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Unveiling the Prognostic Potential of *SLC2A* Gene Family in Glioblastoma Multiforme Using Bioinformatics Approaches

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ABSTRACT

Objective: Glioblastomas (GBMs) are invasive and metastatic cancers with very low overall survival rates. Therefore, it is very important to propose a new biomarker for GBM diagnosis and prognosis. For this purpose, we aimed to investigate the prognostic potential of the *SLC2A* gene family, which has great importance in cancer, in GBM.
Methods: *Solute carrier 2A* (*SLC2A*) gene family expression levels, methylation and overall survival rates were analyzed with TCGA, GEPIA and UALCAN databases. Mutations were evaluated with Kaplan-Meier Plot and UCSC Xena database. Protein-protein interactions were analyzed with String database.
Results: No statistically significant mutation was detected in the *SLC2A* gene family. As a result of the analysis, high expression in *SLC2A1* and *SLC2A5* genes and decrease in *SLC2A6* gene expression were found to be statistically significant. Hypermethylation was detected in the promoter regions of *SLC2A1*, *SLC2A2*, *SLC2A3* and *SLC2A5* genes, while hypomethylation was detected in *SLC2A4* and *SLC2A6* genes. The increase in *SLC2A3* gene expression was associated with the overall survival rate of the patients.
Conclusion: *SLC2A1*, *SLC2A5* and *SLC2A6* gene up-regulation may be a biomarker in the diagnosis of GBM, and *SLC2A3* may be a marker in prognosis.

Keywords: Glioblastoma, *SLC2A* Genes, Bioinformatics

Biyoinformatik Yaklaşımlar Kullanılarak Glioblastoma Multiform'da *SLC2A* Gen Ailesinin Prognostik Potansiyelinin Ortaya Çıkarılması

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ÖZ

Amaç: Glioblastomalar (GBM'ler) çok düşük genel sağkalım oranlarına sahip invaziv ve metastatik kanserlerdir. Bu nedenle, GBM tanısı ve prognozu için yeni bir biyobelirteç önermek çok önemlidir. Bu amaçla, kanserde büyük öneme sahip olan *SLC2A* gen ailesinin GBM'deki prognostik potansiyelini araştırmayı amaçladık.
Yöntemler: *Solute taşıyıcı 2A* (*SLC2A*) gen ailesi ekspresyon düzeyleri, metilasyon ve genel sağkalım oranları TCGA, GEPIA ve UALCAN veri tabanları ile analiz edildi. Mutasyonlar Kaplan-Meier Plot ve UCSC Xena veri tabanı ile değerlendirildi. Protein-protein etkileşimleri String veri tabanı ile analiz edildi.
Bulgular: *SLC2A* gen ailesinde istatistiksel olarak anlamlı bir mutasyon saptanmadı. Analiz sonucunda *SLC2A1* ve *SLC2A5* genlerinde yüksek ekspresyon ve *SLC2A6* gen ekspresyonunda azalma istatistiksel olarak anlamlı bulundu. *SLC2A1*, *SLC2A2*, *SLC2A3* ve *SLC2A5* genlerinin promotör bölgelerinde hipermetilasyon, *SLC2A4* ve *SLC2A6* genlerinde ise hipometilasyon saptandı. *SLC2A3* gen ekspresyonundaki artış hastaların genel sağ kalım oranı ile ilişkili bulundu.
Sonuç: *SLC2A1*, *SLC2A5* ve *SLC2A6* geninin yukarı regülasyonu GBM tanısında bir biyobelirteç olabilir ve *SLC2A3* prognozda bir belirteç olabilir.

Anahtar Kelimeler: Glioblastoma, SLC2A Genleri, Biyoinformatik

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Introduction

Glioblastomas (GBMs) are the most common and malignant brain tumors in the world. Patients have a low survival rate[1]. Especially the 5-year rate of survival of glioblastoma multiforme (GBM) is low in elderly patients. The prognosis of GBM varies according to age and pathological type. The World Health Organization (WHO) has classified central nervous system (CNS) gliomas as low-grade and high-grade[2]. It has a higher prevalence in men than in women and in Caucasians than in other ethnicities[3]. Despite the development of modern approaches to the treatment of GBM, it remains a fatal disease with an extremely poor prognosis[4]. A large number of different genetic and molecular changes occur in GBM during its development. There are many important signaling pathways that lead to the growth and progression of the brain tumor[5].

The increased glucose uptake by cancer cells is called the Warburg effect. Numerous investigations have demonstrated that many cancers overexpress glucose transporter proteins[6]. Overexpression of glucose transporter proteins meets the energy requirements of tumor cells. It also provides cancer cells with sufficient precursor molecules for aerobic glycolysis. Thus, the ATP needs of tumor cells are met[7]. In human cells, glucose transport is mediated by the solute carrier 2A (SLC2A) family. SLC2As are also called the glucose transporter or GLUT family[8]. Based on sequence similarity, the SLC2A1-SLCA4 (GLUT1-4), and SLC2A14 (GLUT14) are group I GLUTs; SLC2A5 (GLUT5), SLC2A7 (GLUT7), SLC2A9 (GLUT9), and SLC2A11 (GLUT11) are group II GLUTSs; and SLC2A6 (GLUT6), SLC2A8 (GLUT8), SLC2A10 (GLUT10), SLC2A12 (GLUT12), and SLC2A13 (GLUT13) are group III[9]. SLC2A family proteins have 12 transmembrane regions, one N-linked glycosylation site, and a cytoplasmic linker domain[10]. Almost all cells in the human body expression the *SLC2A1* gene. The most crucial glucose transporter in the muscle, neurological system, brain and other tissues and organs is this protein. Maintaining a balanced physiological metabolism is crucial for human health[11]. Nevertheless, SLC2A1 is also crucial for the metabolic function of cancer cells. For cancer cells to continue growing and spreading, they must ingest an excessive amount of glucose. High protein expression of SLC2A1 in cells may mean carcinogenesis[12]. SLC2A1, SLC2A2, SLC2A3, and SLC2A4 proteins stimulate glucose uptake by cancer cells, erythrocytes, pancreatic β-cells, neurons, cells of the blood-brain barrier, endothelial, fat and muscle cells[13]. Cancers of the endometrium, liver, breast, lung and stomach can grow and spread as a result of *SLC2A1* overexpression [14-18]. In one study, it was predicted that SLC2A1 might also be associated with GBM prognosis[19]. It has been observed that elevated *SLC2A2* expression is linked to insulin secretion, glucose concentration, autonomic nervous system activity, and the control of body temperature and feeding[20]. According to earlier research, tumor cells use the SLC2A protein to transfer glucose to intracellular reserves in order to meet their high energy requirements. This implies that the invasiveness and development of tumors may be related to the expression of distinct *SLC2A* subtypes[21]. Higher overall survival in cases of breast and liver cancer as well as other cancers is positively correlated with overexpression of *SLC2A2*[22]. The SLC2A3 protein is of major importance in intracellular glucose transport in glycolysis. Glycolytic activity results in an elevated metabolic rate and increased glucose uptake, meeting the increased energy demands of tumor cell proliferation[23,24]. Overexpression of *SLC2A3* has been associated with poorer clinical outcomes, including increased invasion, larger tumor size, advanced pathological stage, tumor recurrence, and vascular embolization[25]. In addition, SLC2A3 leads to changes in the tumor microenvironment through activation of macrophage infiltration, worsening the prognosis in gastric and breast cancer[26]. *SLC2A3* has a high affinity for glucose and has been found to have increased expression in patients with brain tumors[27]. *SLC2A3* expression level has a significant association with the pathological grading of glioma tumors[28]. The association between SLC2A4 overexpression and many types of cancer remains unclear[29]. However, according to the TCGA database, SLC2A4 is a favorable prognostic factor for breast cancer[30]. Davidson et al (1992) reported that *SLC2A5* is expressed in the brush border membrane of human small intestinal enterocytes[31]. Burant et al (1992) stated that SLC2A5 is a fructose transporter and may be responsible for fructose uptake from the lumen of the small intestine[32]. Doege et al (2000) showed that *SLC2A6* was overexpressed in COS-7 cells and had high glucose transport activity[33].

In this study, we aimed to investigate the expression and methylation levels of *SLC2A1*- *SLC2A6* genes belonging to the *SLC2A* family in human GBM tissue and healthy tissue samples using The Cancer Genome Atlas (TCGA) and UALCAN databases, to determine the mutation rates in these genes using Kaplan-Meier Plot and UCSC Xena databases, and finally to determine protein-protein interactions using String databases. There is no study on GBM and *SLC2A* gene families in the literature.

Material and Methods

Sampling and Data Extraction

This is a bioinformatics study planned to reveal the relationship between GBM and *SLC2A1*, *SLC2A2*, *SLC2A3*, *SLC2A4*, *SLC2A5* and *SLC2A6* genes and proteins belonging to the *SLC2A* gene family. Data from GBM patient and control groups were obtained using TCGA (https://www.cancer.gov/tcga) databases for analysis in the study. Ethics committee approvals of the patients were obtained within the scope of the Cancer Genome Project. Access to GBM patient and control group data was provided from the TCGA database on 08.12.2024.

Gene expression, Methylation and Survival analysis

Expression, methylation and survival data of GBM patient and control groups were analyzed using TCGA (https://www.cancer.gov/tcga), GEPIA database (http://gepia.cancer-pku.cn/), UALCAN database (https://ualcan.path.uab.edu/analysis.html).

Mutation analysis

Mutations from GBM patients were analyzed using Kaplan-Meier Plot (https://kmplot.com/analysis/) and UCSC Xena databases (https://xena.ucsc.edu/).

Protein-Protein Interaction

The interactions of SLC2A1-SLC2A6 proteins with each other and with different proteins were analyzed using the String database (https://string-db.org/).

Statistical Analysis

In the evaluation of the data of our study, the expression relationship between GBM and control tissues was evaluated with One-Way ANOVA test using UALCAN databases. Methylation analyses were analyzed with Student's t-test using UALCAN databases. Survival rates of patients were evaluated using UALCAN database. Mutation analyses were analyzed using Kaplan-Meier Plot and UCSC Xena databases. A log-rank *p*-value below 0.05 was considered statistically significant.

Results

Expression level of SLC2A family genes in GBM

Expression levels of *SLC2A1-SLC2A6* genes in GBM tumor and healthy control tissues were analyzed using TCGA and GEPIA databases. As a result of the analysis, no statistically significant relationship was observed in *SLC2A2*, *SLC2A3* and *SLC2A4* genes. However, the difference between GBM tumor tissue and healthy tissue in *SLC2A1*, *SLC2A5* and *SLC2A6* genes was found to be significant (T=163, N=207, $p<0.005$) (Figure 1). The expression level of *SLC2A1* gene in tumor tissue was determined to be higher compared to the healthy control group, but this significant difference in expression level was not found to be associated with the survival rate of the patients ($p=0.95$) (Figure 2). When we evaluated *SLC2A2* gene expression, it was determined that the expression level in tumor tissue was similar to the healthy control tissue and no significant relationship was detected. The patient's survival rate was not shown to be substantially correlated with this relationship in expression level ($p=0.68$) (Figure 2). *SLC2A3* gene expression was found to be higher in tumor tissue compared to the control group. There was no statistical significance in this difference. However, the survival rates of patients with high *SLC2A3* expression were found to be statistically significant ($p=0.033$) (Figure 2). *SLC2A4* gene expression level was lower in tumor tissue compared to the control group, but this difference was not statistically significant ($p=0.96$) (Figure 2). *SLC2A5* gene expression level was found to be higher in tumor tissue. This difference was statistically significant. This statistical difference in expression level is not associated with the survival rate of the patients (p=0.60) (Figure 2). When we evaluated the *SLC2A6* gene, although the decrease in expression level in the tumor tissue was found to be significant, it was not found to be associated with the survival rate of the patients ($p=0.35$). (Figure 2).

Expression levels of *SLC2A1-SLC2A6* genes and other different genes associated with GBM are given in Figure 3. According to Microarray analysis results, *SLC2A1*, *SLC2A3* and *SLC2A5* gene expression levels were determined to be higher in GBM tumor tissue compared to the control group (Figure 3).

Methylation level of SLC2A family genes in GBM

Promoter methylation levels of the *SLC2A* gene family in GBM tumor tissue and healthy control tissue are given in Figure 4. While hypermethylation was observed in *SLC2A1*, *SLC2A2*, *SLC2A3* and *SLC2A5* genes in GBM tumor tissue, hypomethylation was observed in *SLC2A4* and *SLC2A6* genes.

Mutation Analysis

Somatic mutation (Single Nucleotide Polymorphisms and small INDELS-Ensemble somatic mutation Variant) analysis in *SLC2A1*, *SLC2A2*, *SLC2A3*, *SLC2A4*, *SLC2A5* and *SLC2A6* genes in GBM patients was performed in 381 individuals. Five patients with mutations in the SLC2A1 gene and two patients with mutations in *SLC2A2*, *SLC2A3*, *SLC2A4* and *SLC2A5* genes were identified. Only one patient with mutations in the *SLC2A6* gene was identified. No statistical significance was found between those with or without mutations ($p<0.05$) (Figure 5).

Protein-Protein Interaction

The interactions of SLC2A1-SLC2A6 proteins with other proteins were analyzed using the String database (Figure 6). As a result of the analysis, the proteins with the highest homology scores with these proteins were Cellular tumor antigen p53 (Tp53), Hexokinase-4 (GCK), Solute carrier family 2, facilitated glucose transporter member 14 (SLC2A14), Ras-related protein Rab-10 (RAB10), Carbonic anhydrase 6 (CA6), MFS domain-containing protein (SLC2A11-2), respectively (Table 1). When the molecular function of SLC2A family proteins was examined, it was determined that they had the highest Glucose transmembrane transporter activity, the highest Glucose import during the biological process, and when evaluated in terms of KEGG pathways, they were associated with the highest rate of insulin resistance (Figure 7).

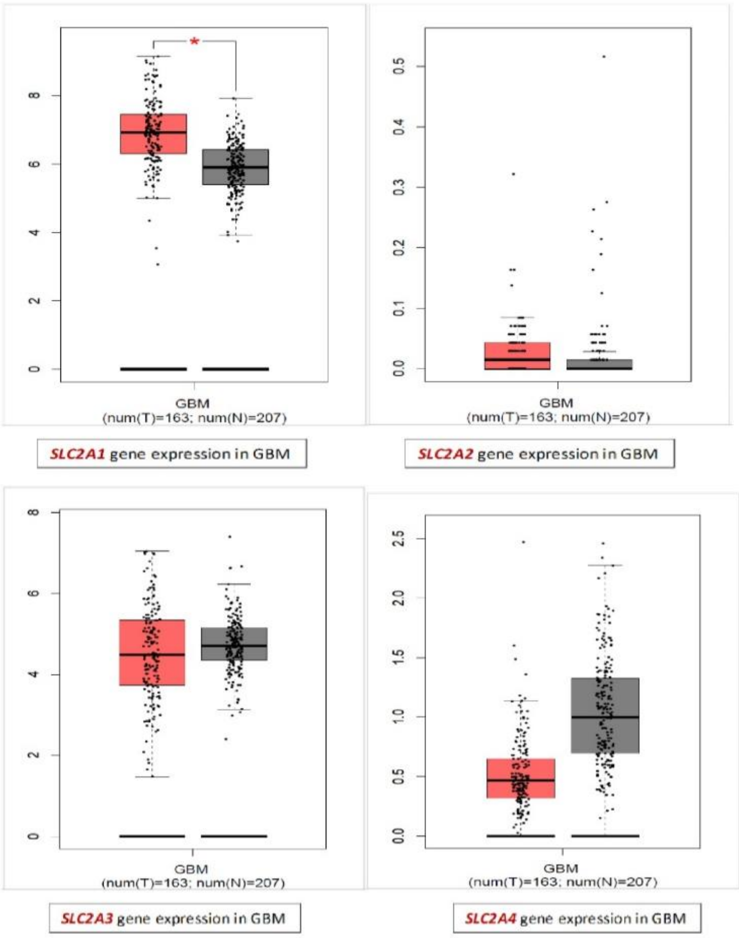
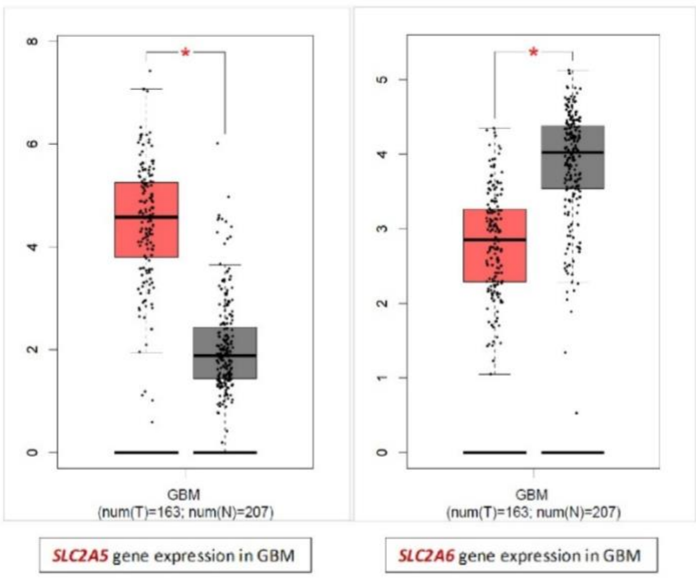


Figure 1.2. Comparison of UALCAN of the high and low expressions of SLC2A1-SLC2A6 in TCGA GBM cohort ($p<0.05$).



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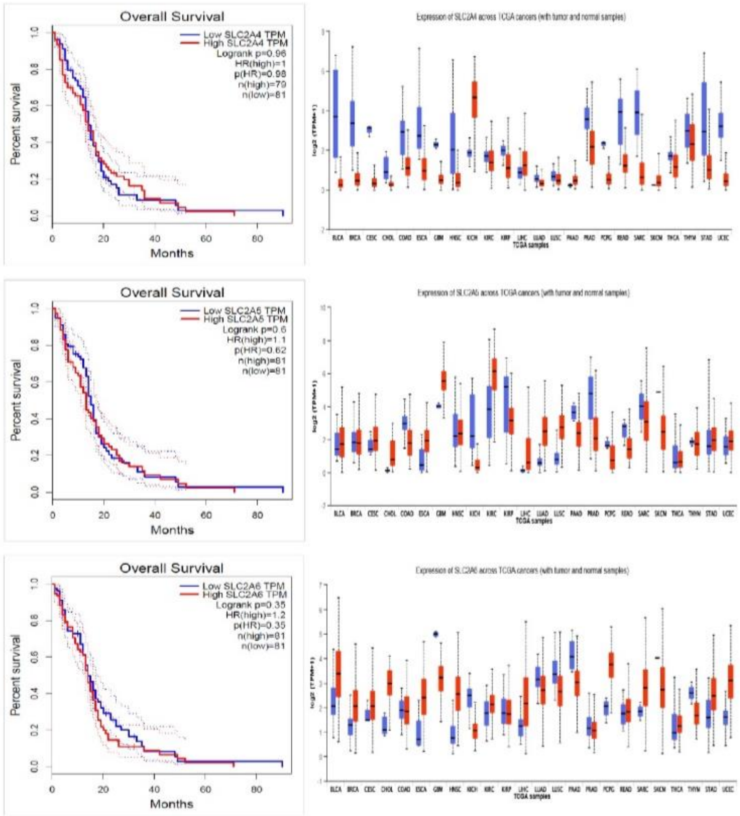

Figure 2.1. A) Comparison of UALCAN survival curves of the high and low expressions of SLC2A1- SLC2A6 in TCGA GBM cohort (p<0.05). Red line indicates the high expressions of mRNA; green line indicates the low expressions of mRNA. B) Expression of SLC2A gene family across TCGA tumors. Red column: GMB, Blue column: normal tissue.

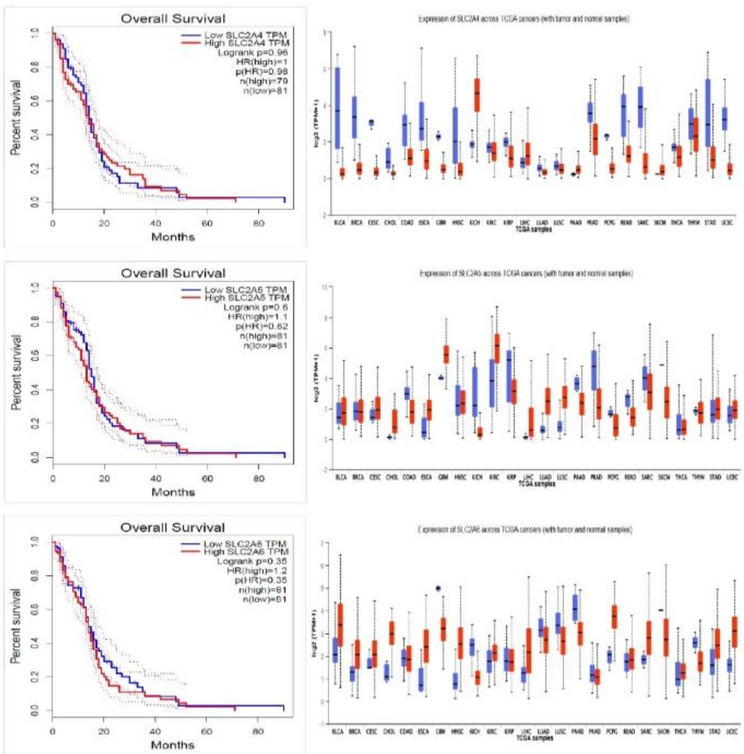

Figure 2.2

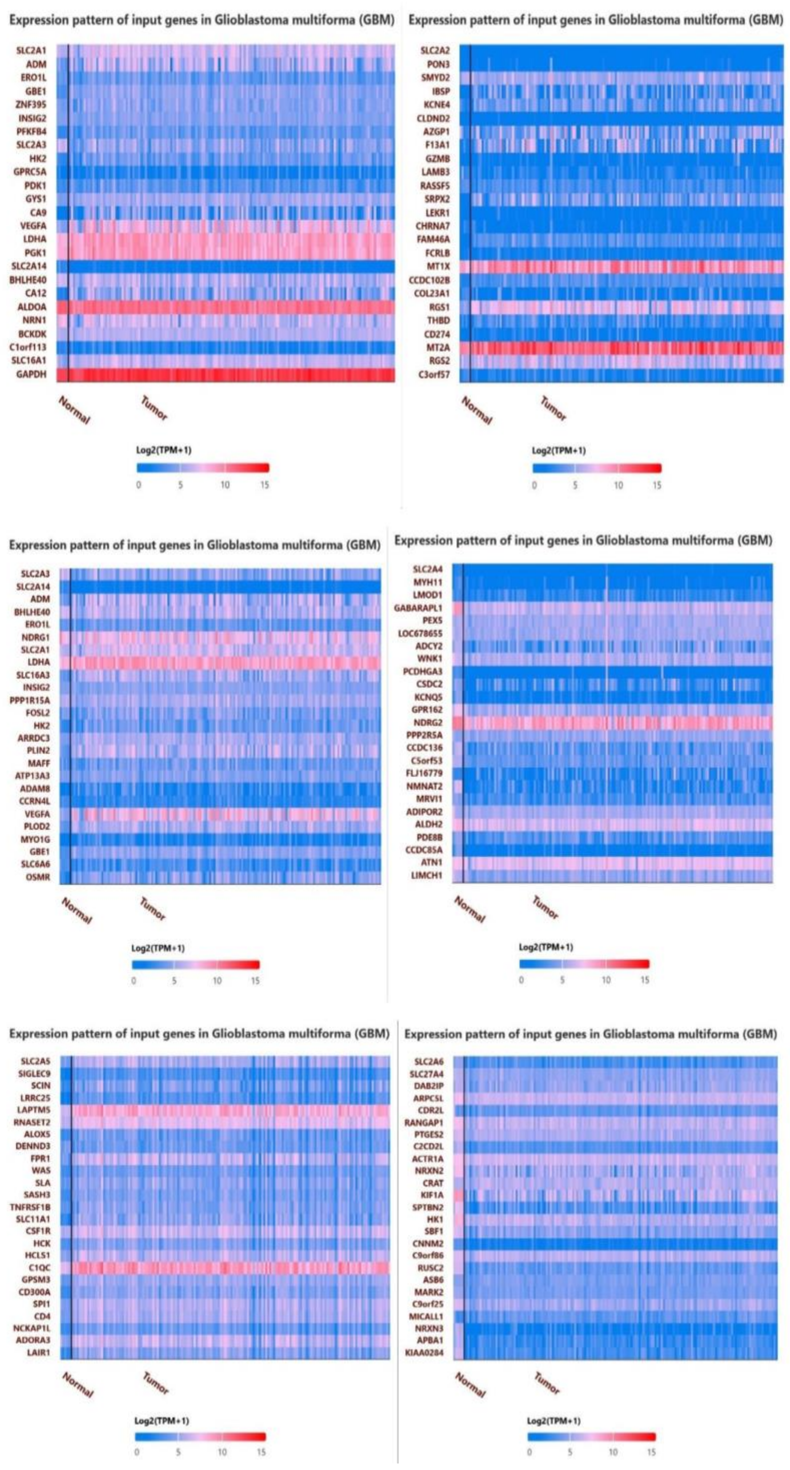

Figure 3. Microarray analysis results of SLC2A1-SLC2A6 gene expressions in relation to other genes. Data were analyzed according to UALCAN and TCGA database.

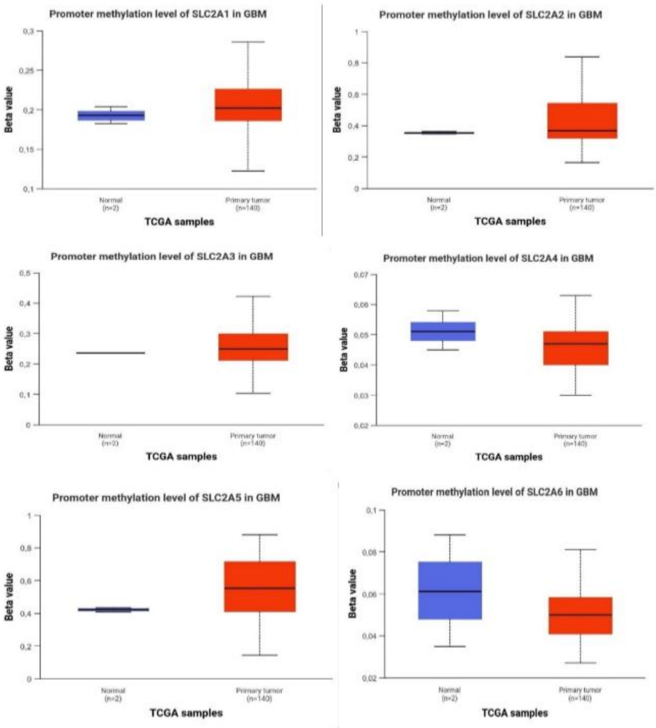

Figure 4. Promoter methylation level of SLC2A- SLC2A6 genes.

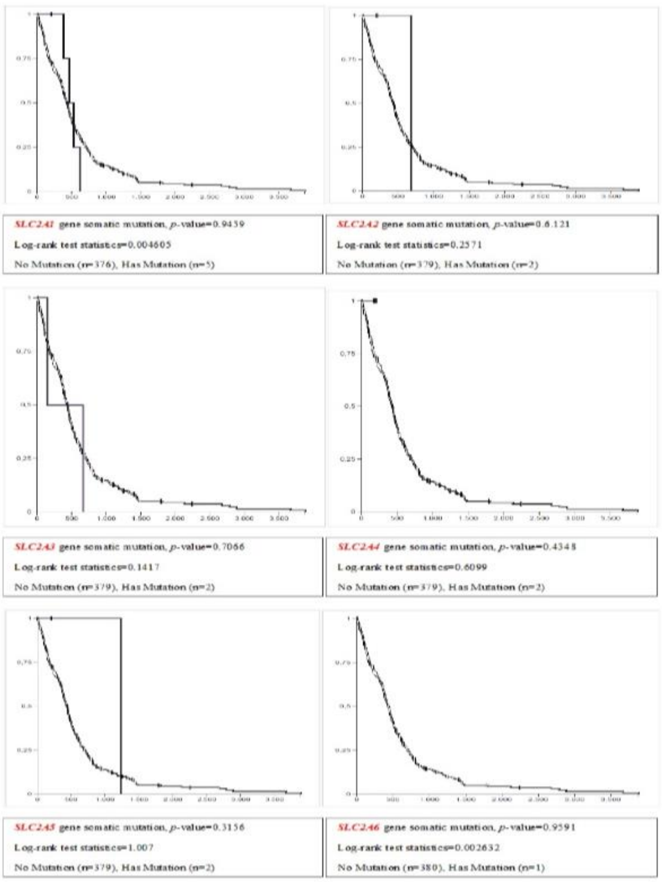

Figure 5. SLC2A1- SLC2A6 genes were analyzed with Kaplan Meier Somatic Mutation (Single Nucleotide Polymorphisms (SNPs) and Small INDELs)-Ensemble Somatic Variant.

Table1. Predicted Functional Proteins Associated with SLC2A1-SLC2A6 Proteins.

Proteins	Proteins Associated	Predicted functional proteins	Homology score
SLC2A1	TP53	Cellular tumor antigen p53	0.967
SLC2A1	SLC2A4	Solute carrier family 2, facilitated glucose transporter member 4	0.909
SLC2A1	SLC2A2	Solute carrier family 2, facilitated glucose transporter member 2	0.906
SLC2A1	HIF1A	Hypoxia-inducible factor 1-alpha	0.902
SLC2A1	BSG	Basigin	0.900
SLC2A1	EPAS1	Endothelial PAS domain-containing protein 1	0.888
SLC2A1	STOM	Erythrocyte band 7 integral membrane protein	0.880
SLC2A1	SLC5A1	Sodium/glucose cotransporter 1	0.874
SLC2A1	LDHA	Lactate dehydrogenase A	0.863
SLC2A1	CA9	Carbonic anhydrase 9	0.849
SLC2A2	GCK	Hexokinase-4	0.961
SLC2A2	HNF1A	Hepatocyte nuclear factor 1-alpha	0.954
SLC2A2	INS	Insulin A chain	0.942
SLC2A2	TP53	Cellular tumor antigen p53	0.926
SLC2A2	SLC2A1	Solute carrier family 2, facilitated glucose transporter member 1	0.906
SLC2A2	SLC2A5	Sodium/glucose cotransporter 1	0.899
SLC2A2	GCG	Glicentin-related polypeptide	0.876
SLC2A2	NEUROD1	Neurogenic differentiation factor 1	0.866
SLC2A2	NKX6-1	Homeobox protein Nkx-6.1	0.862
SLC2A2	NEUROG3	Neurogenin-3	0.854
SLC2A3	SLC2A14	Solute carrier family 2, facilitated glucose transporter member 14	0.868
SLC2A3	CREB1	Cyclic AMP-responsive element-binding protein 1	0.817
SLC2A3	MECP2	Methyl-CpG-binding protein 2	0.781
SLC2A3	HK1	Hexokinase-1	0.737
SLC2A3	HIF1A	Hypoxia-inducible factor 1-alpha	0.736
SLC2A3	PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3	0.736
SLC2A3	LDHA	Lactate dehydrogenase A	0.730
SLC2A3	SLC16A3	Monocarboxylate transporter 4	0.730
SLC2A3	HK2	Hexokinase-2	0.711
SLC2A3	PKM	Pyruvate kinase	0.689
SLC2A4	RAB10	Ras-related protein Rab-10	0.984
SLC2A4	INS	Insulin A chain	0.977
SLC2A4	RAB14	Ras-related protein Rab-14	0.973
SLC2A4	TBC1D4	TBC1 domain family member 4	0.969
SLC2A4	RAB8A	Ras-related protein Rab-8A	0.968
SLC2A4	ASPSCR1	Tether containing UBX domain for GLUT4	0.968
SLC2A4	RAB2A	Ras-related protein Rab-2A	0.955
SLC2A4	VAMP2	Vesicle-associated membrane protein 2	0.945
SLC2A4	IRS1	Insulin receptor substrate 1	0.940
SLC2A4	PPARG	Peroxisome proliferator-activated receptor gamma	0.934
SLC2A5	CA6	Carbonic anhydrase 6	0.866
SLC2A5	SLC5A1	Sodium/glucose cotransporter 1	0.861
SLC2A5	KHK	Ketohexokinase	0.796
SLC2A5	CA3	Carbonic anhydrase 3	0.764
SLC2A5	ENO1	Alpha-enolase	0.745
SLC2A5	SLC22A12	Solute carrier family 22 member 12	0.731
SLC2A5	SLC15A1	Solute carrier family 15 member 1	0.664
SLC2A5	TAS1R3	Taste receptor type 1 member 3	0.618
SLC2A5	G6PC3	Glucose-6-phosphatase 3	0.611
SLC2A5	G6PC2	Glucose-6-phosphatase 2	0.607
SLC2A6	SLC2A11-2	MFS domain-containing protein	0.849
SLC2A6	SLC2A11	Solute carrier family 2, facilitated glucose transporter member 11	0.525
SLC2A6	SLC2A3	Solute carrier family 2, facilitated glucose transporter member 3	0.512
SLC2A6	SLC22A8	Solute carrier family 22 member 8	0.475
SLC2A6	SLC2A7	Solute carrier family 2, facilitated glucose transporter member 7	0.472
SLC2A6	SLC2A1	Solute carrier family 2, facilitated glucose transporter member 1	0.469
SLC2A6	SLC2A2	Solute carrier family 2, facilitated glucose transporter member 2	0.467
SLC2A6	DHDH	Dihydrodiol dehydrogenase	0.466
SLC2A6	SLC2A5	Solute carrier family 2, facilitated glucose transporter member 5	0.465
SLC2A6	NFKBIE	NF-kappa-B inhibitor epsilon	0.463

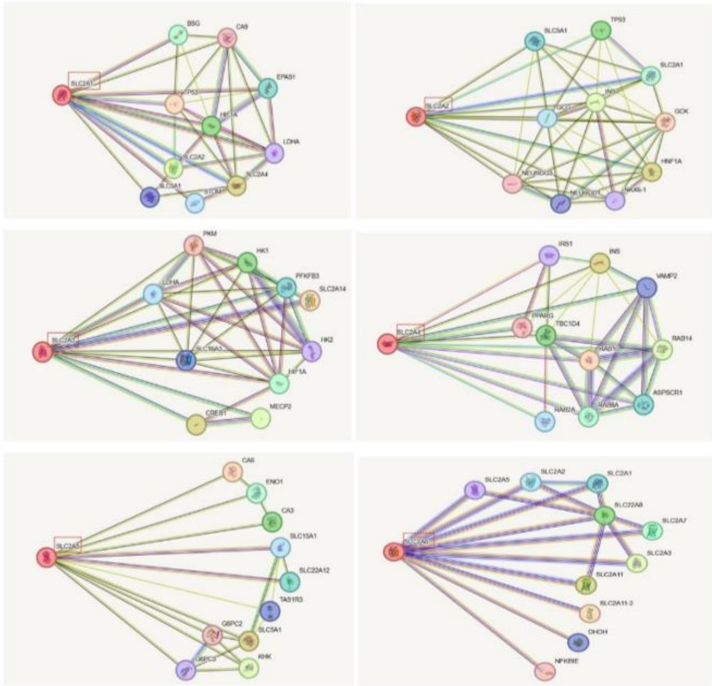

Figure 6. String analysis of known and predicted protein-protein interactions with proteins SLC2A-SLC2A6. Red line indicates evidence of fusion; green line indicates neighborhood evidence; blue line indicates association evidence; purple line indicates experimental evidence; yellow line indicates text mining evidence; light blue line indicates database evidence; black line indicates co-expression evidence.

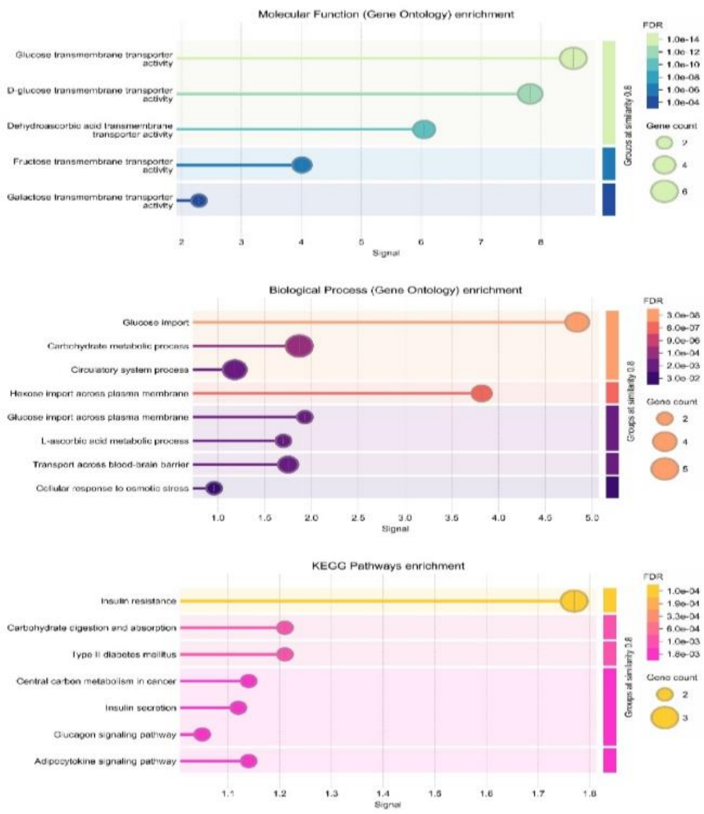

Figure 7. *Diagrams of the molecular function, biological process, and KEGG pathways of SLC2A1-SLC2A6 proteins*

Discussion

Gliomas are classified as grades I to IV according to the level of malignancy determined by their histopathological type. Gliomas with a grade I malignancy level have low proliferative potential and are related to lesions that can be treated with surgical procedures. In contrast, grades II to IV gliomas are highly malignant and invasive. GBM is the most aggressive, invasive and undifferentiated tumor type. GBM is defined as grade IV by WHO[34,35]. Since GBM is aggressive and invasive, early diagnosis is necessary to increase the survival rate of patients. Therefore, new potential biomarkers are needed for the diagnosis and prognosis of GBM. The *SLC2A* gene family may be an important biomarker in GBM. This study is significant since it is the first to use the TCGA database to ascertain the level of expression of SLC2A family genes in 207 normal tissues and 163 GBM tumor tissues. Based on our research, *SLC2A1*, *SLC2A2*, *SLC2A3*, and *SLC2A5* genes were significantly upregulated in GBM as a result of gene expression analysis. However, *SLC2A4* and *SLC2A6* genes were downregulated. Expression levels of *SLC2A* family members are increased in different tumors, thus indicating the potential oncogenic effect of the *SLC2A* family[36]. According to studies, SLC2A1 has a strong affinity for mannose, galactose, and glucose. Additionally, this transporter has been demonstrated to be strongly expressed at the blood-brain barrier, where it controls the rate at which glucose enters the brain. In addition, high expression of *SLC2A1* has been detected in erythrocytes, which rely solely on glycolysis for ATP production, and in the placenta, where SLC2A1-null mice have been shown to utilize glucose extensively, resulting in embryonic lethality[37]. The positive expression rate of *SLC2A1* can approach 50% in a variety of malignant tumor cells, such as those found in the breast, liver, pancreas, ovary, lung, esophagus, brain, kidney, skin, endometrial, colon and cervical regions. Thus, the degree of hypoxia, invasion, and metastasis, as well as the proliferation of malignant tumors, may be associated with SLC2A1[38]. As a result of the analysis, we found that *SLC2A1* gene expression levels were significantly higher in GBM patients. In addition, we detected hypermethylation in the promoter region. Nevertheless, there was no correlation between the patients' survival rate and this elevated expression or hypermethylation. The primary hepatic tissue sugar transporter, SLC2A2, has a decreased affinity for glucose[39]. In a study conducted by Yun et al. (2017) in patients with hepatocellular cancer, SLC2A2 was determined to be associated with clinical stages and was independently associated with the survival rate of patients[40]. In our analysis, the increase in *SLC2A2* gene expression level in GBM tumor tissue was not found to be significant. However, hypermethylation was detected in the promoter region. The increase in expression level was not associated with the survival rate of the patients. Recent studies have shown that SLC2A3 levels are increased in circulating tumor cells that tend to metastasize to the brain. In addition, SLC2A3 is essential for tumor cells to survive in the brain[41]. Additionally, it has been noted that a higher risk of metastasis in head and neck and breast malignancies is positively connected with elevated *SLC2A3* gene expression[42]. In the analysis, the increase in *SLC2A3* gene expression level in GBM tumor tissue was not significant and hypermethylation was detected in the promoter region. Although it was not significant, the increase in expression level was found to be associated with the survival rate of the patients. In the study of Shi et al., *SLC2A4* expression was significantly reduced in breast cancer and hypermethylation in the promoter region was detected[43]. Similarly, we noted a decrease in GBM tumor tissue in our study. However, this decrease was not significant. This decrease in expression level was not found to be associated with the survival rate of the patients. Groenendyk et al. reported that they stopped cell proliferation, migration and metastasis by blocking SLC2A5 fructose transport. In addition, they found that the localization and structure of mitochondria in cancer cells with suppressed *SLC2A5* gene played a role in the metastasis of cancer cells[43]. *SLC2A5* expression is elevated in metastatic liver lesions, lung tumors, brain, colon, testicular, uterine and breast carcinoma[44]. In this study, *SLC2A5* gene expression level was significantly increased in GBM tumor tissue. Hypermethylation was detected in the promoter region. However, the increase in expression level was not found to be associated with the survival rate of the patients *SLC2A6* overexpression can cause mitochondrial damage, stop cancer cells from proliferating, and cause tumor cells to undergo apoptosis[45]. *SLC2A6* gene expression level was significantly decreased and hypomethylation was detected in the promoter region. However, the increase in expression level was not found to be associated with the survival rate of the patients.

Conclusion

Consequently, we believe that *SLC2A1*, *SLC2A5* and *SLC2A6* may be useful prognostic biomarkers for GBM by showing the association of *SLC2A* family genes expression with GBM in this study. Although the increase in expression level was not significant, *SLC2A3* expression was found to be associated with the survival rate of patients. Therefore, it is thought that the increase in *SLC2A1*, *SLC2A5* and *SLC2A6* gene expression may be a biomarker in the diagnosis of GBM, and SLC2A3 may be a marker in prognosis.

References

1. Weller M, Wick W, Aldape K, Brada M, Berger M, Pfister S. M, Sutupp P, Reifenberger, G. Glioma. *Nature reviews Disease primers*. 2015; 1(1): 1-18.
2. Lou J, Hao Y, Lin K, Lin K, Lyu Y, Chen M, Wang H, Zou D, Jiang X, Wang R, Jin D, Lam E, Shao S, Liu Q, Yan J, Wang X, Chen P, Zhang B, Jin B. Circular RNA CDR1as disrupts the p53/MDM2 complex to inhibit Gliomagenesis. Mol Cancer; 2020;19:138.
3. Qazi M.A, Vora P, Venugopal C, Sidhu S.S, Moffat J, Swanton C, & Singh S.K. Intratumoral heterogeneity: pathways to treatment resistance and relapse in human glioblastoma. *Annals of Oncology*. 2017; 28(7): 1448-1456.
4. Ohka F, Natsume A, Wakabayashi T. Current trends in targeted therapies for glioblastoma multiforme. *Neurol Res Int*. 2012; 2012: 878425.
5. Network, TCGAR. Correction: Corrigendum: Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2013; 494(7438): 506-506.
6. Chai YJ, Yi JW, Oh SW, Kim YA, Yi KH, Kim JH, Lee KE. Upregulation of SLC2 (GLUT) family genes is related to poor survival outcomes in papillary thyroid carcinoma: Analysis of data from the Cancer Genome Atlas. *Surgery*. 2017; 161(1):188-194.

7. Ancey P-B, Contat C, Meylan E. Glucose transporters in cancerdfrom tumor cells to the tumor microen vironment. *FEBS J*. 2018;285:2926e43.
8. Macheda ML, Rogers S, Best JD. Molecular and cellular regulation of glucose transporter (GLUT) proteins in cancer. *J Cell Physiol*. 2005;202(3):654–62.
9. M. Mueckler, B. Thorens, The SLC2 (GLUT) family of membrane transporters. *Mol Aspects Med*. 2013; 34 (2–3): 121–138.
10. Mueckler M, Caruso C, Baldwin SA, Panico M, Blench I, Morris HR, et al. Sequence and structure of a human glucose transporter. *Science* 1985;229:941e5.
11. K. Ohtsubo, S. Takamatsu, M.T. Minowa, A. Yoshida, M. Takeuchi, J.D. Marth, Dietary and genetic control of glucose transporter 2 glycosylation promotes insulin secretion in suppressing diabetes. *Cell*. 2005;123 (7): 1307–1321.
12. Thorens B, Mueckler M. Glucose transporters in the 21st century. *Am J Physiol Endocrinol Metab*. 2010;298:E141e5.
13. Chen L.Q, Cheung L.S, Feng L, Tanner W, & Frommer W.B. Transport of sugars. *Annual review of biochemistry*. 84(1), 865-894.
14. Pereira K.M.A Chaves, F.N, Viana T.S.A, Carvalho F.S.R, Costa F.W.G, Alves A.P.N.N, Sousa F.B. Oxygen Metabolism in Oral Cancer: HIF and GLUTs (Review). *Oncol. Lett*. 2013; 6: 311–316.
15. Avanzato D, Pupo E, Ducano N, Isella C, Bertalot G, Luise C, Pece S, Bruna A, Rueda O.M, Caldas C, Fiore D, Sapino A, Lanzetti L. High USP6NLLevels in Breast Cancer Sustain Chronic AKT Phosphorylation and GLUT1 Stability Fueling Aerobic Glycolysis. Cancer Res. 2018; 78: 3432–3444.
16. Sun H.W, Yu X.J, Wu WC, Chen J, Shi M, Zheng L, Xu J. GLUT1 and ASCT2asPredictors for Prognosis of Hepatocellular Carcinoma. *PLoS ONE*. 2016; 11: e0168907.
17. Berlth F, Mönig S, Pinther B, Grimminger P, Maus M, Schlösser H, Plum P, Warnecke-Eberz U, Harismendy O, Drebber U, Bollschweiler E, Hölscher A, Alakus H. Both GLUT-1 and GLUT-14 Are Independent Prognostic Factors in Gastric Adenocarcinoma. Ann. Surg. Oncol. 2015; 22 (Suppl. S3): 822–831.
18. Goldman N.A, Katz E.B, Glenn A.S, Weldon R.H, Jones J.G, Lynch U, Fezzari M.J, Runowicz C.D, Goldberg G.L, Charron M.J. GLUT1 and GLUT8 in Endometrium and Endometrial Adenocarcinoma. *Mod. Pathol*. 2006; 19: 1429–1436.
19. Komaki S, Sugita Y, Furuta T, Yamada K, Moritsubo M, Abe H, Akiba J, Miyagi N, Nakamura H, Miyoshi H, Ohshima K, Morioka M. Expression of GLUT1 in pseudopalisaded and perivascular tumor cells is an independent prognostic factor for patients with glioblastomas. *J Neuropathol Exp Neurol*. 2019; 78(5): 389-397.
20. Mukhopadhyay P, Ye J, Anderson KM, Roychoudhury S, Rubin EH, Halabi S and Chappell RJ. Log-rank test vs MaxCombo and difference in restricted mean survival time tests for comparing survival under nonproportional hazards in immuno-oncology trials: A systematic review and meta-analysis. *JAMA Oncol*. 2022; 8: 1294-1300.
21. Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, Shanley R, Yeh N, Gaspar LE, Braunstein S, et al. Estimating survival in patients with lung cancer and brain metastases: An update of the graded prognostic assessment for lung cancer using molecular markers (lung-molGPA). *JAMA Oncol.* 2017; 3: 827-831.
22. Medina A, Parween S, Ullsten S, Vishnu N, Siu YT, Quach M, et al. Early deficits in insulin secretion, beta cell mass and islet blood perfusion precede onset of autoimmune type 1 diabetes in BioBreeding rats. Diabetologia. 2018;61(4):896–905.
23. Wu T. & Dai Y. Tumor microenvironment and therapeutic response. *Cancer Lett.* 2017; 28: 61–68.
24. Hanahan D & Weinberg R. A. Hallmarks of cancer: The next generation. *Cell.* 2011; 144, 646–674.
25. Estilo C. L, O-charoenrat P, Talbot S, Socci N, Carlson D.L, Ghossein R, Williams T, Yonekawa Y, Ramanathan Y, Boyle J.O, Kraus D.H, Patel S, Shaha A.R, Wong RJ, Huryn J.M, Shah J.P & Singh B. Oral tongue cancer gene expression profiling: Identification of novel potential prognosticators by oligonucleotide microarray analysis. BMC Cancer. 2009; 12, 9–26.
26. Yao X, He Z, Qin C, Deng X, Bai L, Li G & Shi J. SLC2A3 promotes macrophage infiltration by glycolysis reprogramming in gastric cancer. *Cancer cell inter*. 2020; 20: 1-16.
27. Boado RJ, Black KL and Pardridge WM. Gene expression of GLUT3 and GLUT1 glucose transporters in human brain tumors. *Brain Res Mol Brain Res*. 1994; 27: 51-57.
28. Zeng K, Ju G, Wang H & Huang J. GLUT1/3/4 as novel biomarkers for the prognosis of human breast cancer. *Translational cancer research*. 2020; *9*(4): 2363.
29. Szablewski L. Glucose transporters as markers of diagnosis and prognosis in cancer diseases. *Oncol Rev*. 2022;16:561.
30. Shi Z, Liu J, Wang F, Li Y. Integrated analysis of solute carrier family-2 members reveals SLC2A4 as an independent favorable prognostic biomarker for breast cancer. *Channels*. 2021;15:555–68.
31. Davidson N. O, Hausman A.M. L, Ifkovits C.A, Buse J.B, Gould G.W, Burant C.F, Bell G.I. Human intestinal glucose transporter expression and localization of GLUT5. *Am. J. Physiol.* 1992; 262: C795-C800.
32. Burant C.F, Takeda J, Brot-Laroche E, Bell G.I, Davidson N.O. Fructose transporter in human spermatozoa and small intestine is GLUT5. *J. Biol. Chem*. 1992; 267: 14523-14526.
33. Doege H, Bocianski A, Joost H.G, Schurmann A. Activity and genomic organization of human glucose transporter 9 (GLUT9), a novel member of the family of sugar-transport facilitators predominantly expressed in brain and leucocytes. *Biochem. J*. 2001; 350: 771-776, 2000. Note: *Erratum: Biochem. J*. 358: 791-792.
34. Louis DN, Ohgaki H, Wiestler OD, Cavenee W.K, Burger P.C, Jouvet A, Scheithauer B.W, Kleihues P. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007; 114: 97-109.
35. Jovčevska I, Kočevar N, Komel R. Glioma and glioblastoma-how much do we (not) know?. *Mol Clin Oncol*. 2013; 1: 935-41.
36. Gao H, Liang J, Duan J, Chen L, Li H, Zhen T, Zhang F, Dong Y, Shi H, Han A: A prognosis marker SLC2A3 correlates with EMT and immune signature in colorectal cancer. *Front Oncol*. 2021; 11(11): 638099.
37. Wang D, Pascual J.M, Yang H, Engelstad K, Mao X, Cheng J, Yoo J, Noebels J.L, De Vivo D.C. A mouse model for Glut-1 haploinsufficiency. Hum. Mol. *Genet*. 2006; 15: 1169–1179.
38. Majumdar D, Peng XH, Shin DM. The medicinal chemistry of theragnostics, multimodality imaging and applications of nanotechnology in cancer. *Curr Top Med Chem*. 2010;10(12):1211-26.
39. Sandhu S.S, Irwin A.G, Buscombe J.R, Hilson A. J.W, Young H.E, Jarmulowicz M & Kaisary A. V. 21. Metabolic imaging of untreated prostate cancer by positron emission tomography with 18fluorine-labelled deoxyglucose. *Nuclear Med Commun*. 1997; 18(4): 328.
40. Kim Y.H, Jeong D.C, Pak K, Han M.E, Kim J.Y, Liangwen L, Kim H, Kim T.W, Kim T.H, Hyun D.W, Oh S.O. SLC2A2 (GLUT2) as a novel prognostic factor for hepatocellular carcinoma [J]. *Oncotarget*. 2017; 8 (40): 68381–68392.
41. Boral D, Vishnoi M, Liu HN, Yin W, Sprouse M.L, Scamardo A, Hong D.S, Tan T.Z, Thiery J.P, Chang J.C, Marchetti D. Molecular characterization of breast cancer CTCs associated with brain metastasis. *Nat Commun*. 2017;8(1):196.
42. Cosset E, Ilmjarv S, Dutoit V, et al. Glut3 addiction is a druggable vulnerability for a molecularly defined subpopulation of glioblastoma. *Cancer Cell*. 2017;32 (6):856–868.e855.
43. Groenendyk J, Stoletov K, Paskevicius T, Li W, Dai N, Pujol M., ... & Michalak M. Loss of the fructose transporter SLC2A5 inhibits cancer cell migration. *Front in Cell and Develop Biol*. 2022; 10: 896297.
44. Uldry M, and Thorens B. The SLC2 family of facilitated hexose and polyol transporters. *Pflugers Arch*. 2004; 447: 480–489.
45. Dai C, Man Y, Zhang L, Zhang X, Xie C, Wang S, ... & Shi Y. Identifying SLC2A6 as the novel protective factor in breast cancer by TP53-related genes affecting M1 macrophage infiltration. *Apoptosis*. 2024; 1-21.