The evolutionary pattern of mutations in glioblastoma reveals therapy-mediated selection.

Muscat AM¹,², Wong NC, Drummond KJ, Algar EM, Khasraw M, Verhaak R, Field K, Rosenthal MA, Ashley DM.

¹ School of Medicine, Deakin University, Geelong, Victoria, Australia.
² Cancer Services, Barwon Health, Geelong, Victoria, Australia.

Glioblastoma presents as a heterogeneous disease with poor prognosis despite the use of multimodal therapy. Analysis of genomic DNA changes between initial diagnosis and recurrence in response to standard treatment protocols would enhance understanding of disease progression and better inform new treatment strategies. A cohort of 21 patients with primary glioblastoma were examined between diagnosis and first recurrence. This study presented a rare opportunity to characterize molecular alterations in tumors observed in three patients who received no therapeutic intervention, other than surgery, offering a unique control. We focused this study by comparing the dynamic mutation profiles between the primary tumors and their matched recurrent counterparts. Molecular profiling of tumors was performed using multiplexed targeted deep sequencing of 409 well characterized cancer-associated genes, achieving a mean read depth of 1272 x. Three levels of evidence suggested an evolutionary pattern consistent with a response to therapy-mediated selection pressures exists in treated patients: 1) variant burden was reduced in recurrent tumors, 2) neutral evolutionary dynamics apparent in untreated tumors shifted toward a non-neutral mode of evolution in treated patients at recurrence, and 3) the recurrent tumor of one patient displayed an increased mutation rate attributable to a temozolomide-associated hypermutator phenotype. Our observations suggest that current treatment modalities are likely to fail in achieving long term remission with the majority of relapse samples containing distinct mutations when compared to primary diagnostic samples.

KEYWORDS: glioblastoma; mutation profiling; neutral evolution; selection pressure; tumor heterogeneity

PMID: 29487696  PMCID: PMC5814263  DOI: 10.18632/oncotarget.23541

Free PMC Article