

Probing the Genomics of Primary and Metastasized Brain Tumors

Can the genes of cancer cells unlock better treatments?

Brain cancer researchers face two difficult challenges that have hindered progress. One concerns the dearth of information about how to treat rare tumors with high morbidity or mortality, such as craniopharyngioma, which affects fewer than two in one million people per year. The second involves a lack of knowledge about how common cancers that have metastasized to the brain differ from the original primary tumors. At the Massachusetts General Hospital Cancer Center, neuro-oncologist Priscilla Brastianos, MD, has developed new approaches to overcome both challenges.

FORMIDABLE CRANIOPHARYNGIOMAS

In 1939, Harvey Cushing, the father of neurosurgery, declared craniopharyngioma “the most formidable of intracranial tumors” because of the extreme sensitivity required to remove them surgically. The tumors wrap around structures at the base of the brain, including the pituitary gland, hypothalamus, cranial nerves, ventricular system, visual pathways and major blood vessels. The standard therapy (surgery, if possible, or radiation or both) itself can be debilitating.

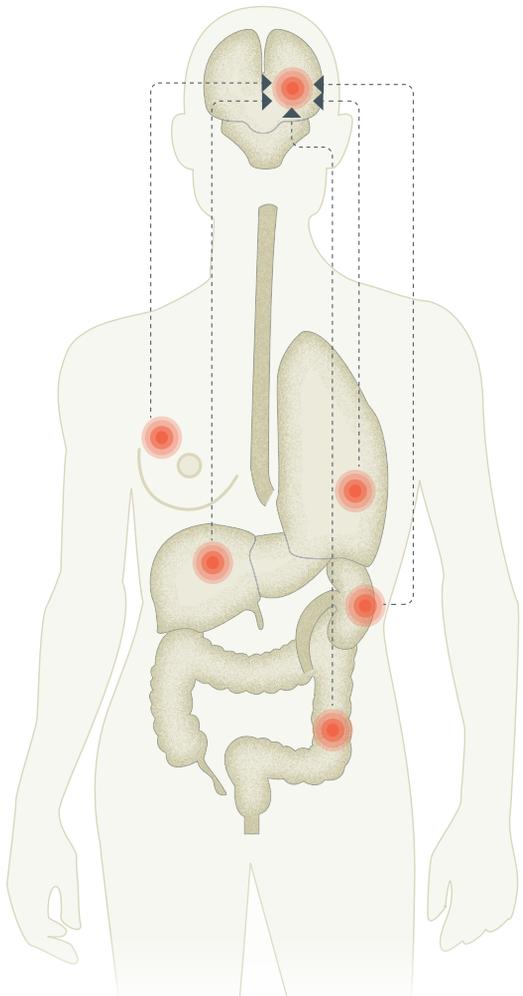
Craniopharyngiomas are grouped into two subtypes reflecting tumor locations: the adamantinomatous form affects children and the papillary form occurs predominantly in adults. But researchers have not known whether the subtypes differ in

their genetic mutations or just in their location or the patient age of onset.

Dr. Brastianos notes that it required “an amazing international collaborative effort” to collect sufficient tumor samples for *(continued on page 6)*

Secondary Tumors

Lung cancer, breast cancer, melanoma and renal cell carcinoma commonly metastasize to the brain. Overall, approximately 10 to 15 percent of patients with cancer will develop brain metastases, yet researchers have limited understanding of the molecular evolution that leads to those secondary tumors.



[continued from page 5] a small study. Using those 15 samples, she and Sandro Santagata, MD, PhD, from the Brigham and Women's Hospital, conducted the first whole exome sequencing of craniopharyngiomas.

In a recent study published in *Nature Genetics*¹, Dr. Brastianos reported that each of the two subtypes has a high rate of mutations in a particular cancer gene, but the mutated genes in each subtype are mutually exclusive and have quite different biological activities. An astonishing 96 percent of the childhood adamantinomatous form of the tumor had a mutation in a β -catenin gene (CTNNB1), which affects cell-to-cell adhesion and gene transcription through the Wnt pathway, while 95 percent of the adult papillary tumor samples had a mutation in the BRAF gene, which affects cell growth rates. Surprisingly, few other mutations occurred in either subtype.

Moreover, the driving mutation occurred in 100 percent of the cancer cells in each tumor, indicating that the tumor is clonal: the mutation was present in the tumor initiating cell (cell of origin or cancer stem cell) and was passed down to each descendant cell as the tumor evolved. Consequently, because each subtype of craniopharyngioma tumor is dependent on only one driving mutation (β -catenin or BRAF), both subtypes should be particularly sensitive to selective inhibitors.

Dr. Brastianos says that because the mutations are mutually exclusive,

identifying them can be used to confirm a diagnosis. Moreover, papillary craniopharyngioma patients may benefit immediately from today's FDA-approved BRAF inhibitors. β -catenin and Wnt-signaling inhibitors are in development.

BRAIN METASTASES ON THE RISE

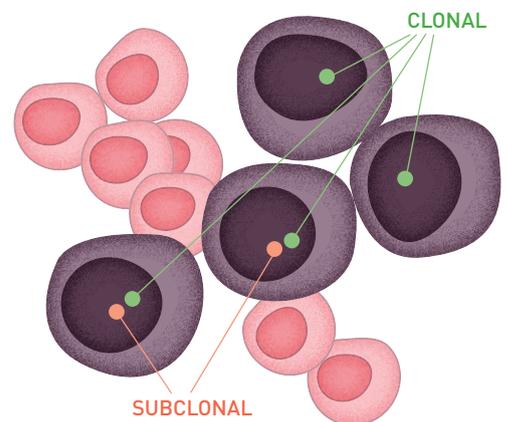
Many prevalent malignancies—lung cancer, breast cancer, melanoma, renal cell carcinoma—metastasize to the brain, which Dr. Brastianos calls “a sanctuary for cancer” that may not respond to targeted therapies. That's a problem, because as cancer therapies for primary tumors improve, more patients are living long enough to develop brain metastases. Some 200,000 people a year now present with brain metastases, and half of those patients will die because of the cancer in their brain, often within months.

Dr. Brastianos leads a multi-disciplinary brain metastasis clinic at Mass General Cancer Center to provide individualized treatment and support for such patients and to conduct clinical and translational research. The goal is to establish clinical protocols specifically for patients with brain metastases, and to integrate lessons from the clinic into work in the lab—and then to take what researchers learn in the lab back to patients. This is the first program of its kind in brain metastases in the country.

Dr. Brastianos collaborated with researchers worldwide to collect 101 matched primary tumor, brain metastasis and normal tissue samples from patients, and then conducted the largest, most comprehensive genotyping

Cancer Cell Fraction (CCF) of Biopsy

Analyzing the fraction of cancer cells that harbor a mutation indicates which mutations may be clonal—present in all cancer cells sequenced from a tumor, representing founder and earlier events. Subclonal mutations are present in only some of the cancer cells sequenced, representing later events.



study to date characterizing those brain metastases and showing how they differ from the primary tumors². Dr. Brastianos worked with Scott Carter, PhD, and Gad Getz, PhD, at the Broad Institute of Harvard and MIT using the latest analytic sequencing tools to understand how brain metastases evolve from the primary tumor. Dr. Brastianos found that as the brain metastasis evolves, it develops a heterogeneous set of mutations that differ from those in the primary tumor—which also evolves. This research suggests that therapies may need to change as brain metastases continue to evolve with new mutations. Dr. Brastianos hopes to identify the genetic changes that specifically drive brain metastases.

For Dr. Brastianos, this research is both professionally and personally urgent. “My mother recently passed away from metastatic breast cancer,” she says. “Her illness shaped me as a physician and researcher, and I'm dedicating my life to solving this problem.” ■

¹ Brastianos, Priscilla K., Amaro Taylor-Weiner, Peter E. Manley, Robert T. Jones, Dora Dias-Santagata, Aaron R. Thorner, Michael S. Lawrence et al. “Exome Sequencing Identifies BRAF Mutations in Papillary Craniopharyngiomas.” *Nature Genetics* 46, no. 2 (February 2014): 161–65.

² Abstract: Genomic characterization of 101 brain metastases and paired primary tumors reveals patterns of clonal evolution and selection of driver mutations: <http://www.abstractsonline.com/Plan/ViewAbstract.aspx?mID=3404&sKey=7f09a126-5b6f-48fc-aad5-657245a12efb&cKey=dee7c068-525b-4ca9-a5e1-27605260d53b&mKey=6ffe1446-a164-476a-92e7-c26446874d93>.

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