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Genetic profiles of brain metastases differ from those of primary tumors

New mutations in metastases may indicate need for changes in drug treatment

MASSACHUSETTS GENERAL HOSPITAL

The development of brain metastases is a devastating complication of cancer, leading to the death of more than half of patients whose cancer spreads to the brain. A new study finds that, while brain metastases share some genetic characteristics with the primary tumors from which they originated, they also carry unique genetic mutations, indicating that the evolutionary pathways of the metastatic and the primary tumors have diverged, which may change sensitivities to targeted therapy drugs. The report from an international collaboration is receiving early online publication in *Cancer Discovery* to coincide with a presentation at the European Cancer Congress and European Society for Medical Oncology meeting in Vienna.

"Our study demonstrates that, while brain metastases and primary tumors share a common ancestry, they continue to evolve separately," says Priscilla Brastianos, MD, director of the Brain Metastasis Program at the Massachusetts General Hospital (MGH) Cancer Center, co-lead and co-corresponding author of the *Cancer Discovery* paper. "This is tremendously important, as we demonstrate that brain metastases may have clinically significant mutations that have not been detected either in the primary tumor biopsy or in metastases from other parts of the body. We also showed that multiple brain metastases from the same patient share nearly all clinically significant mutations."

Brain metastases commonly develop from melanomas, lung or breast cancers and can appear despite the primary tumor's being well controlled by drugs that target mutations driving its growth. Once brain metastases develop, patients usually die within a matter of months, and patients with brain metastases are typically excluded from most clinical trials. In treating cancers known to be driven by targetable gene mutations, treatment planning is usually based on genetic analysis of tissue from the primary tumor. Since the treatment of brain metastases often involves removal of the metastasis, samples of the that tumor are often available for analysis. The current study was designed to investigate whether the genetic profiles of brain metastases are identical to those of the primary tumors.

The research team conducted whole-exome gene sequencing on three tissue samples - primary tumor, brain metastasis and normal tissue - from each of 86 patients with lung, breast or kidney cancers. In each instance, while the investigators found that the primary tumor and the metastasis

shared some mutations, the brain metastases had new mutations that were not related to those of the primary tumors. In 4 of the 86 patients, the brain metastases actually appeared to have originated from additional primary tumors.

The new mutations detected in the metastases often signaled potential sensitivity to targeted therapy drugs that would not have been effective against the primary tumors. Overall, more than half of the patients appeared to have clinically targetable new mutations in their brain metastases. Analysis of samples of multiple brain metastases from the same patient showed that nearly all of the significant mutations appeared in all of the brain metastases. In contrast, metastases from other parts of the body differed significantly from the brain metastases.

"It has been unclear whether brain metastases from well controlled primary tumors develop because the chemotherapy drugs don't cross the blood-barrier or because of different genetic mutations in the metastasis," says Brastianos, an instructor in Medicine at Harvard Medical School. "Our data suggest that genetic differences may contribute to the formation and treatment resistance of brain metastases. While the clinical impact of directly targeting brain-metastasis-specific mutations needs to be evaluated more fully, something we are now investigating, we believe that routinely looking for clinically significant alterations in brain metastases may open the door to new therapeutic options for these patients."

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Brastianos is the co-lead and co-corresponding author of the *Cancer Discovery* paper along with Scott Carter, PhD, of the Broad Institute and Harvard School of Public Health. Additional co-authors include co-corresponding authors Gad Getz, PhD, MGH Cancer Center, and William Hahn, MD, PhD, Dana-Farber Institute; co-authors Tracy Batchelor, MD, MGH Neuro-Oncology, David Louis, MD, MGH Pathology, Sandro Santagata, MD, PhD, Brigham and Women's Hospital, and investigators from Memorial Sloan-Kettering Cancer Center, Vall D'Hebron Institute in Spain and Seoul National University College of Medicine in Korea.

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Massachusetts General Hospital, founded in 1811, is the original and largest teaching hospital of Harvard Medical School. The MGH conducts the largest hospital-based research program in the United States, with an annual research budget of more than $760 million and major research centers in AIDS, cardiovascular research, cancer, computational and integrative biology, cutaneous biology,

human genetics, medical imaging, neurodegenerative disorders, regenerative medicine, reproductive biology, systems biology, transplantation biology and photomedicine. In July 2015, MGH returned into the number one spot on the 2015-16 U.S. News & World Report list of "America's Best Hospitals."