

UNVEILING PROGNOSTIC HUB GENES FOR THE MANAGEMENT OF GLIOMAGENESIS THROUGH TRANSCRIPTOME PROFILING

M. POORNIMAA^{1,2}, V. SHANTHI¹,
K. RAMANATHAN^{1,*}

¹ Department of Biotechnology, School of Bio Sciences and Technology, Vellore Institute of Technology, Vellore - 632014, Tamil Nadu, India

² Department of Biotechnology, St Joseph's College of Engineering, OMR, Chennai - 600119, Tamil Nadu, India

Address for correspondence: Ramanathan K.,
e-mail: kramanathan@vit.ac.in

Despite recent advancements, glioma prognosis remains poor, with a median survival of 15 months with a high relapse rate. Thus, the current study aimed to shed light on identifying prospective candidate hub genes as potential biomarkers related to the pathogenesis of gliomas. The integrative pipeline, including quality control, normalization, principal component analysis (PCA), and immunohistochemistry, identified differentially expressed genes (DEGs), which were then validated. Gene ontology (GO) and KEGG pathway analysis were utilized to functionally elucidate the hub genes. Interestingly, the present study identified novel hub genes such as TP53, SRC, UBA52, UBB, and CDK1. Of note, ours is the first report on the UBA52 and UBB which unveils the use of these hub genes as potential biomarkers. These genes were mainly involved in crucial oncological pathways that annotated their resemblance with glioma. Finally, potential candidate drugs were predicted against three key gene targets, namely TP53, SRC and CDK1, using the DGIdb database to manage glioblastoma effectively. Indeed, we believe that the exploration of UBB and UBA52 would present exciting opportunities for scientific advancement in the field of glioma treatment strategy. Overall, the results from our study provide a new avenue for the precise understanding of prognostic and diagnostic biomarkers that could serve as specific therapeutic targets for averting gliomagenesis in the near future.

Key words: glioma WHO grades, differential gene expression, hub genes, protein interaction networks, drug-gene interaction.

ВИЯВЛЕННЯ ПРОГНОСТИЧНИХ
ВУЗЛОВИХ (ХАБІВ) ГЕНІВ ДЛЯ КОНТРОЛЮ
ГЛІОМАГЕНЕЗУ ЗА ДОПОМОГОЮ

© ІНСТИТУТ КЛІТИННОЇ БІОЛОГІЇ ТА ГЕНЕТИЧНОЇ
ІНЖЕНЕРІЇ НАН УКРАЇНИ, 2026

ТРАНСКРИПТОМНОГО ПРОФІЛЮВАННЯ

Попри нещодавні наукові досягнення, прогнозування гліоми залишається на низькому рівні, середній термін виживання становить 15 місяців, а частота рецидивів є високою. Тому метою даного дослідження було пролити світло на ідентифікацію потенційних вузлових генів (генів-хабів) як можливих біомаркерів, пов'язаних із патогенезом гліом. Інтегративний підхід, що охопив контроль якості, нормалізацію, аналіз головних компонентів (PCA) та імуногістохімію, дозволив ідентифікувати диференційно експресовані гени (DEG), які потім були валідовані. Для функціонального дослідження вузлових генів було використано генну онтологію (GO) та аналіз шляхів KEGG. Цікавим є той факт, що в цьому дослідженні було ідентифіковано нові вузлові гени, зокрема, TP53, SRC, UBA52, UBB та CDK1. Варто зазначити, що наше дослідження є першим звітом про UBA52 та UBB, який розкриває використання цих вузлових генів як потенційних біомаркерів. Ці гени були в основному залучені до важливих онкологічних шляхів, що підтверджувало їх схожість з гліомою. Зрештою, за допомогою бази даних DGIdb було передбачено потенційні лікарські препарати для ефективного лікування гліобластоми, спрямовані на три ключові генетичні мішені, а саме TP53, SRC та CDK1. Ми вважаємо, що дослідження UBB та UBA52 відкриє захоплюючі можливості для наукового прогресу в галузі стратегії лікування гліоми. Загалом, результати нашого дослідження відкривають нові перспективи для точного розуміння прогностичних та діагностичних біомаркерів, які можуть слугувати конкретними терапевтичними мішенями для запобігання гліомагенезу в найближчому майбутньому.

Ключові слова: ступені гліоми за BOOЗ, диференціальна експресія генів, вузлові гени, мережі взаємодії білків, взаємодія «препарат-ген».

REFERENCES

- Ahluwalia, M.S., de Groot, J., Liu, W.M., and Gladson, C.L., Targeting SRC in glioblastoma tumors and brain metastases: rationale and preclinical studies, *Cancer Lett*, 2010, vol. 298, no. 2, pp.139–149. <https://doi.org/10.1016/j.canlet.2010.08.014>
- Ahmadi-Beni, R., Shahbazi, S., and Khoshnevisan, A., An integrative bioinformatics investigation and experimental validation of critically involved genes in high-grade gliomas, *Diagn. Pathol.*, 2022, vol. 17, no. 1, pp. 73. <https://doi.org/10.1186/s13000-022-01253-0>
- Aldape, K., Zadeh, G., Mansouri, S., Reifenberger, G., and von Deimling, A., Glioblastoma: pathology, molecular mechanisms and markers, *Acta Neuro-*

- pathol.*, 2015, vol. 129, no. 6, pp. 829–848. <https://doi.org/10.1007/s00401-015-1432-1>
- Ashburner, M., Ball, C.A., Blake, J.A., Botstein, D., Butler, H., Cherry, J.M., Davis, A.P., Dolinski, K., Dwight, S.S., Eppig, J.T., and Harris, M.A., Gene ontology: tool for the unification of biology, *Nat. Genet.*, 2000, vol. 25, no. 1, pp. 25–29. <https://doi.org/10.1038/75556>
- Bazai, F.K., Hassan, M.U., Tayyab, H., Naudhani, S., Siraj, S., Tariq, M., Shah, S.A., Ahmad, J., and Daud, S., Targeted Sequencing of HEXA Gene Shows Missense Substitution (p. Arg499His) in a Large Pakistani Family with Tay-Sachs Disease, *Cytol. Genet.*, 2024, vol. 58, no. 5, pp. 486–492. <https://doi.org/10.3103/S0095452724050025>
- Biswal, D., and Li, S., Transcription Factors in Cardiac Remodeling: Latest Advances, *Cytol. Genet.*, 2024, vol. 58, no. 3, pp. 234–245. <https://doi.org/10.3103/S0095452724030034>
- Cao, F., Fan, Y., Yu, Y., Yang, G., and Zhong, H., Dissecting prognosis modules and biomarkers in glioblastoma based on weighted gene Co-expression network analysis, *Cancer Manag. Res.*, 2021, pp. 5477–5489. <https://doi.org/10.2147/CMAR.S310346>
- Chen, Z., and Xu, W., Targeting E3 ubiquitin ligases to sensitize cancer radiation therapy, *Precis. Radiat. Oncol.*, 2019, vol. 3, no. 3, pp. 105–110. <https://doi.org/10.1002/pro6.1069>
- Chin, C.H., Chen, S.H., Wu, H.H., Ho, C.W., Ko, M.T., and Lin, C.Y., cytoHubba: identifying hub objects and sub-networks from complex interactome, *BMC Syst. Biol.*, 2014, vol. 8, p. S11. <https://doi.org/10.1186/1752-0509-8-S4-S11>
- Ciechanover, A., and Schwartz, A.L., The ubiquitin system: pathogenesis of human diseases and drug targeting, *Biochim. Biophys. Acta (BBA)-Mol. Cell Res.*, 2004, vol. 1695, no. 1–3, pp. 3–17. <https://doi.org/10.1016/j.bbamer.2004.09.018>
- Cirotti, C., Contadini, C., and Barila, D., SRC kinase in glioblastoma: News from an old acquaintance, *Cancers*, 2020, vol. 12, no. 6, pp. 1558. <https://doi.org/10.3390/cancers12061558>
- Cotto, K.C., Wagner, A.H., Feng, Y.Y., Kiwala, S., Coffman, A.C., Spies, G., Wollam, A., Spies, N.C., Griffith, O.L., and Griffith, M., DGIdb 3.0: a re-design and expansion of the drug–gene interaction database, *Nucleic Acids Res.*, 2018, vol. 46(D1), pp. D1068–D1073. <https://doi.org/10.1093/nar/gkx1143>
- Cuddapah, V.A., Robel, S., Watkins, S., and Sontheimer, H., A neurocentric perspective on glioma invasion. <https://doi.org/10.1038/nrn3765>
- Cui, D.J., Chen, C., Yuan, W.Q., Yang, Y.H., and Han, L., Integrative analysis of ferroptosis-related genes in ulcerative colitis, *J. Int. Med. Res.*, 2021, vol. 49, no. 9, pp.03000605211042975. <https://doi.org/10.1177/0300060521104297>
- Duffy, M.J., Lamerz, R., Haglund, C., Nicolini, A., Kalousov, M., Holubec, L., and Sturgeon, C., Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update, *Int. J. Cancer*, 2014, vol. 134, no. 11, pp. 2513–2522. <https://doi.org/10.1002/ijc.28384>
- Gao, M., Yang, J., Gong, H., Lin, Y., and Liu, J., Trametinib inhibits the growth and aerobic glycolysis of glioma cells by targeting the PKM2/c-Myc axis, *Front. Pharmacol.*, 2021, vol. 12, p. 760055. <https://doi.org/10.3389/fphar.2021.760055>
- Ge, S.X., Jung, D., and Yao, R., ShinyGO: a graphical gene-set enrichment tool for animals and plants, *Bioinformatics*, 2020, vol. 36, no. 8, pp. 2628–2629. <https://doi.org/10.1093/bioinformatics/btz931>
- Goodwin, C.R., Rath, P., Oyinlade, O., Lopez, H., Mughal, S., Xia, S., Li, Y., Kaur, H., Zhou, X., Ahmed, A.K., and Ho, S., Crizotinib and erlotinib inhibits growth of c-Met+/EGFRvIII+ primary human glioblastoma xenografts, *Clin. Neurol. Neurosurg.*, 2018, vol. 171, pp. 26–33. <https://doi.org/10.1016/j.clin-neuro.2018.02.041>
- Gulfidan, G., Soyulu, M., Demirel, D., Erdonmez, H.B.C., Beklen, H., Sarica, P.O., Arga, K.Y., and Turanli, B., Systems biomarkers for papillary thyroid cancer prognosis and treatment through multi-omics networks, *Archives Biochem. Biophys.*, 2022, vol. 715, pp. 109085. <https://doi.org/10.1016/j.abb.2021.109085>
- He, C., Lu, S., Wang, X.Z., Wang, C.C., Wang, L., Liang, S.P., Luo, T.F., Wang, Z.C., Piao, M.H., Chi, G.F., and Ge, P.F., FOXO3a protects glioma cells against temozolomide-induced DNA double strand breaks via promotion of BNIP3-mediated mitophagy, *Acta Pharmacol. Sinica*, 2021, vol. 42, no. 8, pp. 1324–1337. <https://doi.org/10.1038/nature07960>
- Hoeller, D., and Dikic, I., Targeting the ubiquitin system in cancer therapy, *Nature*, 2009, vol. 458, no. 7237, pp. 438–444. <https://doi.org/10.1038/nature07960>
- Hong, M., Tao, S., Zhang, L., Diao, L.T., Huang, X., Huang, S., Xie, S.J., Xiao, Z.D., and Zhang, H., RNA sequencing: new technologies and applications in cancer research, *J. Hematol. Oncol.*, 2020, vol. 13, no. 1, pp. 166. <https://doi.org/10.1186/s13045-020-01005-x>
- Houles, T., Lavoie, G., Nourreddine, S., Cheung, W., Vaillancourt-Jean, É., Guérin, C.M., Bouttier, M., Grondin, B., Lin, S., Saba-El-Leil, M.K., and Angers, S., CDK12 is hyperactivated and a synthetic-lethal target in BRAF-mutated melanoma, *Nat. Commun.*, 2022, vol. 13, no. 1, pp. 6457. <https://doi.org/10.1038/s41467-022-34179-8>

- Hsu, J.B.K., Chang, T.H., Lee, G.A., Lee, T.Y., and Chen, C.Y., Identification of potential biomarkers related to glioma survival by gene expression profile analysis, *BMC Med. Genom.*, 2019, vol. 11, no. Suppl. 7, pp. 34. <https://doi.org/10.1186/s12920-019-0479-6>
- Huang, T., Xu, T., Wang, Y., Zhou, Y., Yu, D., Wang, Z., He, L., Chen, Z., Zhang, Y., Davidson, D., and Dai, Y., Cannabidiol inhibits human glioma by induction of lethal mitophagy through activating TRPV4, *Autophagy*, 2021, vol. 17, no. 11, pp. 3592–3606. <https://doi.org/10.1080/15548627.2021.1885203>
- Jian, F., Yanhong, J., Limeng, W., Guoping, N., Yiqing, T., Hao, L., and Zhaoji, P., TIMP2 is associated with prognosis and immune infiltrates of gastric and colon cancer, *Int. Immunopharmacol.*, 2022, vol. 110, pp. 109008. <https://doi.org/10.1016/j.intimp.2022.109008>
- Kurita, M., Mishima, K., Tsubomura, M., Takashima, Y., Nose, M., Hirao, T., and Takahashi, M., Transcriptome analysis in male strobilus induction by gibberellin treatment in *Cryptomeria japonica* D. Don, *Forests*, 2020, vol. 11, no. 6, pp. 633. <https://doi.org/10.3390/f11060633>
- Lei, X., Zhang, M., Guan, B., Chen, Q., Dong, Z., and Wang, C., Identification of hub genes associated with prognosis, diagnosis, immune infiltration and therapeutic drug in liver cancer by integrated analysis, *Hum. Genom.*, 2021, vol. 15, no. 1, pp. 39. <https://doi.org/10.1186/s40246-021-00341-4>
- Lin, L.L., Huang, H.C., and Juan, H.F., Discovery of biomarkers for gastric cancer: a proteomics approach, *J. Proteom.*, 2012, vol. 75, no. 11, pp. 3081–3097. <https://doi.org/10.1016/j.jprot.2012.03.046>
- Liu, C., Peng, Z., Li, P., Fu, H., Feng, J., Zhang, Y., Liu, T., Liu, Y., Liu, Q., Liu, Q., and Li, D., IncRNA RMST suppressed GBM cell mitophagy through enhancing FUS SUMOylation, *Mol. Ther. Nucleic Acids*, 2020, vol. 19, pp. 1198–1208. <https://doi.org/10.1016/j.omtn.2020.01.008>
- Maiti, P., Scott, J., Sengupta, D., Al-Gharaibeh, A., and Dunbar, G.L., Curcumin and solid lipid curcumin particles induce autophagy, but inhibit mitophagy and the PI3K-Akt/mTOR pathway in cultured glioblastoma cells, *Int. J. Mol. Sci.*, 2019, vol. 20, no. 2, pp. 399. <https://doi.org/10.3390/ijms20020399>
- Maksoud, S., The role of the ubiquitin proteasome system in glioma: analysis emphasizing the main molecular players and therapeutic strategies identified in glioblastoma multiforme, *Mol. Neurobiol.*, 2021, vol. 58, no. 7, pp. 3252–3269. <https://doi.org/10.1007/s12035-021-02339-4>
- Murali, P., and Karuppasamy, R., Identification of novel mutant (R132H) isocitrate dehydrogenase 1 inhibitors for glioma therapy, *J. Comput. Biophys. Chem.*, 2022, vol. 21, no. 06, pp. 647–661. <https://doi.org/10.1142/S2737416522500260>
- Murali, P., and Karuppasamy, R., Exploration of natural product database for the identification of potent inhibitor against IDH2 mutational variants for glioma therapy, *J. Mol. Model.*, 2023, vol. 29, no. 1, pp. 6. <https://doi.org/10.1007/s00894-022-05409-z>
- Nayak, C., and Singh, S.K., Integrated transcriptome profiling identifies prognostic hub genes as therapeutic targets of glioblastoma: evidenced by bioinformatics analysis, *ACS Omega*, 2022, vol. 7, no. 26, pp. 22531–22550. <https://doi.org/10.1021/acsomega.2c01820>
- Nehoff, H., Parayath, N.N., McConnell, M.J., Taurin, S., and Greish, K., A combination of tyrosine kinase inhibitors, crizotinib and dasatinib for the treatment of glioblastoma multiforme, *Oncotarget.*, 2015, vol. 6, no. 35, pp. 37948. <https://doi.org/10.18632/oncotarget.5698>
- Olivier, M., Hollstein, M., and Hainaut, P., TP53 mutations in human cancers: origins, consequences, and clinical use, *Cold Spring. Harb. Perspect. Biol.*, 2010, vol. 2, no. 1, pp. a001008. <https://doi.org/10.1101/cshperspect.a001008>
- Ou, C., Peng, Q., and Zeng, C., An integrative prognostic and immune analysis of PTPRD in cancer, *Math. Biosci. Eng.*, 2022, vol. 19, no. 6, pp. 5361–5379. <https://doi.org/10.3934/mbe.2022251>
- Panigrahi, D.P., Praharaj, P.P., Bhol, C.S., Mahapatra, K.K., Patra, S., Behera, B.P., Mishra, S.R., and Bhutia, S.K., The emerging, multifaceted role of mitophagy in cancer and cancer therapeutics, *In Seminars Cancer Biol.*, 2020, vol. 66, pp. 45–58. <https://doi.org/10.1016/j.semcancer.2019.07.015>
- Piva, R., Cancelli, I., Cavalla, P., Bortolotto, S., Dominguez, J., Draetta, G.F., and Schiffer, D., Proteasome-dependent degradation of p27/kip1 in gliomas, *J. Neuropathol. Exp. Neurol.*, 1999, vol. 58, no. 7, pp. 691–696. <https://doi.org/10.1097/00005072-199907000-00002>
- Ramesh, P., Veerappapillai, S., and Karuppasamy, R., Gene expression profiling of corona virus microarray datasets to identify crucial targets in COVID-19 patients, *Gene Rep.*, 2021, vol. 22, pp. 100980. <https://doi.org/10.1016/j.genrep.2020.100980>
- Santamagna, D., Barrière, C., Cerqueira, A., Hunt, S., Tardy, C., Newton, K., Cáceres, J.F., Dubus, P., Malumbres, M., and Barbacid, M., Cdk1 is sufficient to drive the mammalian cell cycle, *Nature*, 2007, vol. 448, no. 7155, pp. 811–815. <https://doi.org/10.1038/nature06046>
- Sigmond, J., Honeywell, R.J., Postma, T.J., Dirven,

- C.M.F., De Lange, S.M., Van der Born, K., Laan, A.C., Baayen, J.C.A., Van Groenigen, C.J., Bergman, A.M., and Giaccone, G., Gemcitabine uptake in glioblastoma multiforme: potential as a radiosensitizer, *Ann. Oncol.*, 2009, vol. 20, no. 1, pp. 182–187. <https://doi.org/10.1093/annonc/mdn543>
- Song, Z., Pan, Y., Ling, G., Wang, S., Huang, M., Jiang, X., and Ke, Y., Escape of U251 glioma cells from temozolomide-induced senescence was modulated by CDK1/survivin signaling, *Am. J. Transl. Res.*, 2017, vol. 9, no. 5, pp. 2163.
- Tang, Z., Li, C., Kang, B., Gao, G., Li, C., and Zhang, Z., GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses, *Nucleic Acids Res.*, 2017, vol. 45, no. W1, pp. W98–W102. <https://doi.org/10.1093/nar/gkx247>
- Tomkins, J.E., and Manzoni, C., Advances in protein-protein interaction network analysis for Parkinson's disease, *Neurobiol. Dis.*, 2021, vol. 155, pp. 105395. <https://doi.org/10.1016/j.nbd.2021.105395>
- Torrisi, F., Vicario, N., Spitale, F.M., Cammarata, F.P., Minafra, L., Salvatorelli, L., Russo, G., Cuttone, G., Valable, S., Gulino, R., and Magro, G., The role of hypoxia and SRC tyrosine kinase in glioblastoma invasiveness and radioresistance, *Cancers*, 2020, vol. 12, no. 10, pp. 2860. <https://doi.org/10.3390/cancers12102860>
- Toschi, L., Finocchiaro, G., Bartolini, S., Gioia, V., and Cappuzzo, F., Role of gemcitabine in cancer therapy, *Future Oncol.*, 2005, vol. 1, no. 1, pp. 7–17. <https://doi.org/10.1517/14796694.1.1.7>
- Vlachostergios, P.J., Voutsadakis, I.A., and Papandreou, C.N., The ubiquitin-proteasome system in glioma cell cycle control, *Cell Div.*, 2012, vol. 7, no. 1, pp. 18. <https://doi.org/10.1186/1747-1028-7-18>
- Wang, G., Yang, X., Qi, M., Li, M., Dong, M., Xu, R., and Zhang, C., Systematic analysis identifies REST as an oncogenic and immunological biomarker in glioma, *Sci. Rep.*, 2023, vol. 13, no. 1, pp. 3023. <https://doi.org/10.1038/s41598-023-30248-0>
- Wang, Q., Bode, A.M., and Zhang, T., Targeting CDK1 in cancer: mechanisms and implications, *NPJ Precis. Oncol.*, 2023, vol. 7, no. 1, pp. 58. <https://doi.org/10.1038/s41698-023-00407-7>
- Wheeler, D.L., Iida, M., and Dunn, E.F., The role of Src in solid tumors, *The oncologist*, 2009, vol. 14, no. 7, pp. 667–678. <https://doi.org/10.1634/theoncologist.2009-0009>
- Xu, B., Prediction and analysis of hub genes between glioblastoma and low-grade glioma using bioinformatics analysis, *Medicine*, 2021, vol. 100, no. 3, pp. e23513. <https://doi.org/10.1097/MD.00000000000023513>
- Yin, X., Wu, Q., Hao, Z., and Chen, L., Identification of novel prognostic targets in glioblastoma using bioinformatics analysis, *Biomed. Eng. Online*, 2022, vol. 21, no. 1, pp. 26. <https://doi.org/10.1186/s12938-022-00995-8>
- Zhang, J., Liu, L., Xue, Y., Ma, Y., Liu, X., Li, Z., Li, Z., and Liu, Y., Endothelial monocyte-activating polypeptide-II induces BNIP3-mediated mitophagy to enhance temozolomide cytotoxicity of glioma stem cells via down-regulating MiR-24-3p, *Front. Mol. Neurosci.*, 2018, vol. 11, pp. 92. <https://doi.org/10.3389/fnmol.2018.00092>
- Zhang, S., Xiang, X., Liu, L., Yang, H., Cen, D., and Tang, G., Bioinformatics analysis of hub genes and potential therapeutic agents associated with gastric cancer, *Cancer Manag. Res.*, 2021, pp. 8929–8951. <https://doi.org/10.2147/CMAR.S341485>
- Zhang, Y., Dube, C., Gibert Jr, M., Cruickshanks, N., Wang, B., Coughlan, M., Yang, Y., Setiady, I., Deveau, C., Saoud, K., and Grello, C., The p53 pathway in glioblastoma, *Cancers*, 2018a, vol. 10, no. 9, pp. 297. <https://doi.org/10.3390/cancers10090297>
- Zhang, Y., Xia, Q., and Lin, J., Identification of the potential oncogenes in glioblastoma based on bioinformatic analysis and elucidation of the underlying mechanisms, *Oncol. Rep.*, 2018, vol. 40, no. 2, pp. 715–725. <https://doi.org/10.3892/or.2018.6483>
- Zhang, Y., Yang, X., Zhu, X.L., Hao, J.Q., Bai, H., Xiao, Y.C., Wang, Z.Z., Hao, C.Y., and Duan, H.B., Bioinformatics analysis of potential core genes for glioblastoma, *Biosci. Rep.*, 2020, vol. 40, no. 7, pp. BSR20201625. <https://doi.org/10.1042/BSR20201625>
- Zhao, Z., Meng, F., Wang, W., Wang, Z., Zhang, C. and Jiang, T., Comprehensive RNA-seq transcriptomic profiling in the malignant progression of gliomas, *Sci. Data*, 2017, vol. 4, no. 1, pp. 1–7. <https://doi.org/10.1038/sdata.2017.24>

Received February 21, 2025

Received May 20, 2025

Accepted January 18, 2026