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Genetic screening of brain metastases could reveal new targets for treatment

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Unravelling the genetic sequences of cancer that has spread to the brain could offer unexpected targets for effective treatment, according to new research presented to the 2015 European Cancer Congress [1] today (Sunday) and published simultaneously in *Cancer Discovery* [2].

Researchers will tell the Congress that they found that the original, or primary, cancer in a patient's body may have important differences at a genetic level from cancer that has spread to the patient's brain (brain metastases). This insight could suggest new lines of treatment.

Dr Priscilla Brastianos, MD, a neuro-oncologist and Director of the Brain Metastasis Program at Massachusetts General Hospital, Boston, USA, will say: "Brain metastases are a devastating complication of cancer. Approximately eight to ten percent of cancer patients will develop brain metastases, and treatment options are limited. Even where treatment is successfully controlling cancer elsewhere in the body, brain metastases often grow rapidly."

Dr Brastianos and her colleagues studied tissue samples from 104 adults with cancer. In collaboration with Dr Scott Carter and Dr Gad Getz at the Broad Institute, Cambridge, USA, they analysed the genetics of biopsies taken from the primary tumour, brain metastases and normal tissues in each adult. For 20 patients, they also had access to metastases elsewhere in the body.

Brain metastases often manifest years after the primary tumour. Before

this study was carried out, the extent to which the genetic profiles of brain metastases differ from that of the primary was unknown.

The researchers found that, in every patient, the brain metastasis and primary tumour shared some of their genetics, but there were also key differences. In 56% of patients, genetic alterations that potentially could be targeted with drugs were found in the brain metastasis but not in the primary tumour.

"We found genetic alterations in brain metastases that could affect treatment decisions in more than half of the patients in our study," Dr Brastianos will say. "We could not detect these genetic alterations in the biopsy of the primary tumour. This means that when we rely on analysis of a primary tumour we may miss mutations in the brain metastases that we could potentially target and treat effectively with drugs."

This study also found that if a patient had more than one brain metastasis, each was genetically similar.

To date, scientists have had limited understanding of how cancers change genetically, or evolve, as they spread from the primary tumour. The researchers used their findings to map the evolution of a cancer through a patient's body, and draw up a so-called phylogenetic tree for each patient to demonstrate how the cancer had spread and where each metastasis had come from.

They concluded that brain metastases and the primary tumour share a common genetic ancestor. Once a cancer cell, or clone, has moved from the primary site to the brain, it continues to develop and amass genetic mutations. The genetic similarity of the brain metastases in individual patients suggests that each brain metastasis has developed from a single clone entering the brain.

The genetic changes in brain metastases are independent of any occurring at the same time in the primary tumour, and in metastases elsewhere in the body, the researchers said.

Characterisation of the genetics of a patient's primary cancer can be used to optimise treatment decisions, so that drugs that target specific mutations in the cancer can be chosen. However, brain metastases are not routinely biopsied and analysed.

Dr Brastianos will say: "When brain metastasis tissue is available as part of clinical care, we are suggesting sequencing and analysis of that sample. It may offer more therapeutic opportunities for the patient. Genetic characterisation of even a single brain metastasis may be superior to that of the primary tumour or a lymph node biopsy for selection of a targeted treatment."

The need for new approaches to treating brain metastases is urgent, she will say. "Brain metastases represent an unmet need in current cancer care. More than half of the patients diagnosed with brain metastasis will die within a few months."

Dr Brastianos will say that more research is needed. "The clinical relevance of this finding needs to be studied more in prospective clinical trials. We still need to determine whether targeting the genetic mutations in the brain will lead to improved clinical outcomes."

Professor Peter Naredi, the ECCO scientific co-chair of the Congress, who was not involved in the research, commented: "In my view Dr Brastianos and colleagues very elegantly show what we mean with precision medicine, how genetic profiling can support our understanding of the metastatic process and how it opens up different pathways for treatment. It is not enough to rely on the characteristics of the primary tumour because brain metastases have other specific gene alterations and

in many patients this gives us better treatment alternatives."

More information: [1] The European Cancer Congress is the 18th congress of the European CanCer Organisation (ECCO) and the 40th congress of the European Society for Medical Oncology (ESMO).

[2] "Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets", by Priscilla K. Brastianos et al. DOI: 10.1158/2159-8290.CD-15-0369. Published online in *Cancer Discovery*: cancerdiscovery.aacrjournals.o … .CD-15-0369.abstract

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