ABSTRACT

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Glioma progression is shaped by genetic evolution and microenvironment interactions.

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The factors driving therapy resistance in diffuse glioma remain poorly understood. To identify treatment-associated cellular and genetic changes, we analyzed RNA and/or DNA sequencing data from the temporally separated tumor pairs of 304 adult patients with isocitrate dehydrogenase (IDH)-wild-type and IDH-mutant glioma. Tumors recurred in distinct manners that were dependent on IDH mutation status and attributable to changes in histological feature composition, somatic alterations, and microenvironment interactions. Hypermutation and acquired CDKN2A deletions were associated with an increase in proliferating neoplastic cells at recurrence in both glioma subtypes, reflecting active tumor growth. IDH-wild-type tumors were more invasive at recurrence, and their neoplastic cells exhibited increased expression of neuronal signaling programs that reflected a possible role for neuronal interactions in promoting glioma progression. Mesenchymal transition was associated with the presence of a myeloid cell state defined by specific ligand-receptor interactions with neoplastic cells. Collectively, these recurrence-associated phenotypes represent potential targets to alter disease progression.

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