Neuro Oncol. 2026 Jan 2:noaf298. doi: 10.1093/neuonc/noaf298. Online ahead of print.

Epigenetic evolution of IDHwt glioblastomas

Bo Deng [1], Rania Head [1], Kaspar Draaisma [2], Ann Hoeben [3], Slávka Lukacova [4], Giuseppe Lombardi [5], Sieger Leenstra [6], Monique Hanse [7], Ruth E M Fleischeuer [8], Colin Watts [9], Nicos Angelopoulos [10], Thierry Gorlia [11], Vincent Bours [12], Martin J Van Den Bent [1], Pierre A Robe [2 12], Youri Hoogstrate [1], Pim J French [1]

PMID: 41485099 DOI: 10.1093/neuonc/noaf298

Abstract

Background: Although the genetic evolution of IDHwt glioblastomas has extensively been investigated, limited studies have addressed the epigenetic evolution. Understanding the epigenetic evolution is particularly relevant as demethylation of the MGMT promoter may form a means of treatment resistance.

Methods: We generated whole genome DNA methylation data of 64 matched primary-recurrent samples from IDHwt glioblastoma patients. Data were combined with three publicly available datasets into a cohort consisting of 418 samples. MGMT promoter methylation was determined using the MGMT-STP27 algorithm. CoxPH regression was used to investigate the impact of identified changes on survival.

Results: Our analysis demonstrate that the methylome of IDHwt glioblastomas was highly stable (93%). Changes that occur could mostly be allocated to differences in tumor purity. Conversion from a methylated MGMT promoter to unmethylated status at progression occurred infrequently (9/66, 13.6%), but significantly more often than the converse (4/113, 3.5%). Conversion was associated with worse overall- and progression-free survival compared to patients whose tumors remained MGMT methylated. Despite a large survival difference between patients with MGMT promoter-methylated and unmethylated tumors, very few CpGs were differentially methylated between samples from MGMT methylated and unmethylated tumors. Of the ones that were, the vast majority were located within the MGMT gene body and were inversely correlated with MGMT promoter methylation status.

Conclusion: The methylome of IDHwt glioblastomas is highly stable at tumor progression. In this series, only 7% of tumors showed change in MGMT promoter methylation status at progression.

Keywords: MGMT; glioblastoma; methylation.