Leveraging eQTL Analysis to Identify Genes Associated with Glioblastoma Multiforme Survival

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Background

- Glioma is the most prevalent malignant brain tumor, comprising almost 80% of malignant brain tumors in adults.
- Glioblastoma Multiforme (GBM), the most common form of glioma, has an average survival post diagnosis of 12 to 15 months.
- Integrative genomic, computational and molecular biology research may help elucidate the drivers and therapeutic targets in gliomas, specifically in GBM.
- The aim of this project is to assess how genomic loci known to associate with GBM risk associate with gene expression, and whether the associated genes correlate with GBM disease progression.

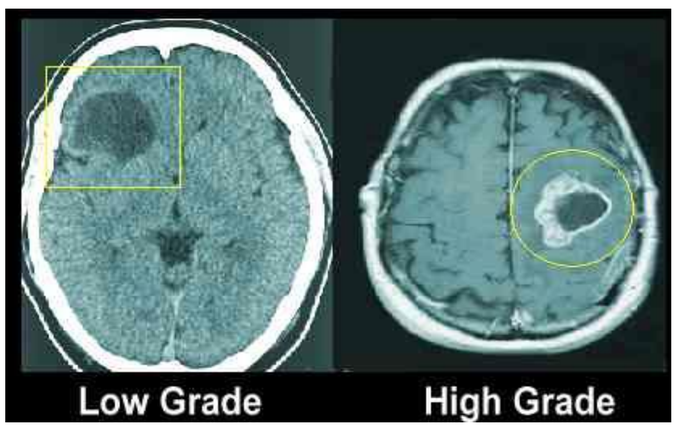

Fig 1: MRI scan of glioma and GBM (http://www.aboutcancer.com/mri_gbm.htm)

Methods

- This leverages data from the GTEx (a large rapid autopsy molecular profiling program of non-cancerous tissues) and the Cancer Genome Atlas (TCGA).
- We carried out extensive literature review to identify SNPs (Single Nucleotide Polymorphism) associated with glioblastoma
- Literature review resulted in 27 risk loci.
- We obtained RNAseq gene expression profiles for all normal brain tissue samples and obtained brain-specific eQTLs (*Cis* and *Trans*) from the GTEx portal.
- P value of 0.05 was used to filter genes
- Queried our filtered unique genes on GBM mRNA expression data in TCGA and derived clinical information relating to these patients.
- Subsequently, survival analysis was carried out using our genes of interests as exposures.
- Next t-test was carried out on data from Black or African American patients and White patients to determine if the genes are differentially expressed between the two races.
- Correlation coefficient was calculated to observe the roles the filtered genes play across age.

Patient Characteristics

Race (African-American White Asian)	50 495 13
Sex (Male Female)	342 216
Average survival (Months)	16.5
Average diagnostic age	57.8
Average days to fatality from diagnosis	479.7

Table 1: Patient characteristics from TCGA GBM provisional dataset.

Results

- 423 unique SNP-gene pairs comprising 279 unique genes associated with the identified loci were obtained after filtering.
- A total of 12 were derived after the COXPH survival analysis.
- From the survival analysis carried out, the three most significant genes were PRKCH, QSOX1 and ZBTB46 using specific criteria.
- For better visualization, survival curves and correlation plots were created for some of the significant genes.
- From the t-test, it was proven that all 12 genes are not differentially expressed between the two studied races.

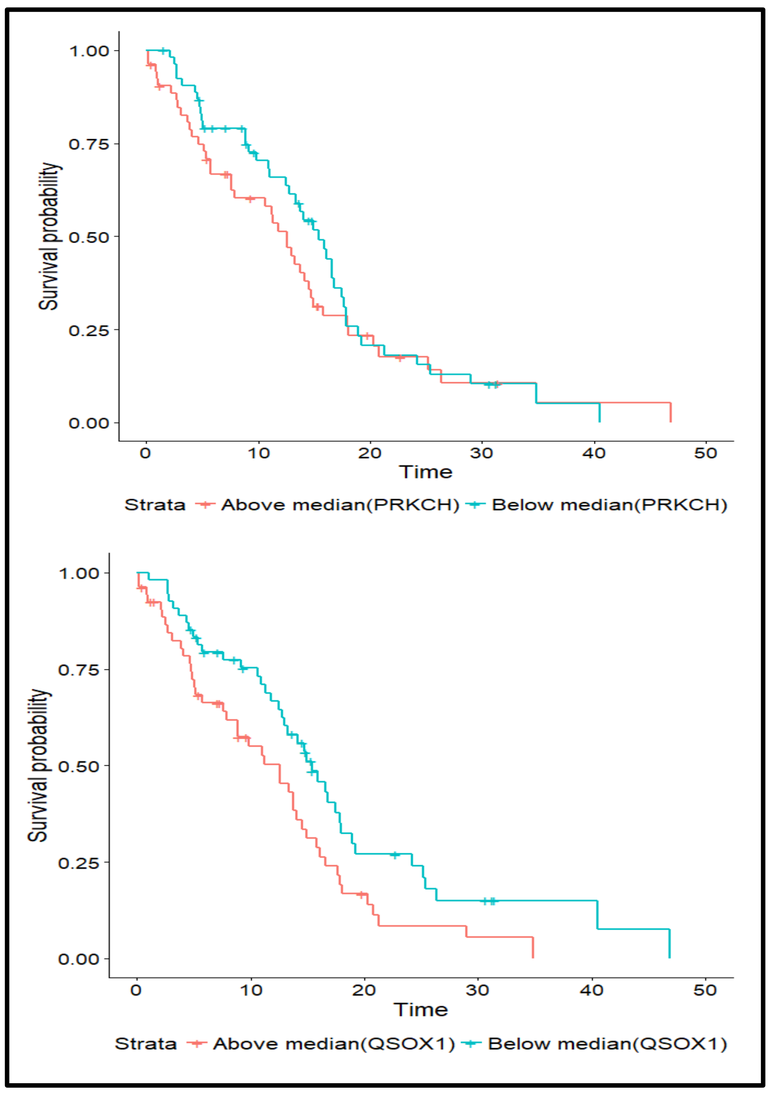

Figure 2: Survival curve for the 3 most significant genes.

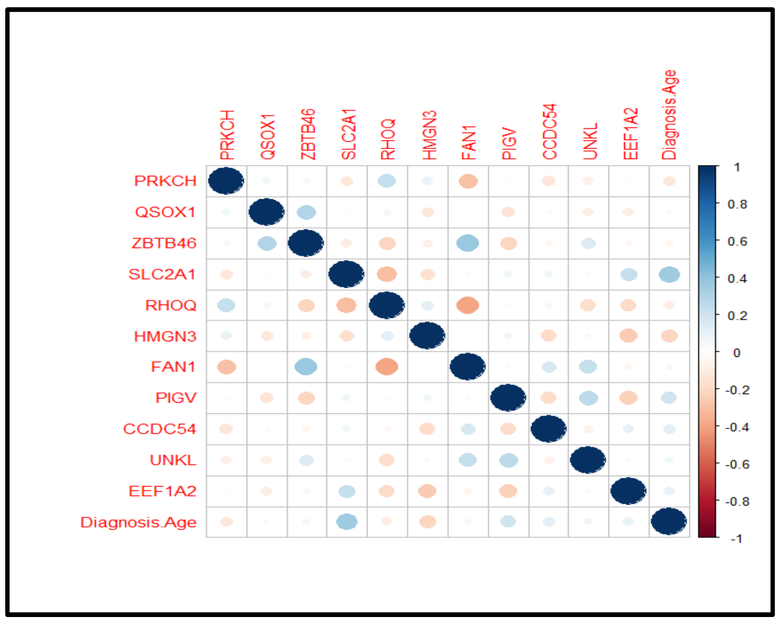

Figure 3: Correlation coefficient plot for the identified genes.

Conclusions

- This project highlights possible functional roles for known GBM risk SNPs by identifying 279 genes which are transcriptionally associated with these risk loci.
- Through survival analysis using patient outcome clinical data, it was identified that a subset of these genes may predict disease progression.
- PRKCH belongs to a family of serine and threonine kinases that phosphorylates a variety of proteins. PRKCH is activated in several tumors causing cell proliferation, migration and tumor progression.
- QSOX1 oxidizes thiols during protein folding. Over expression of this enzyme has been seen in several types of cancer as tumor cells can take advantage of the oxidative environment.
- ZBTB46 is a transcriptional factor that imposes classical dendritic cell (cDC) identity. Tumor microenvironment can convert tumor DC into immunosuppressive T-cells.
- Future validation in independent cohorts may help clarify the potential clinical prognostic and treatment prediction roles for these genes.