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Research Article

Quaking Gene Expression as a Prognostic Marker in Neural Inflammation Disorders

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ABSTRACT

Background and objectives: Cancer stem cells (CSCs) may contribute to tumor initiation, distant metastasis, and chemo-resistance. Quaking (QKI) is a RNA binding protein, a tumor suppressor, and a well-known stem cell biomarker in central nervous system (CNS) cancer. The aim of this study was to identify the potential of QKI mRNA as a prognostic marker for CNS cancer.

Methods: The Cancer Genome Atlas (TCGA) was investigated for gene expression profile within CNS cancer data. Further analysis was done through cBioPortal and COSMIC to explore the QKI gene mutation(s). Moreover, QKI mRNA levels were evaluated by using SAGE Genie tools. The Kaplan-Meier Plotter was utilized to identify prognostic role of QKI mRNA levels in these cancers.

Results: Higher levels of QKI mRNA were detected in brain cancer tissues. Altered QKI gene expression was observed in 2% (56/2,958) of patients. Missense QKI gene mutation rate was 35.29%. The QKI gene alterations led to deleterious amino acid changes, including P181R, Q112P, and A220G. Altered QKI gene expression was significantly correlated with reduced survival rate ($p<0.05$).

Conclusion: The QKI gene is most expressed in brain tissues. In patients with gliomas, altered QKI expression/mutation is associated with a shorter survival rate. The findings of this study indicate that the QKI gene mutations can be considered as a potential prognostic biomarker for brain malignancies.

Keywords: Quaking; Biomarker; The Cancer Genome Atlas; neural inflammation disorders

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INTRODUCTION

The extracellular matrix, mesenchymal stem cells, cancer-associated fibroblasts, endothelial cells, immune cells, and a complex network of cytokines and growth factors make up the tumor microenvironment (1). Tumor tissues are composed of a variety of cancer cells, including cancer stem cells (CSCs), which can differentiate into cancer cells (2,3). The stem cell niche is a milieu in which tissue-specific stem cells in normal organs maintain their stemness. The most common and deadly primary brain tumor is glioblastoma (GBM). Glioma stem cells are thought to have a role in tumors' resistance to standard therapy. These cells have distinct surface markers, control specific signaling pathways, and play an important role in the development of glioma vessels (4,5). Niches have been identified in multiple cancers, and they often assimilate the signals of niches for the tissues from which the CSCs appeared (6,8). However, it is not understood how these cells still manage to preserve their nature when they invade and migrate from their homes to other areas where ideal niches are less likely to be available (9).

Brain tumors and metastases represent a heterogeneous set of conditions (10). Primary brain tumors such as astrocytic tumors, oligodendrogliomas, ependymomas, and mixed gliomas are all referred to as gliomas (11). Adults' most usual lethal brain tumor is grade IV glioma also known as GBM, with over 10,000 cases diagnosed annually in the United States (12). Evidence shows that a population of GBM cells has a stable ability to self-renew and produce new tumors that keep the features of original tumors (13,14).

The ability of stem cells to invade and migrate raises the question of how these cells maintain their stemness when they come into contact with varied ingredient compositions of a new microenvironment (15). Therefore, looking for genetic changes could help CSCs to keep stemness outside their niches (16). The Quaking gene (QKI), as a tumor suppressor gene, may poten¬tially affect CSC stemness. The gene encodes QKI, a STAR-family RNA-binding protein that is involved in RNA homeostasis (19,20). The RNA-binding protein QKI is highly expresses in brain cells (17), and play a regulatory role in brain development via modulating the stability of mRNAs that promote differentiation and inhibiting cell cycle progress (18). In the present study, the significance of QKI mRNA in human central nervous system (CNS) cancer was evaluated by using the Cancer Genome Atlas (TCGA) data portals.

MATERIALS AND METHODS

Analysis for QKI mutations

The Catalog of Somatic Mutations in Cancer (COSMIC) database was used to analyze QKI mutations (21). Pie charts were generated for a distribution survey and substitutions on the coding strand in CNS cancer.

CBioPortal analysis for alteration frequency of QKI

Alteration frequency of QKI mRNA was performed using cBioPortal for Cancer Genomics (22,23). All searches were performed according to the cBioPortal's online instructions. The database query was based on mutation and altered expression of the QKI in six CNS/brain studies (Brain Low Grade Glioma (TCGA, Firehose Legacy), Brain Low Grade Glioma (TCGA PanCancer Atlas), GBM (TCGA, Cell 2013), GBM (TCGA, Nature 2008), Low-Grade Gliomas (UCSF, Science 2014), Merged Cohort of LCG and GBM (TCGA, Cell 2016), including 3010 samples of 2958 patients (summarized in Figure 1). The overlapped studies were discarded.

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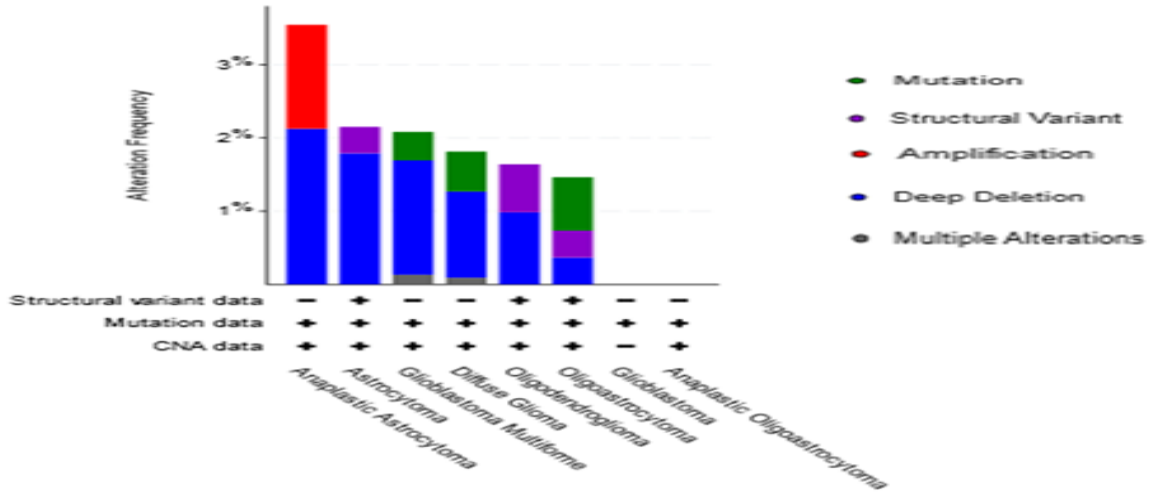

Figure 1. Summary of QKI gene alteration in glioma samples analyzed by cBioPortal

Serial analysis of gene expression (SAGE)

All available published SAGE data were used to analyze QKI expression in normal and cancerous tissues. Digital QKI gene expression profiles were analyzed using SAGE Genie tools (24).

Kaplan-Meier plotter analysis

The prognostic value of the QKI gene in CNS cancer was analyzed using the Kaplan-Meier plotter (25) and PPISURV (26). Overall survival of the patient with high and low levels of QKI was shown by using a Kaplan-Meier survival plot.

RESULTS

QKI mutation in glioma

The information of mutations and mutation types were generated using cBioPortal. Mutation data for QKI were only provided in 17 patients (Table 1). Missense mutation rate was 35.29% (6/17). Furthermore, deletions resulting from frameshifts were observed in 29.41% (5/17) of mutant samples of glioma cancer. Missense mutations were G163984476 in 50% (3/6), G163956153 in 33.33% (2/6), and C163899861 in 16.67% (1/6) of patients. Alteration frequency of QKI mutation in CNS cancer was analyzed by using cBioPortal. Moreover, 56 of 2,958 (2%) patients had altered QKI gene.

QKI mRNA in Glioma cancer tissues

The expression profile of QKI was found by using the SAGE Digital Gene Expression Display. Higher levels of QKI mRNA were mainly in the brain, spinal cord, breast, stomach, skin, and muscle cancer tissues, compared with their matched normal tissues (Figure 2).

No correlation was observed between the QKI gene expression and its relative protein copy numbers in different types of QKI gene alterations (Figure 3), while the opposite role of QKI mRNA was observed in CNS cancer (p=0.005). In addition, we analyzed the prognostic roles of QKI mRNA in subtypes of CNS cancer, and the results showed that QKI mRNA had no influence on mixed-type CNS cancer (p=0.14).

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Table 1. Altered *QKI* gene information in 17 patients

Sample ID	Cancer type	Cancer Type Detailed	Protein Change	Mutation Type	Copy	Variant Type	Sex
TCGA-28-5208-01	Glioma	Diffuse Glioma	V99Lfs*31	Frame_Shift_Del	DEL	Diploid	Male
TCGA-06-0650-01	Glioma	Diffuse Glioma	P181R	Missense_Mutation	SNP	Diploid	Female
TCGA-06-0155-01	Glioma	Diffuse Glioma	Q112P	Missense_Mutation	SNP	ShallowDel	Male
TCGA-28-5207-01	Glioma	Diffuse Glioma	R256Kfs*18	Frame_Shift_Del	DEL	DeepDel	Male
TCGA-06-0237-01	Glioma	Diffuse Glioma	X312_splice	Splice_Site	DEL	Gain	Female
TCGA-OX-A56R-01	Glioma	Diffuse Glioma	E174del	In_Frame_Del	DEL	ShallowDel	Male
TCGA-FG-5965-01	Glioma	Diffuse Glioma	A220G	Missense_Mutation	SNP	Diploid	Female
TCGA-FG-5965-01	Glioma	Oligoastrocytoma	A220G	Missense_Mutation	SNP	Diploid	Female
TCGA-FG-5965-01	Diffuse Glioma	Oligoastrocytoma	A220G	Missense_Mutation	SNP	Diploid	Female
TCGA-28-5208-01	Glioma	Glioblastoma Multiforme	V99Lfs*31	Frame_Shift_Del	DEL	Diploid	Male
TCGA-06-0650-01	Glioma	Glioblastoma Multiforme	P181R	Missense_Mutation	SNP	Diploid	Female
TCGA-28-5207-01	Glioma	Glioblastoma Multiforme	R256Kfs*18	Frame_Shift_Del	DEL	DeepDel	Male
TCGA-06-0237-01	Glioma	Glioblastoma Multiforme	X312_splice	Splice_Site	DEL	Gain	Female
TCGA-HT-7689-01	Diffuse Glioma	Oligodendroglioma	QKI-AKAP7	fusion	FUSION	ShallowDel	Female
TCGA-DU-6404-01	Diffuse Glioma	Oligodendroglioma	PACRG-QKI	fusion	FUSION	Diploid	Female
TCGA-HT-8114-01	Diffuse Glioma	Oligoastrocytoma	PACRG-QKI	fusion	FUSION	Diploid	Male
TCGA-WY-A859-01	Diffuse Glioma	Astrocytoma	NSD2-QKI	fusion	FUSION	Diploid	Female

Data includes six duplicate mutations in patients with multiple samples

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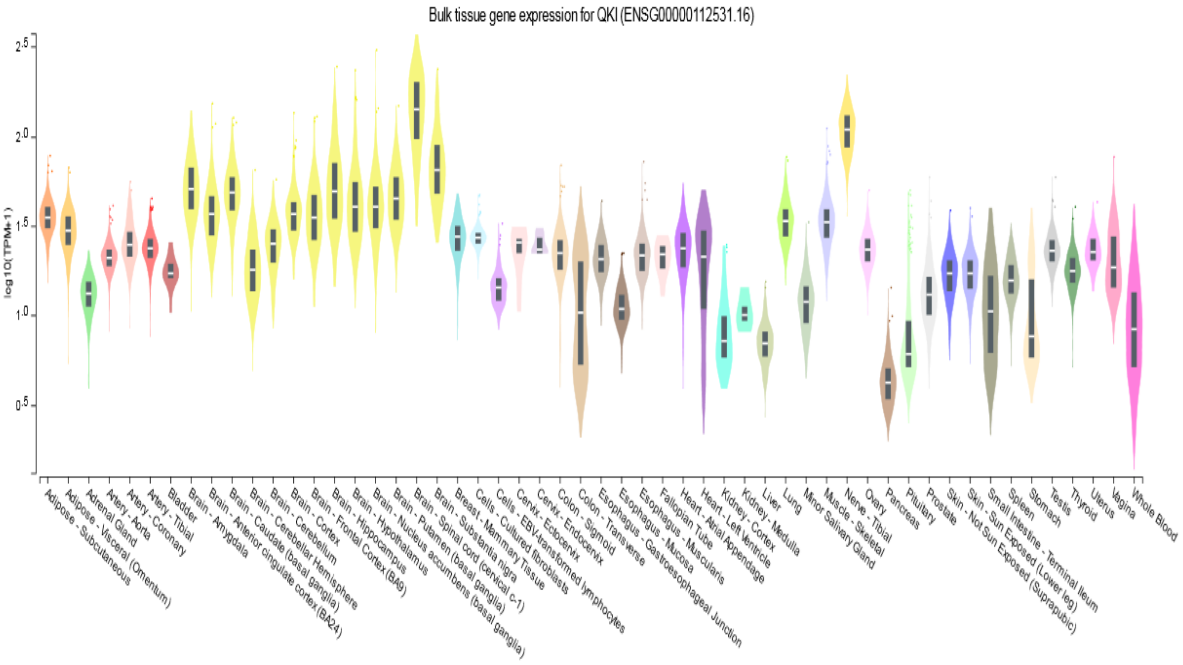

Figure 2. The alteration frequencies of the *QKI* gene across different cancer studies. Expression of the *QKI* gene was highest in brain (GTEx portal) (38).

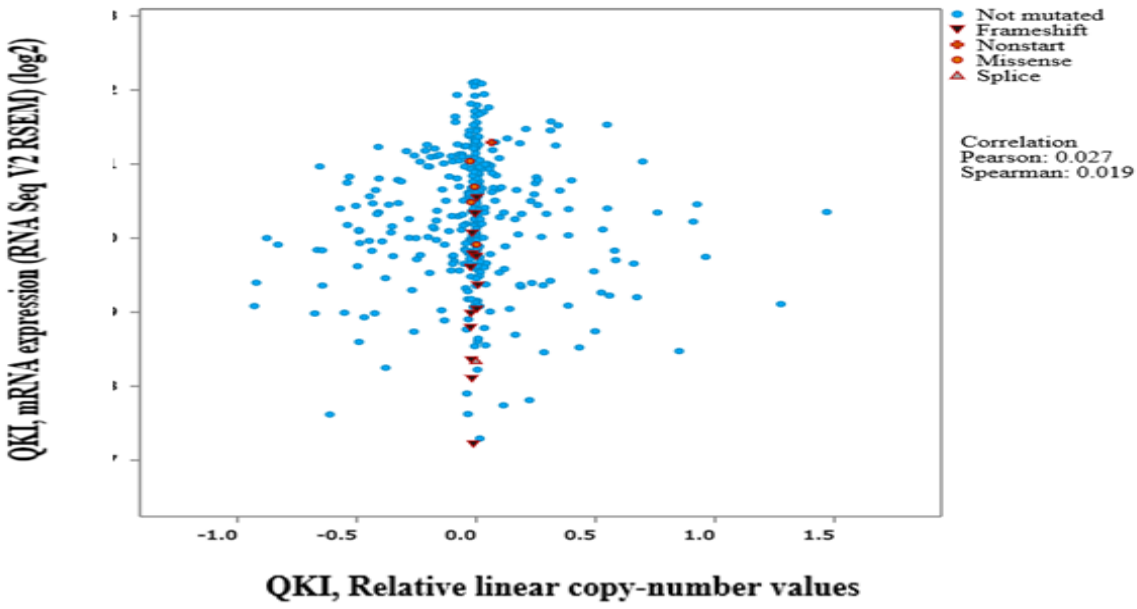

Figure 3. The mRNA expression of QKI

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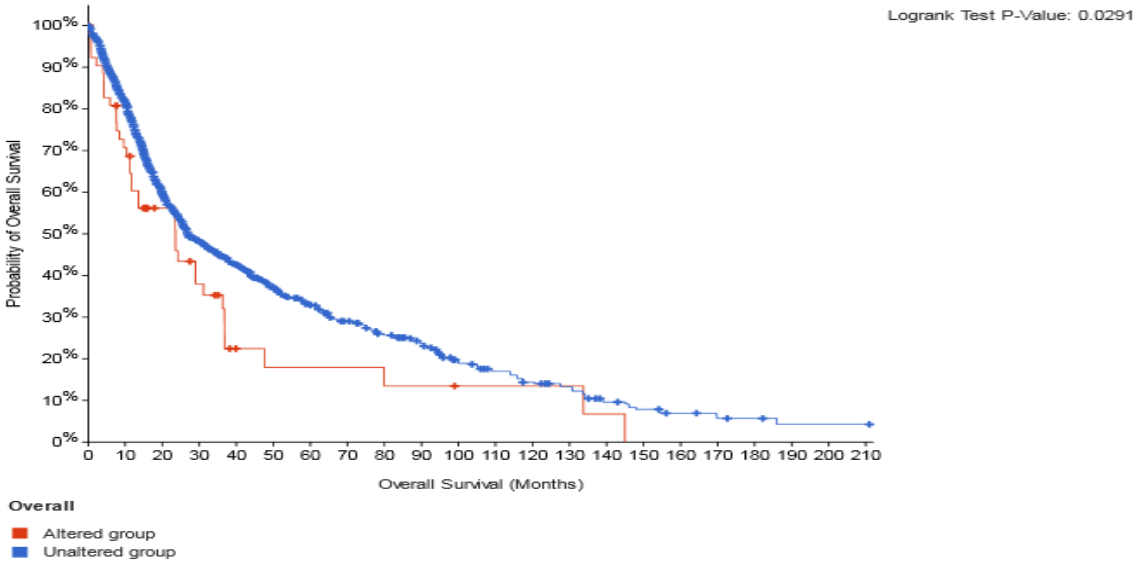
Determination of QKI gene alterations across different cancers and overall survival rate

The QKI gene alterations (including mutations) led to amino acid changes with deleterious impacts on protein function. These included P181R, Q112P, and A220G. The QKI mutations and deletions were less frequent than amplifications in cancer patients. In addition, the QKI gene was notably amplified in several cancers, including stomach, skin, colon, and CNS cancers. In stomach cancer, QKI protein mutations were observed in 17 patients.

Further data showed significantly reduced overall survival rate of patients with altered QKI gene when compared to the unaltered group (Figure 4).



	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
Altered group	55	38	23.60 (11.70 - 36.79)
Unaltered group	2759	1338	26.93 (25.70 - 30.67)

Figure 4. Disease-free survival Kaplan-Meier estimate. Data show that patients with altered QKI gene had less overall survival (~6 years) than those with unaltered QKI gene (p=0.0291)

DISCUSSION

The niche is unique where preserved stem cells are undifferentiated and circulated through self-renewal. As seen for somatic stem cells, many studies have identified a niche for CSCs that are important for preserving their self-renewal and promoting tumorigenesis (6,8). However, these

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seemingly specialized CSC niches are absent when CSCs invade other areas or tissues by various routes and metastasize to distant organs via circulation. This raises the question how CSCs keep their self-renewal power outside their niches. Shingu et al. showed that postnatal deletion of Pten and Trp53 could expand the neural stem cell (NSC) population in subventricular zones (SVZs). The lack of NSC self-renewal outside SVZs suggests the inability of NSCs to uphold self-renewal outside their niches, thereby preventing Pten−/−; Trp53−/− premalignant-NSCs from developing into gliomas. They also suggested that Qk deletion in Pten−/−; Trp53−/− premalignant-NSCs improved self-renewal, especially outside their niches, promoting gliomagenesis (3).

Previously, Zheng et al. showed that deletion of Pten and Trp53 in embryonic NSCs could raise sphere-forming capacity/stemness by upregulating Myc, leading to low-grade development and showing that embryonic development NSCs are more manageable to transform than postnatal NSCs (27). Nevertheless, in the model of Zheng et al. (with deletion of Pten and Trp53 in embryonic NSCs), GBM developed with a much more extended latency period (105 days versus 300 days) and lower penetrance (92% versus 25%), suggesting that other genetic or epigenetic changes still must be gained to allow embryonic premalignant neural stem cells to preserve self-renewal outside their niches, to per¬mit full progression of glioma.

The QKI gene has long been studied as a critical gene for oligodendrocyte differentiation and myelin formation (20,28). Other studies confirmed that QKI is needed for oligodendrocyte differentiation (3). This gene is also important for developing smooth muscle, endothelial cells, and monocytes or macrophages (20). In addition, QKI is expressed in NSCs and is a major regulator of self-renewal and differentiation. It has been shown that QKI may regulate RNA homeostasis, including RNA stability, splicing, translation, miRNA processing, and circular RNA biogenesis (19,21).

In support of the importance of QKI as a tumor sup¬pressor, a previous analysis of the TCGA database of GBM demonstrated QKI as the sole gene within the small common region of the 6q26 deletions (32% deletion rate and 1.7% mutation rate) (3,29). Furthermore, QKI downregulation by methylation of the QKI locus (chromosome 6, base 163,755,107) was also

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reported in 50 of 250 (20%) GBM samples (30). In angiocentric glioma, nearly 90% of tumors have an MYB-QKI translocation, which disrupts QKI (31,32). Other than in gliomas, QKI is a tumor suppressor in other malignancies, including gastric (33), breast (34), colon (35), prostate (36), and oral (37) cancers.

CONCLUSION

Expression of the QKI gene is highest in the brain tissue. Altered QKI gene expression/mutation is correlated with short survival rates in patients with gliomas. The results of the present study suggest that the QKI gene alteration could be considered as a novel prognosis biomarker for CNS/brain cancers.

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Ethics approvals and consent to participate

Not applicable.

Conflict of interest

The authors declare that there is no conflict of interest regarding publication of this article.

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