Genomic expression patterns distinguish long-term from short-term glioblastoma survivors: A preliminary feasibility study

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Abstract

We used microarray analysis to investigate associations between genotypic expression profiles and survival phenotypes in patients with primary glioblastoma (GBM). Tumor samples from 7 long-term glioblastoma survivors (> 24 months) and 13 short-term survivors (< 9 months) were analyzed to detect differential patterns of gene expression between these groups and to identify genotypic subclasses of glioblastomas that correlate with survival phenotypes. Five unsupervised and three supervised clustering algorithms consistently and accurately grouped the tumors into genotypic subgroups corresponding to the two clinical survival phenotypes. Three unique prospective mathematical classification algorithms were subsequently trained to use expression data to stratify unknown glioblastomas between survival groups and performed this task with 100% accuracy in validation studies. A set of 1478 genes with significant differential expression (p < 0.01) between long-term and short-term survivors was identified, and additional mathematical filtering was used to isolate a 43-gene "fingerprint" that distinguished survival phenotypes. Differential regulation of a subset of these genes was confirmed using RT-PCR. Gene ontology analysis of the fingerprint demonstrated pathophysiologic functions for the gene products that are consistent with current models of tumor biology, suggesting that differential expression of these genes may contribute etiologically to the observed differences in
These results demonstrate that unique expression profiles characterize genotypic subsets of primary GBMs associated with differential survival phenotypes, and these profiles can be used in a prospective fashion to assign unknown tumors to survival groups. Future efforts will focus on building more robust classifiers and identifying additional subclasses of gliomas with phenotypic significance.

**Keywords:** Glioma; Glioblastoma; Genomics; Microarray; Classification

**Article Outline**

**Results**
- Using expression profiles for phenotypic class discovery
  - Selection of genes differentially expressed between long-term and short-term survivors
  - Unsupervised analysis
  - Supervised analysis
  - Building a prospective classifier—using genotype to predict phenotype
  - The survival fingerprint—analyzing differential expression patterns that distinguish survival phenotypes
  - Identifying genes that distinguish survival groups
  - Verifying expression data
  - Functional characteristics of genes that distinguish survival groups

**Discussion**
- Patient selection and inclusion criteria
- Differences in extent of initial resection between survival groups
- Class discovery
- Differential genomic variability between phenotypic groups
- Functional significance of the survival fingerprint

**Conclusions**

**Materials and methods**
- Inclusion criteria
- Sample selection
- Demographics
- Histologic examination
- RNA extraction and purification from tissue samples
- Control RNA
- Microarrays
- Real-time RT-PCR
- Data analysis

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**Appendix A. Supplementary data**

**References**

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