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Presence of Viral DNA in Whole-Genome Sequencing of Brain Tumor Tissues from The Cancer Genome Atlas

E. Susan Amirian,[a,b] Melissa L. Bondy,[a,b] Qianxing Mo,[a] Matthew N. Bainbridge,[c] Michael E. Scheurer[a,b]

Dan L. Duncan Cancer Center,[a] Department of Pediatrics,[b] and Human Genome Sequencing Center,[c] Baylor College of Medicine, Houston, Texas, USA

Determining the potential role of viruses in brain tumorigenesis has proven to be extremely elusive. Even with the development of newer technologies, establishing the presence of the virus, the temporality of the infection, and the influence of viral factors in carcinogenesis remains challenging. A few recent studies have contributed to the controversy surrounding the question of whether viral factors could explain a proportion of glioma risk (1–3). At least one such study has examined transcriptome sequencing (RNA-Seq) data in an attempt to detect the presence of viral transcripts in brain tumor tissues and has failed to identify viral RNA transcripts or protein expression (1). Here, we wish to clarify how these data, along with our own preliminary findings on viral DNA sequences in tumor tissues, can contribute to our ever-evolving understanding of the associations between viruses and gliomagenesis.

The absence of viral RNA transcripts, as detected by RNA-Seq, does not necessarily indicate that the virus is not present or influential in the target tissue. It is possible that viruses that are expressed during transformation or in the early stages of carcinogenesis may enter latency or fail to be expressed due to cancer-associated mutations after the tumor has developed. The plausibility of this depends on the natural history of infection for each particular virus. Alternatively, some viruses may be able to contribute to the carcinogenic process without being expressed (4). Viruses that integrate their own DNA into the host's genome can initiate insertional mutagenesis. Hepatitis B virus and certain oncogenic avian viruses provide examples of viruses that can spur carcinogenesis, at least partially, through this mechanism (5, 6). Therefore, studies that examine only RNA-Seq data may be unable to completely ascertain whether such viruses could be contributing to carcinogenesis.

We recently examined whole-genome sequencing data, available through The Cancer Genome Atlas (TCGA) (http://cancergenome.nih.gov), to determine whether human herpesvirus 6A/B (HHV-6A/B) viral DNA sequences were present in tumor and blood samples from 13 low-grade glioma (LGG) and 23 glioblastoma multiforme (GBM) patients. Among LGG cases, 38% had DNA sequences from tumor tissues that aligned to the HHV-6A genome, and 62% had sequences that aligned to HHV-6B. Approximately 8% and 31% of LGG patients had HHV-6A and HHV-6B sequences, respectively, in both blood and tumor tissues. Among GBM patients, 30% had HHV-6A sequences present in tumor tissues, and 74% had HHV-6B sequences. Only 4% had HHV-6A sequences in blood and tumor tissues, whereas 30% had HHV-6B in both. Although we detected DNA sequences that align to these and other viruses in our preliminary analyses of TCGA data, one study recently reported that no RNA transcripts aligning to known viruses were found in LGG and GBM tumor tissues, using TCGA RNA-Seq data (1). For viruses, such as HHV-6, that integrate into nongeneic regions and establish latency, we do not believe our findings are contradictory to theirs. However, we would like to recommend that appropriate distinctions be made regarding how findings from DNA versus RNA sequencing studies are interpreted and how each contributes to our understanding of associations between viruses and brain tumors.

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Address correspondence to Michael E. Scheurer, scheurer@bcm.edu.

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