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The Cancer Genome Atlas exposes more secrets of lethal brain tumor

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When The Cancer Genome Atlas launched its massively collaborative approach to organ-by-organ genomic analysis of cancers, the brain had both the benefit, and the challenge, of going first.

TCGA ganged up on glioblastoma multiforme (GBM), the most common and lethal of brain tumors, with more than 100 scientists from 14 institutions tracking down the genomic abnormalities that drive GBM.

Five years later, older and wiser, TCGA revisited glioblastoma, producing a broader, deeper picture of the drivers – and potential therapeutic targets – of the disease published in the Oct. 10 issue of *Cell*.

"The first paper in 2008 characterized glioblastoma in important new ways and illuminated the path for all TCGA organ studies that have followed," said senior author Lynda Chin, M.D., professor and chair of Genomic Medicine and scientific director of the Institute for Applied Cancer Science at The University of Texas MD Anderson Cancer Center.

"Our new study reflects major improvements in technology applied to many more tumor samples to more completely characterize the landscape of genomic alterations in glioblastoma," said Chin, who was also co-senior author of the first paper while she was on the faculty of Dana-Farber Cancer Institute in Boston.

"Information generated by this unbiased, data-driven analysis presents new opportunities to discover genomics-based biomarkers, understand disease mechanisms and generate new hypotheses to develop better, targeted therapies," Chin said.

About 23,000 new cases of GBM are predicted in the United States during 2013 and more than 14,000 people expected to die of the disease. Most patients die within 15 months of diagnosis.

Well of rich, detailed data will nurture better treatment

New information about genetic mutations, deletions and amplifications; gene expression and epigenetic regulation; structural changes due to chromosomal alterations, proteomic effects and the molecular networks that drive GBM make for a deep, broad dataset that will underpin research and clinical advances for years to come.

"Our main contribution is this tremendous resource for the GBM research community, which is already heavily relying on the earlier TCGA study," said co-lead author Roeland Verhaak, Ph.D., assistant professor of Bioinformatics and Computational Biology at MD Anderson. "Whatever new treatments people come up with for GBM, I'm very confident that their discovery and development will in some way have benefited from this rich and detailed data set," he said.

The *Cell* paper describes analysis of tumor samples and molecular data from 599 patients at 17 study sites. Detailed clinical information including treatment and survival was available for almost all cases.

New targetable mutations

In addition to confirming significantly mutated genes discovered earlier, such as the tumor suppressors TP53, PTEN and RB1 and the oncogene PIK3CA, the analysis identified 61 new mutated genes. The most frequent mutations occurred in from 1.7 to 9 percent of cases.

Two of these, BRAF and FGFR, might have more immediate clinical relevance, Verhaak noted. MD Anderson neuro-oncologists are checking to see if patients have these mutations. Drugs are available to address those variations now, Verhaak said. The BRAF point mutation in GBM is the same commonly found in melanoma, which is treated by a new class of drugs.

More twists and turns for EGFR

The larger data set and an improved analytical algorithm allowed major refinement of gene amplification and deletion information. For example, common amplification events were found to occur more frequently than previously known, including amplification of the epidermal growth factor receptor (EGFR) on chromosome 7.

EGFR is both amplified and mutated frequently in GBM; yet therapeutic efforts targeting EGFR so far have failed. "We found EGFR is more frequently altered than we already thought," Verhaak said.

Overall, the EGFR gene was mutated, rearranged, amplified or otherwise altered in 57 percent of tumors. Increased EGFR protein levels in GBM cells correlated with the many mechanisms of EGFR alteration, Verhaak said.

A treatment based on EGFR still has great potential, he noted. But strategies to target EGFR will need to address the likelihood that different alterations of EGFR might be present in the same tumor and affect the impact of targeted drugs.

Breaking GBM into molecular subtypes

Verhaak and other researchers in recent years have begun to classify GBM tumors by gene expression. Four such subgroups—neural, proneural, mesenchymal and classical—were further characterized by DNA methylation pattern, signaling pathway activity and by clinical measures such as survival and treatment response. Methylation of a gene turns it off.

Understanding the subgroups could establish biomarkers to guide treatment and identify new therapeutic targets.

The team found, for example, that the survival advantage of the proneural subtype depends on a specific DNA methylation pattern known as G-CIMP and that DNA methylation of the MGMT gene may serve as a biomarker of treatment response in the classical subtype.

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