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Cooperativity within and among Pten, p53, and Rb Pathways Induces High-Grade Astrocytoma in Adult Brain.

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Abstract

Mutations in the PTEN, TP53, and RB1 pathways are obligate events in the pathogenesis of human glioblastomas. We induced various combinations of deletions in these tumor suppressors in astrocytes and neural precursors in mature mice, resulting in astrocytomas ranging from grade III to grade IV (glioblastoma). There was selection for mutation of multiple genes within a pathway, shown by somatic amplifications of genes in the PI3K or Rb pathway in tumors in which Pten or Rb deletion was an initiating event. Despite multiple mutations within PI3K and Rb pathways, elevated Mapk activation was not consistent. Gene expression profiling revealed striking similarities to subclasses of human diffuse astrocytoma. Astrocytomas were found within and outside of proliferative niches in the adult brain.

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