is reported to be located in the central nervous system myelin paranodal loop membrane the mice [31]. It's pathogenic role is predicted in mouse model [32]. Besides its role in glioblastoma [33], this gene has role in psychopathologies such as suicidality, depression and some others [34]. The second highly significant downregulated gene was Myelin-associated oligodendrocyte basic protein (MOBP). A diversified functional gene in the CNS [35], it showed roles in Parkinson's disease [36], dementia [37], schizophrenia [38], and several others. Sodium channel, voltage gated, type II beta subunit (SCN2B) showed logFC -14.1 is involved in cell-cell adhesion and cell migration. This gene has been studied in epilepsy [39, 40], its vital role in brain aging associated with synaptic plasticity [41]; etc. Using the GSEA analysis, we have found that Olfactory signaling pathway, Detection of chemical stimulus, Autonomic nervous system development were enriched. Our results are in accordance with the other researchers [42, 43].

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