Novel Cancer Drug Targets from Comparison of Patient-Matched Genomic Profiles

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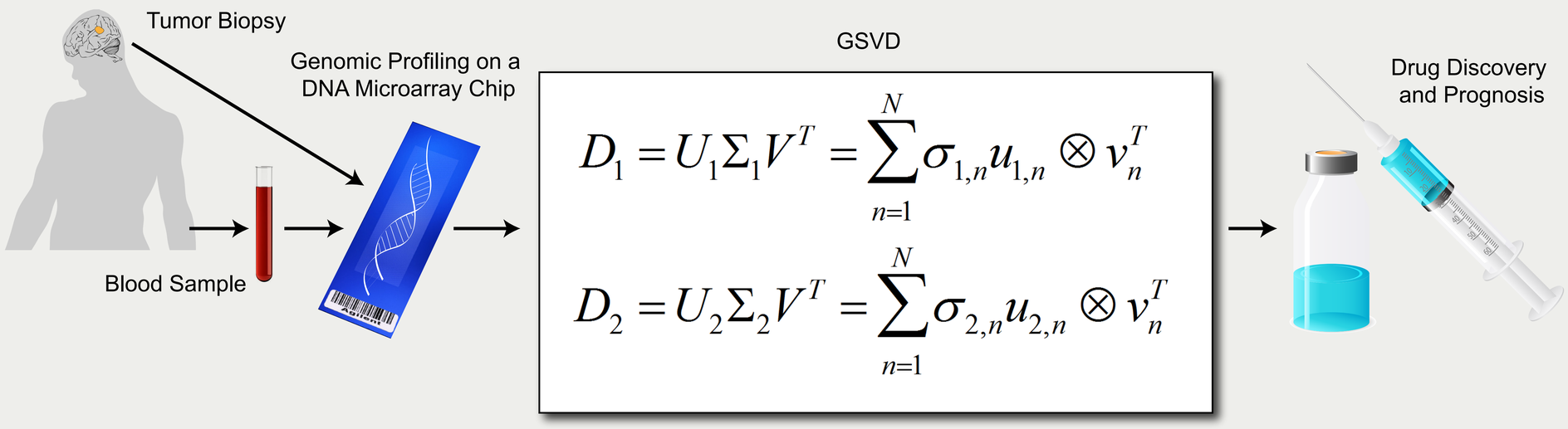
Introduction

The Cancer Genome Atlas (TCGA)[1] is a national effort to accelerate cure for cancer. This initiative chose to study Glioblastoma multiforme (GBM), a fast-growing and most common brain tumor in adults. Patients with GBM have a poor prognosis and usually survive less than 15 months following diagnosis. Currently there are no effective long-term treatments for this disease.



We describe the Generalized Singular Value Decomposition[2] (GSVD) comparative modeling of TCGA patient-matched GBM and DNA copy-number profiles that discovers novel cancer drug targets.

Mathematical Method: GSVD

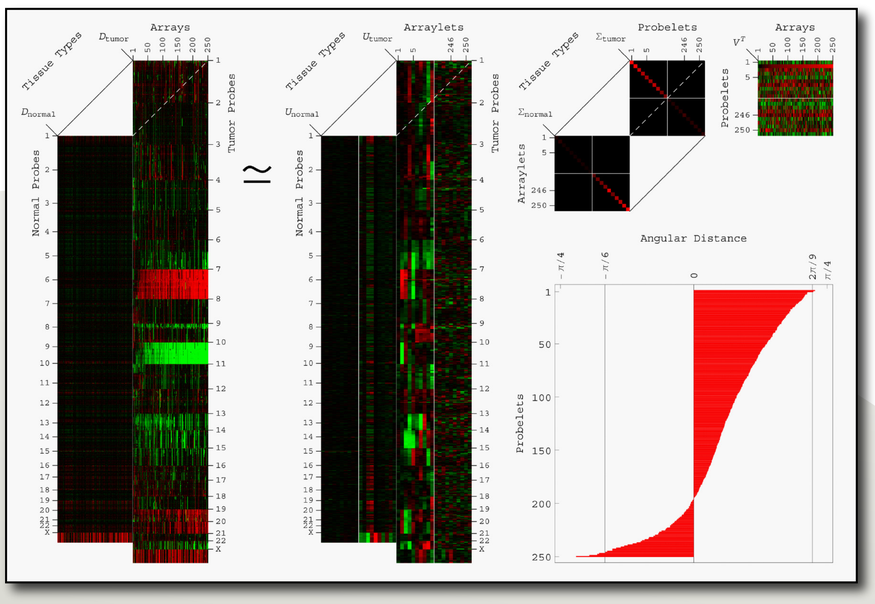


Figure 1: GSVD

GSVD Identifies and Removes Experimental Variations

The GSVD removes from the global pattern copy-number variations that occur in the normal human genome, e.g., female-specific X chromosome amplification (Fig. 2 *d–f*), and experimental variations, (Fig. 3) without a-priori knowledge of these variations.

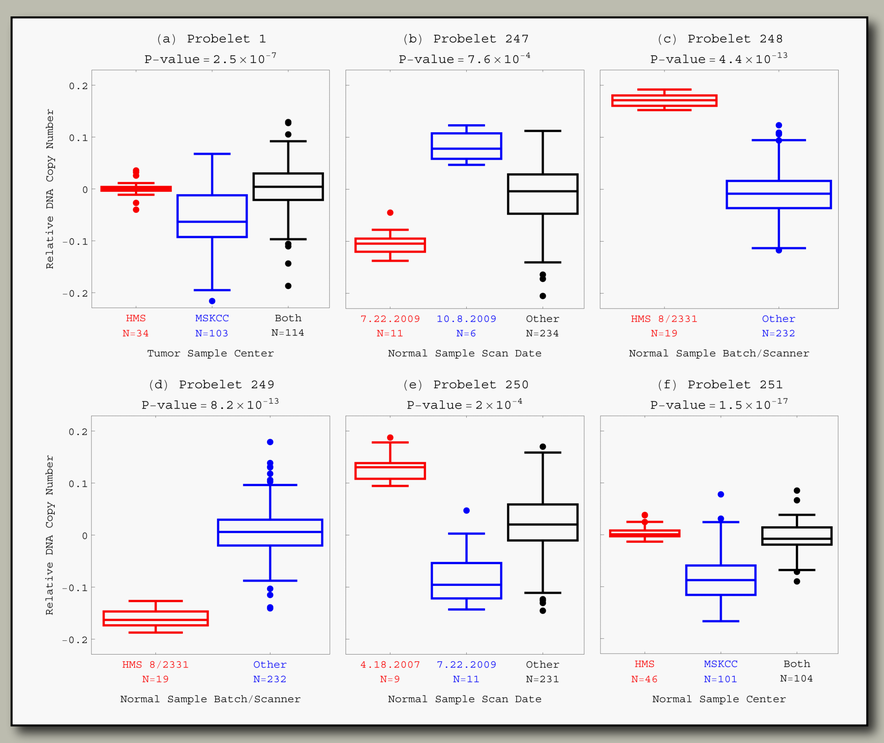


Figure 3: Boxplots visualization of the experimental variations

GSVD Discovers Novel Drug Targets

The GSVD uncovers one global pattern of tumor-exclusive co-occurring copy-number alterations (CNAs) that is correlated, possibly coordinated, with GBM survival and response to chemotherapy (Fig. 2 *a–c*, Fig. 4).

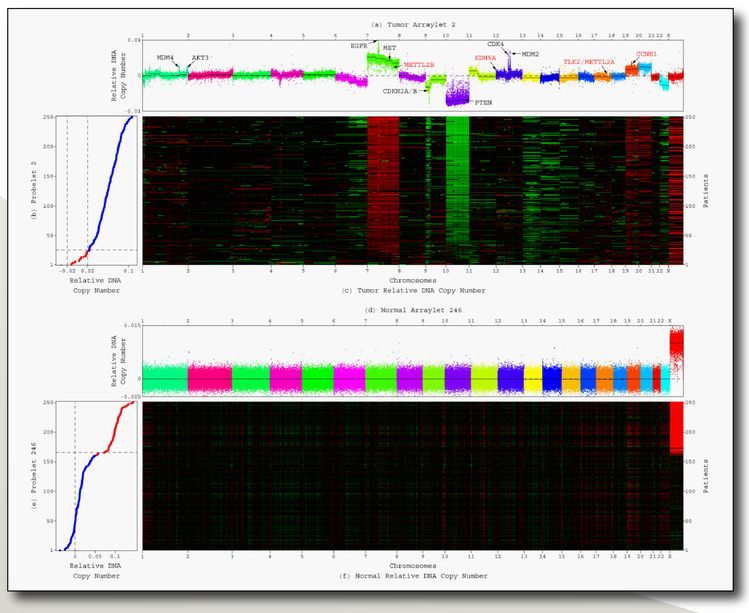


Figure 2: Global patterns of CNAs revealed by GSVD

- The pattern reveals novel CNAs including the cell cycle-regulated serine/threonine kinase encoding *TLK2*, the cyclin E1-encoding *CCNE1* which has been linked with many cancers but not GBM, and the Rb-binding protein-encoding *KDM5A* which has been recently implicated in cancer drug tolerance.

- Amplification of *TLK2*, which encodes for a biochemically putative drug target, has been correlated with overexpression in several other cancers.[3,4] The Kaplan-Meier[5] median survival time with *TLK2/METTL2A* amplification is 5 months longer than that for the remaining patients, suggesting that drug-targeting the kinase that *TLK2* encodes may affect not only the pathogenesis but also the prognosis of GBM[6,7].

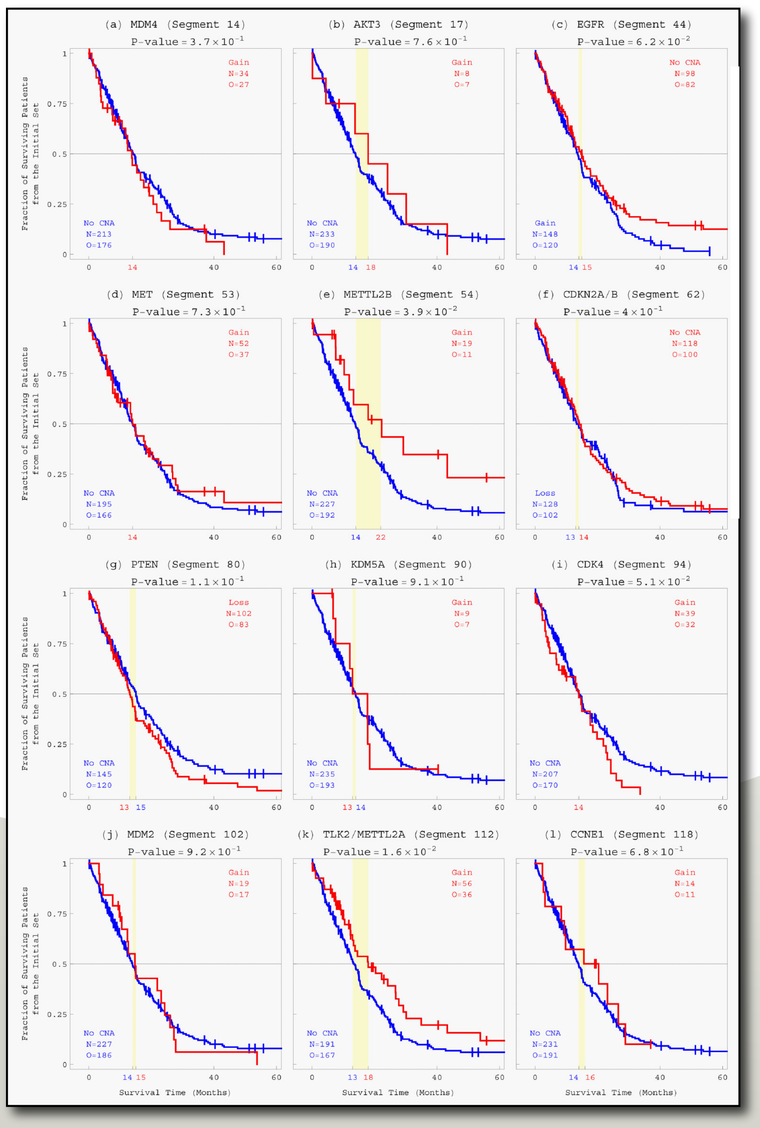


Figure 4: Kaplan-Meier survival curves

Conclusion

The global pattern revealed by GSVD includes most known GBM-associated changes in chromosome numbers and focal CNAs and uncovers several previously unreported CNAs, including the biochemically putative drug target-encoding *TLK2.*

Acknowledgements

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References

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