MGMT CpG island is invariably methylated in adult astrocytic and oligodendroglial tumors with IDH1 or IDH2 mutations.

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Abstract
We have previously identified a region containing 16 CpGs within the MGMT CpG islands which is critical for the transcriptional control of MGMT (Malley, Acta Neuropathol 2011). To investigate the patterns and incidence of MGMT methylation in astrocytic and oligodendroglial tumors, we quantitatively assessed methylation at these 16 CpGs using bisulfite modification followed by pyrosequencing of 362 gliomas not treated with temozolomide, and correlated the findings with previously identified patterns of genetic abnormalities, patients’ age and survival. The MGMT gene was considered to be methylated when the mean methylation of the 16 CpGs was 10% or higher. This cut-off value distinguished diffuse astrocytomas with high and low MGMT expression. Within each tumor type, the patterns of methylation were highly variable and also highly heterogeneous across the 16 CpGs. A high incidence of MGMT methylation was observed in all subtypes of gliomas included in this study. Among a subset of 97 tumors where conventional methylation-specific PCR (MSP) was also applied, methylation was detected by both methods in 54 tumors, while the pyrosequencing results identified a further 17 tumors. No additional cases were found using MSP alone, indicating that pyrosequencing is a robust method for methylation analysis. All tumors with IDH1/IDH2 mutations except two had MGMT methylation, while there were many tumors with MGMT methylation, particularly primary glioblastomas, which had no mutations of IDH1/2. We suggest that MGMT methylation may be one of the earliest events in the development of astrocytic and oligodendroglial tumors.