4262: Mathematically Universal and Biologically Consistent Astrocytoma Genotype Encodes for Transformation and Predicts Survival Phenotype

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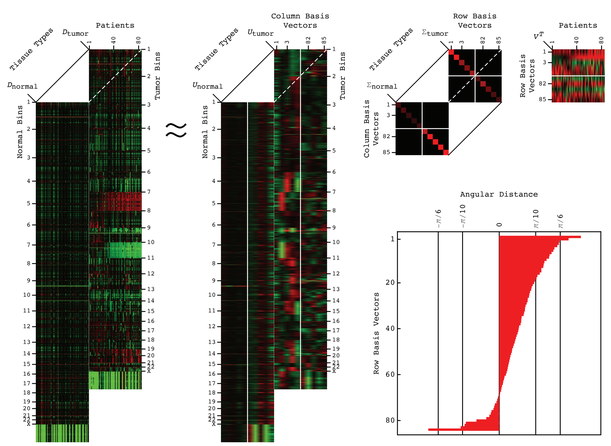
Mathematical Framework: GSVD

Recurring DNA alterations have been recognized as a hallmark of cancer for over a century, and observed in astrocytoma genomes for decades. Only recently, however, a copy-number genotype predictive of an astrocytoma survival phenotype was discovered, and only by using the generalized singular value decomposition (GSVD) [1,2]. We formulated the GSVD as a comparative spectral decomposition that can simultaneously identify the similar and dissimilar between two column-matched matrices, and, therefore, create a single coherent model from two datasets recording different aspects of a single phenomenon [3–5].



In recent comparisons of microarray-profiled patient-matched glioblastoma (GBM) and, separately, lower-grade astrocytoma tumor and normal genomes, the GSVD invariably separated the tumor-exclusive genotype and phenotype from those that occur in the normal genomes and from experimental batch effects. The tumor-exclusive genotype invariably predicted the survival phenotype statistically better than any other indicator of astrocytoma.

Here we use the GSVD to compare whole-genome sequencing (WGS) read count profiles of patient-matched astrocytoma tumor and normal DNA. The GSVD uncovers a tumor-exclusive genome-wide pattern of copy-number alterations (CNAs) [6].

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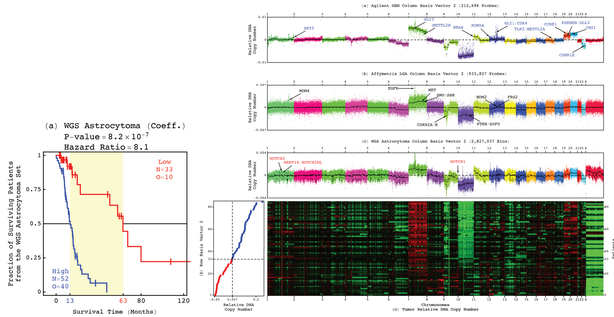
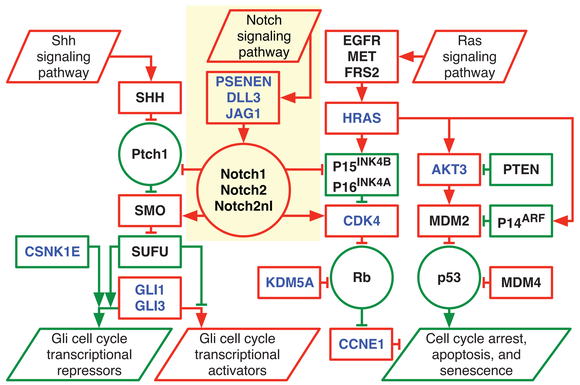
Biological Results: Astrocytoma Genotype-Phenotype

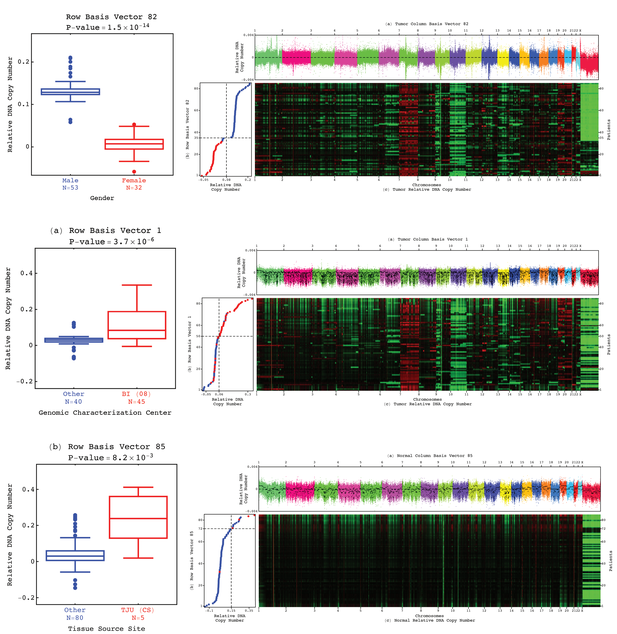
We find that, first, this WGS astrocytoma pattern is bounded by the microarray GBM and lower-grade astrocytoma patterns. Like the microarray patterns, the WGS pattern is correlated with an approximately one-year median survival time.



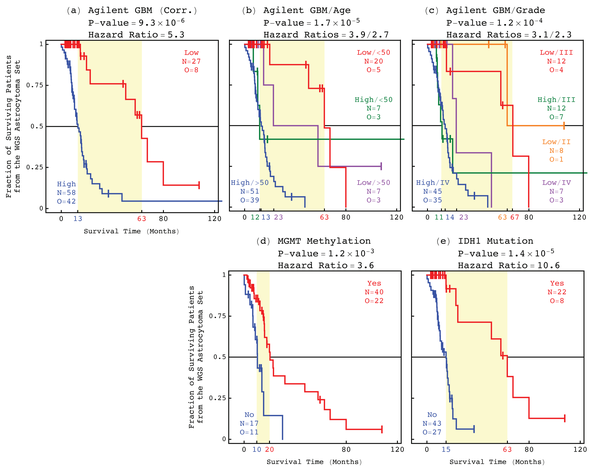
By filling in gaps in the genome, the WGS pattern reveals that this biologically consistent genotype encodes for transformation via the Notch together with the Ras and Shh signaling pathways.



Second, like the GSVDs of the microarray profiles, the GSVD of the WGS profiles separates the tumor exclusive pattern from normal copy-number variations (CNVs) and from experimental sources of variation. These include the WGS technology-specific effects of guanine-cytosine (GC) content variations across the tumor and normal genomes, which are correlated with experimental batches.



Third, by identifying the biologically consistent phenotype among the WGS-profiled tumors, the GBM pattern proves to be a technology-independent predictor of astrocytoma survival and responses to chemotherapy and radiation, statistically better than the patient's age and tumor's grade, the best other indicators of astrocytoma, and existing tests for *MGMT* promoter methylation and *IDH1* mutation.



Conclusion

We conclude that by using the complex structure of the data, rather than simplifying them as is commonly done, comparative spectral decompositions, such as the GSVD, underlie a mathematically universal description of the genotype-phenotype relations in cancer that other methods miss [7–9].

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