Clinical and Experimental Health Sciences

The Role of The Tissue-Level Yap–Taz Pathway in Glioma Development

Sinan Fındık [1], Ebru Arslan [2], Pınar Ata [3], Yaşar Bayri [4], Adnan Dağçınar [5]

[1] Marmara University, Institute of Health Sciences, Department of Neuroscience, Istanbul, Türkiye.
[2] Marmara University, Institute of Health Sciences, Department of Medical Genetics, Istanbul, Türkiye.
[3] Marmara University, Faculty of Medicine, Department of Medical Genetics, Istanbul, Türkiye.
[4] Acıbadem Healthcare Group, Kartal Hospital, Brain and Neurosurgery, Istanbul-Türkiye.
[5] Marmara University, Faculty of Medicine, Department of Brain and Neurosurgery, Istanbul, Türkiye.

Correspondence Author: Sinan Fındık
E-mail: sinangenetik@gmail.com
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ABSTRACT

Objective:The aim of this research is to evaluate the tissue-level expression of LATS1, YAP1, PI3KCG, and WWTR1 genes, which are key components of the Hippo-YAP/TAZ signaling pathway, in relation to glioma development.

Methods:This research included tissue samples collected from 30 patients aged between 18 and 80 years who underwent neurosurgical resection at the institution's affiliated hospital with a diagnosis of glioma. Tumor tissue samples were processed for total RNA isolation. Complementary DNA (cDNA) synthesis was subsequently performed, followed by quantitative polymerase chain reaction (qPCR) analysis to assess the relative expression levels of the selected genes. All procedures were conducted in compliance with standardized molecular protocols, and data were statistically analyzed using appropriate methods to determine expression differences.

Results:Among the genes analyzed, YAP1 demonstrated a statistically significant 2.6-fold downregulation in glioma tissues compared to adjacent non-tumoral tissues ($p = 0.03$). Expression changes in other genes were observed, but did not reach statistical significance within the scope of this study.

Conclusion:Our findings suggest that YAP1 may play a critical role in glioma pathogenesis. The observed downregulation indicates a potential dysregulation of the Hippo-YAP/TAZ signaling pathway in tumor development. These results underscore the importance of further investigating YAP1 and related signaling components as potential therapeutic targets in glioma and other central nervous system tumors. Future studies with larger patient cohorts and functional analyses are warranted to validate these preliminary findings.

Keywords:Glioma, YAP/TAZ, Hippo signaling pathway, gene expression

1. INTRODUCTION

Gliomas represent the most common and aggressive group of primary brain tumors in adults, accounting for approximately 80% of all malignant brain neoplasms (1,2). Despite advances in treatment strategies, the prognosis for high-grade gliomas remains poor, with a median survival of only 14–16 months following diagnosis (3,4). This reality necessitates a deeper understanding of glioma biology at the molecular level and the development of novel biomarkers (5,6).

A variety of intracellular signaling pathways are known to play a role in glioma development and progression, including PI3K/AKT/mTOR, MAPK/ERK (7), p53 (8), RB (9), the Wnt/β-catenin signaling pathway (10), Hedgehog (11), and NF-κB (12).

In recent years, the Hippo-YAP/TAZ pathway, whose key components include Yes-associated protein (YAP) and PDZ-binding motif (TAZ/WWTR1), has gained attention for its role in glioma development (13–16). In this pathway, YAP and TAZ/WWTR1 are phosphorylated by LATS1/2 and thereby inactivated; when the pathway is suppressed, they translocate into the nucleus and activate genes that promote cell proliferation and survival (17–23). Although aberrant activity of YAP/TAZ has been associated with various cancers, their specific roles in gliomas remain unclear (23–28). The available data are conflicting and are mostly derived from in vitro experiments or animal models (29–35). Therefore, investigating the expression of Hippo pathway-related genes in human glioma tissues may help elucidate the underlying

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molecular mechanisms (33–38). The generation of such new scientific data is essential not only to clarify the biological roles of these genes in glioma pathogenesis, but also to assess their potential as biomarkers for diagnosis, prognosis, and prediction of therapeutic response.

In this context, the aim of our study is to analyze the tissue-level expression of the YAP1, WWTR1, LATS1, and PI3KCG genes in tumor samples surgically resected from adult glioma patients using quantitative PCR, in order to evaluate potential alterations in the Hippo-YAP/TAZ signaling pathway and to elucidate its possible role in glioma development.

Table 1 presents a total of 45 glioma-associated genes retrieved from the Human Phenotype Ontology (HPO), listed in the format of Gene Symbol followed by NCBI Gene ID.

Table 1. *A total of 45 glioma-associated genes listed in the Human Phenotype Ontology (HPO) Gene Symbol (NCBI Gene ID)*

NF2 (4771)	IFNG (3458)	PMS2 (5395)
APC (324)	TSC2 (7249)	TGFBR2 (7048)
ZFTA (65998)	ERBB2 (2064)	KRAS (3845)
TSC1(7248)	IDH1 (3417)	EPCAM (4072)
MDM2 (4193)	NF1 (4763)	PIK3CA (5290)
CHEK2 (11200)	RPS20 (6224)	PMS1 (5378)
CDKN2A (1029)	MUTYH (4595)	PTEN (5728)
TP53 (7157)	POLD1 (5424)	IDH2 (3418)
MLH1 (4292)	SEMA4A (64218)	MSH3 (4437)
CDKN1B (1027)	BMPR1A (657)	FGFR1 (2260)
MEN1(4221)	ATM (472)	NSD1 (64324)
CDKN2B (1030)	BRCA2 (675)	APC2 (10297)
CDKN2C (1031)	POLE (5426)	NBN (4683)
CDKN1A (1026)	MSH6 (2956)	SMO (6608)
SETBP1 (26040)	MSH2 (4436)	SPRED1 (161742)

2. METHODS

2.1.Ethical Approval and Informed Consent

This case-control study was approved by the Ethics Committee for Non-Drug and Medical Device Research of the Marmara University Faculty of Medicine on September 20, 2024 (Protocol No: 09.2024.1069), in accordance with international ethical standards and guidelines. Written informed consent was obtained from all participants prior to enrollment, documented with wet signatures. Participants provided explicit consent for both participation and the use of their data. The anonymity and confidentiality of all study participants were rigorously protected throughout the research process.

2.2. Inclusion and Exclusion Criteria

The study included a total of 30 glioma patients and 20 control individuals. Glioma group samples were obtained from patients aged 18–80 years who underwent neurosurgical resection at the institution's affiliated hospital, had no prior history of recurrence, and had not received chemotherapy or radiotherapy before surgery. Control samples consisted of dura mater tissues collected as surgical waste from patients undergoing neurosurgical procedures for non-neoplastic conditions (e.g., acute subdural hematoma, aneurysm, hemangioblastoma), with no pathological evidence of tumor. Samples with insufficient RNA and/or cDNA quantity or quality, or samples in which the target genes could not be amplified via qPCR, were excluded from the study.

2.3. Tissue Collection

Tumor tissues obtained from patients with a preoperative diagnosis of glioma, later confirmed by histopathological evaluation, were weighed using a precision balance. Specimens were stored at +4°C in RNAlater solution until the RNA isolation step.

2.4. RNA Isolation from Tissue Samples

Total RNA was isolated using RNAzol® RT reagent. Tissue samples were mechanically fragmented, transferred to tubes with ceramic beads, and treated with 1 mL of RNAzol® RT. Homogenization was performed using the MagNA Lyser® system at 7000 rpm for two 15-second cycles. The supernatant was transferred to 2 mL tubes, mixed with 0.4 mL RNase-free water, vortexed, and incubated for another 15 minutes. Following centrifugation at 12,000 × g for 15 minutes to remove DNA and proteins, the supernatant was mixed with 0.4 mL of 75% ethanol and incubated for 10 minutes. mRNA was precipitated by centrifugation at 12,000 × g for 8 minutes. RNA pellets were washed twice with 75% ethanol and centrifuged at 4000 × g for 1 minute. After ethanol evaporation, pellets were dissolved in 30 µL of nuclease-free water. RNA concentration and purity were assessed using a NanoDrop™ 2000/2000c spectrophotometer. Samples were stored at –80°C until cDNA synthesis.

2.5. cDNA Synthesis

Complementary DNA (cDNA) synthesis was performed using a commercial kit (OneScript® Plus cDNA Synthesis Kit, Applied Biological Materials [abm], Canada) with an input concentration of 200 ng/µL of total RNA. Reaction components and their respective volumes are provided in Table 2, and the total reaction volume was adjusted to 20 µL with nuclease-free water. The reverse transcription reaction was carried out in a T100 Thermal Cycler under the following optimized conditions: 15 minutes at 53°C, followed by 5 minutes at 85°C. The concentration and purity of synthesized cDNA were verified using the NanoDrop™ 2000/2000c. Samples were stored at -20°C until use in RT-qPCR.

Table 2. *Component volumes for cDNA synthesis using the OneScript® Plus cDNA Synthesis Kit*

Component	Amount
5× RT Buffer	4 µL
dNTPs	1 µL
Oligo Primer	1 µL
mRNA	Adjusted to 200 ng/µL
OneScript Plus RTase	1 µL
Nuclease-Free Water	To a final volume of 20 µL

2.6 Quantification of Gene Expression by Real-Time PCR (RT-qPCR)

Following cDNA synthesis, the expression levels of LATS1, YAP1, PI3KCG, and WWTR1 genes were quantified using a commercial real-time PCR kit (Blastaq™ 2X qPCR MasterMix, Applied Biological Materials [abm], Canada), in accordance with the manufacturer's protocol. The reaction components and volumes are listed in Table 3. GAPDH was used as the internal reference gene. Template cDNA was diluted to contain 100 ng/µL per reaction. All RT-qPCR analyses were performed on a BIO-RAD® CFX96 Real-Time PCR Detection System. Thermal cycling conditions are detailed in Table 4.

Table 3. *Components and volumes used for gene expression analysis with the Blastaq™ 2X qPCR MasterMix kit*

Component	Amount (per reaction)
BlasTaq™ 2X qPCR MasterMix	10 µL
Forward Primer (10 µM)	0.5 µL
Reverse Primer (10 µM)	0.5 µL
cDNA Template	1 µL
Nuclease-Free Water	Up to 20 µL total volume

Table 4. *RT-qPCR reaction conditions*

Step	Temperature	Time	Cycles
Initial Denaturation	95 °C	3 minutes	1 cycle
Denaturation	95 °C	15 seconds	
Annealing/Extension	60 °C	1 minute	40 cycles
Melt Curve Analysis	65 °C → 95 °C	0.5 °C increment every 5 seconds	1 cycle

2.7 Statistical Analysis

Comparative expression analyses were performed between the glioma and control groups based on cycle threshold (Ct) values for target and reference genes. A Ct cut-off value of 37 was defined; samples exceeding this threshold were repeated to ensure data reliability. For each sample, ΔCt values were calculated by subtracting the Ct of GAPDH from that of the target gene. Then, mean ΔCt values of the control group were used as calibrators to calculate ΔΔCt values for the glioma samples. The ΔΔCt values were further analyzed using the 2^-ΔΔCt method to determine fold changes in gene expression. All calculations were performed using GeneGlobe software, and raw data were recorded in Microsoft Excel for statistical analysis. The statistical significance of the study was evaluated based on p values, while additional measures supporting clinical relevance such as fold regulation and fold change effect sizes, are also presented in Table 5.

Table 5. *Expression analysis results demonstrating significant downregulation of the YAP1 gene in glioma patients*

Gene Symbol	Fold Regulation	Fold Change	p-Value
LATS1	-1.42	0.71	0.970677
YAP1	-2.60	0.39	0.033092
PI3KCG	-2.39	0.42	0.253500
WWTR1	-1.32	0.76	0.669688
GAPDH (Housekeeping)	1.00	1.00	***N/A**

(*) The designation of "N/A" (Not applicable) for the p-value in the GAPDH (Housekeeping) row is due to its role as the reference/normalizing gene. Since GAPDH expression is fixed at 1.00 for both fold regulation and fold change, no statistical test is applicable; therefore, a p-value is not computed.

3. RESULTS

Quantitative gene expression analysis performed using GeneGlobe software revealed a fold change value of 0.39 for the YAP1 gene, indicating an approximate 61% reduction in expression compared to the control group. This substantial decrease supports the downregulation of YAP1 in glioma tissue samples. Furthermore, the corresponding fold regulation value of –2.60 reinforces the interpretation that YAP1 expression is significantly suppressed in glioma patients.

Importantly, the p-value of 0.033092 confirms that this difference is statistically significant, suggesting that the observed downregulation is unlikely to be due to random variation.

The p values for the other genes were calculated as follows: LATS1: 0.970677, PI3KCG: 0.253500, and WWTR1: 0.669688. Collectively, the data summarized in Table 5 demonstrate a significant downregulation of YAP1 gene expression in glioma patients, supporting its potential involvement in glioma pathogenesis.

4. DISCUSSION

In this study, we investigated the role of the Hippo-YAP/TAZ signaling pathway in glioma pathogenesis through targeted gene expression analysis. Our findings demonstrated a statistically significant downregulation of the YAP1 gene in glioma patients. Analysis via GeneGlobe software revealed a fold change of 0.39, a fold regulation of –2.60, and a p-value of 0.033092, collectively indicating a marked and statistically meaningful reduction in YAP1 expression in tumor tissues compared to healthy controls. While YAP1 has been widely recognized for its oncogenic potential in various solid tumors, its function in central nervous system malignancies, particularly gliomas, appears to be more context-dependent. The significant downregulation observed in our cohort supports the hypothesis that YAP1 may exhibit a tumor-suppressive role in glioma biology, in contrast to its well-established oncogenic role in other cancers.

Given the complex interplay between Hippo pathway components and their potential crosstalk with other

oncogenic signaling cascades (e.g., PI3K/AKT, MAPK/ERK), a more comprehensive analysis of the entire pathway and its regulatory networks is warranted. The variability in the expression and function of YAP/TAZ across tumor types and within glioma subtypes highlights the necessity for context-specific investigations rather than generalized assumptions based on other malignancies.

In contrast to our findings, the 2012 study by Ji et al. reported a significant association between reduced LATS1 gene expression and glioma progression; specifically, lower LATS1 levels were observed in high-grade gliomas, highlighting its potential tumor suppressor role (39). Additionally, in the 2016 study by Li et al., TAZ (WWTR1) expression was found to be upregulated in glioma samples and positively correlated with tumor grade (40). In other cancer types, LATS1 has been associated with breast cancer and head and neck squamous cell carcinomas; PI3KCG has been shown to exhibit hyperactivation in solid tumors such as colorectal and gastric cancers; and increased expression of WWTR1 (TAZ) has been linked to metastasis in a wide range of cancers including melanoma, head and neck, breast, and lung cancers.

Our study provides novel, tissue-level evidence regarding YAP1 gene expression in glioma patients**,** contributing to the growing body of literature on Hippo signaling in neuro-oncology. However, to validate and expand upon these preliminary findings, future research should include larger patient cohorts**,** comparative analysis across glioma subtypes**,** and integrative assessment of additional Hippo pathway components**.** Such investigations will be critical to fully elucidate the functional implications of YAP1 dysregulation and its potential utility as a biomarker or therapeutic target in glioma.

5. CONCLUSION

This study examined the expression of YAP1, a central Hippo-YAP/TAZ pathway component, in glioma tissues and found it significantly downregulated compared to healthy controls. These results suggest a potential tumor-suppressive role for YAP1 in glioma, contrasting its established oncogenic role in other solid tumors and indicating its function may vary by tumor subtype and biological context.

The reduced YAP1 expression highlights glioma's molecular heterogeneity and implies that the Hippo pathway may act in a context-dependent manner, modulated by tumor type and microenvironment. Thus, the YAP-TAZ axis should be reconsidered not only as an oncogenic driver but as a modulator of tumor behavior in the CNS.

Though preliminary, these findings offer important insight into glioma pathogenesis. Validation through larger cohorts, subtype-specific analyses, and comprehensive evaluation of Hippo components is essential to clarify the clinical relevance and therapeutic potential of YAP1 dysregulation in neuro-oncology.

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