Medical Prediction from Comparison of Patient-Matched Genomic Profiles

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Introduction

Despite recent large-scale profiling efforts, the best prognostic predictor of glioblastoma multiforme (GBM), the most common brain tumor in adults, remains the patient's age at diagnosis [1]. We describe a global pattern of tumor-exclusive co-occurring copy-number alterations (CNAs) that is correlated, possibly coordinated with GBM survival and response to chemotherapy [2].

Methods

The pattern is revealed by generalized singular value decomposition (GSVD) [3,4] comparison of patient-matched (but probe-independent) aCGH profiles of GBM and normal blood samples from The Cancer Genome Atlas (TCGA).

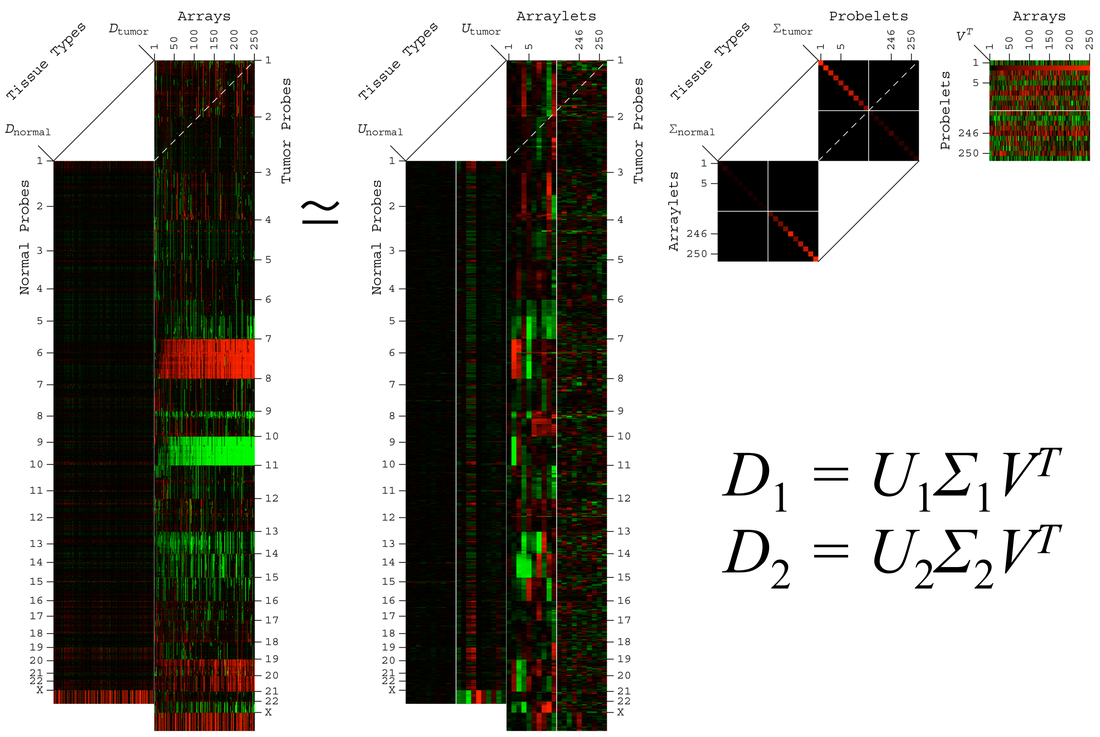

Figure 1: GSVD

Results

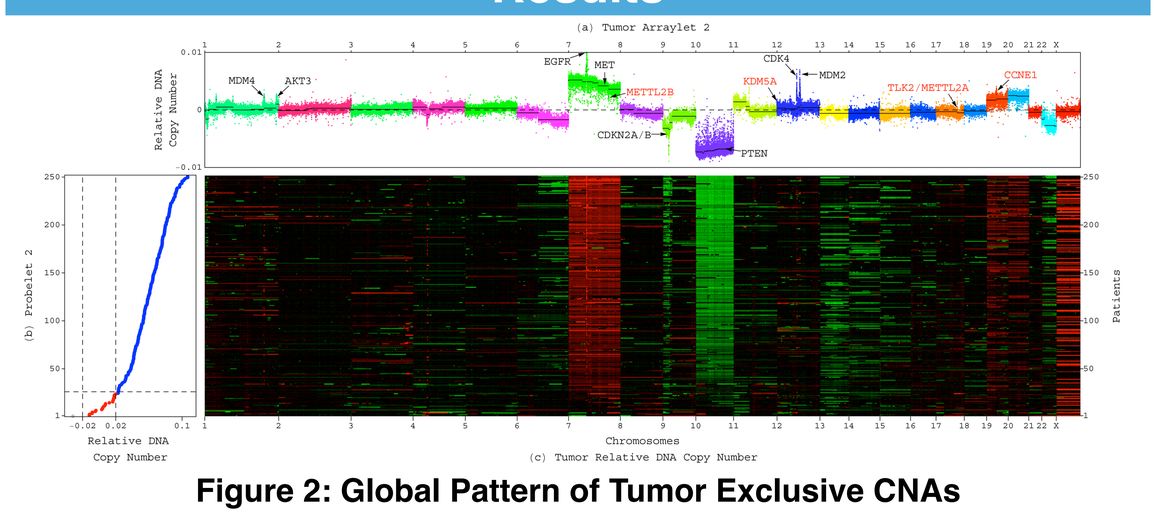

Figure 2: Global Pattern of Tumor Exclusive CNAs

We find that the GSVD classifies the patients into two groups of significantly different prognoses. A group of ~10% of the patients displays low, approximately zero, relative copy numbers in the global pattern. The Kaplan-Meier (KM) median survival time is ~29 months, which is more than twice longer than that of the group with high copy numbers (Fig. 3*a*), with a log-rank test P-value $<10^{-3}$.

The KM median survival time difference between the patients >50 or <50 years old at diagnosis is ~11 months (Fig. 3*b*), approximately two thirds of the ~16 months difference observed for the global pattern. The univariate Cox proportional hazard ratio we calculate for age is 2, similar to the 2.3 for the global pattern. Taken together, the prognostic contribution of the global pattern is comparable to that of age.

To examine whether the weight of the global pattern in a patient's GBM aCGH profile is correlated with the patient's age at diagnosis, we classify the patients into four groups, with prognosis of longer-term survival according to both, only one or neither of the classifications (Fig. 3*c*). Within each age group, the subgroup of patients with negligible weights of the global pattern in their profile consistently exhibits longer survival than the remaining patients.

Survival analyses of an inclusive confirmation set of 344 patients (Fig. 3 *d*–*f*), and separately an independent validation set of 184 patients (Fig. 3 *g*–*i*) give qualitatively similar results to these of the initial set of 251 patients (Fig. 3 *a*–*c*).

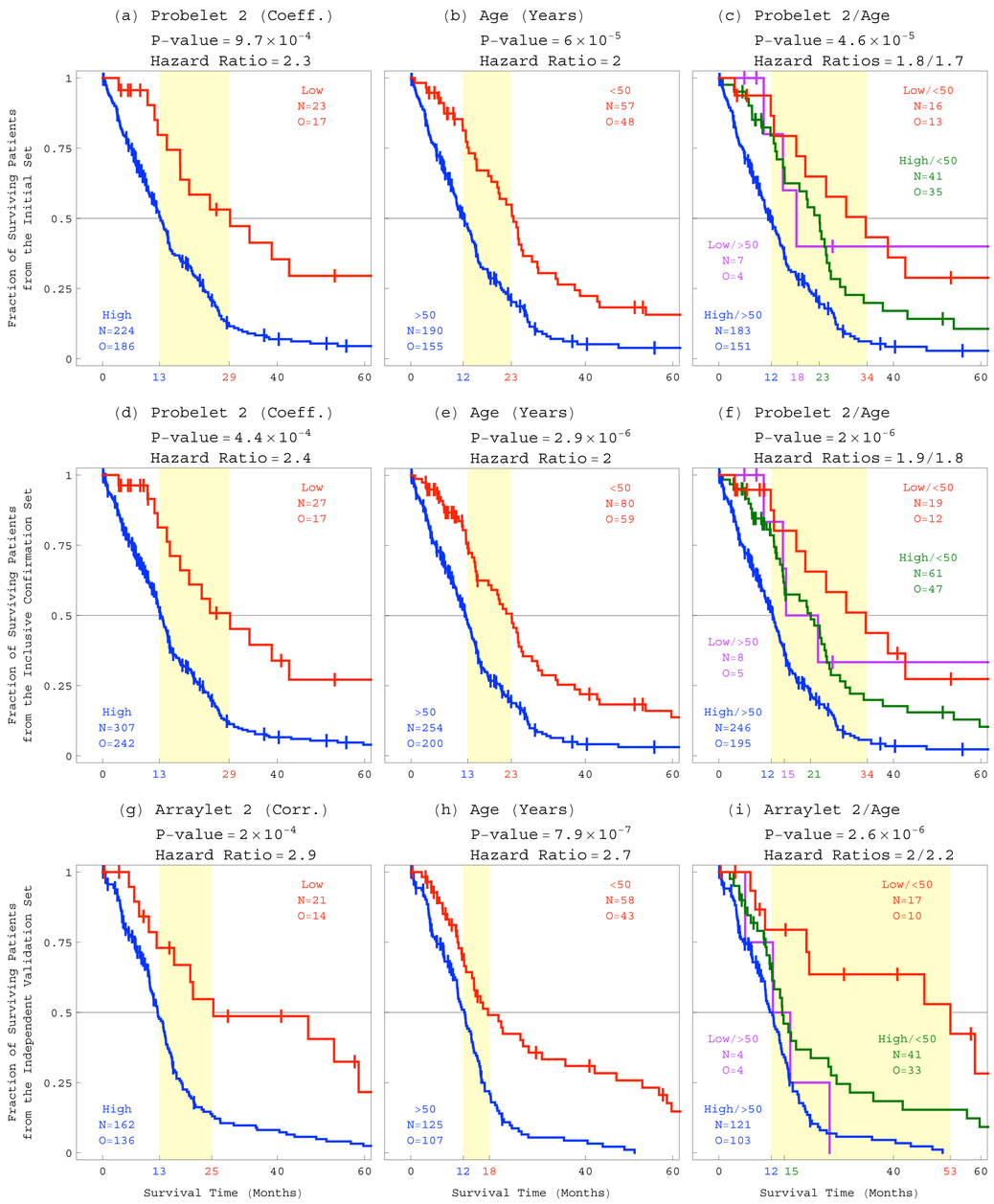

Figure 3: Kaplan-Meier Survival Curves

Conclusions

i. The global pattern is independent of age, and combined with age, makes a better predictor than age alone. We find that the pattern provides a better prognostic predictor than the chromosome numbers or any one focal CNA that it identifies, suggesting that the GBM survival phenotype is an outcome of its global genotype.

ii. GSVD comparison of matched profiles of a larger set of TCGA patients, inclusive of the initial set, confirms the global pattern.

iii. GSVD classification of the GBM profiles of an independent set of patients validates the prognostic contribution of the pattern [5].

We find, confirm and validate that a negligible weight of the global pattern in a patient's GBM aCGH profile is indicative of a significantly longer GBM survival time, especially among chemotherapy patients, implying an improved response to treatment.

Recent experiments [6] verify that GSVD modeling of DNA microarray data can correctly predict previously unknown global mechanisms [7]. This GSVD comparative modeling, therefore, draws a mathematical analogy between the prediction of cellular modes of regulation and the prognosis of cancers.

References

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