Observation of the frequency of MGMT methylation, BRAF V600E mutation and IDH1/2 mutations in a Greek brain tumor cohort

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Background

In the last few years, extensive molecular studies have identified diagnostic and prognostic markers in Gliomas. 1p19q co-deletion, O(6)-methylguanine DNA methyltransferase (MGMT) status, and mutations of isocitrate dehydrogenases 1 and 2 (IDH1/IDH2) are currently the three most pertinent markers in diffuse gliomas.

The RAS/RAF (MAPK) signalling pathway is one of the most prominent pathways for regulation, cell growth, proliferation, differentiation and apoptosis in malignant cells. The role of aberrant activation of RAS signalling in gliomas pathogenesis is not clear at this time. BRAF, an immediate downstream target of the Ras protein has been identified as a frequent target of activating mutations in gliomas.

Recently, genomic aberrations of the B-RAF oncogene have been described in adult malignant gliomas, however the clinical and prognostic significance of BRAF mutation for overall survival has yet to be established.

Objective

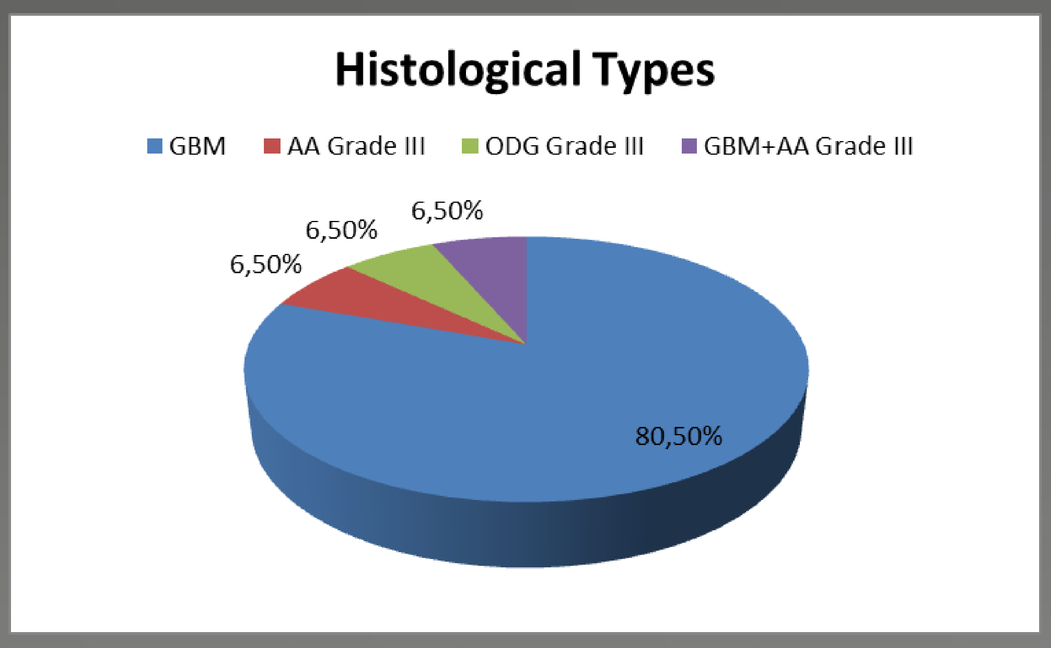
The purpose of this study was to evaluate a possible correlation between MGMT status, IDH1 and BRAF mutations and the clinicopathological features as well as prognosis in Malignant Gliomas patients.

Patients and Methods

We collected tissue samples of primary tumor biopsies from 31 adult patients with histologically proven malignant gliomas. Of 31 patients, 80,5% had Glioblastoma Multiforme, 6,5% Anaplastic Astrocytoma grade III and 6,5% Oligodendrioglioma grade III and 6,5% Anaplastic Astrocytoma with Glioblastoma Multiforme.

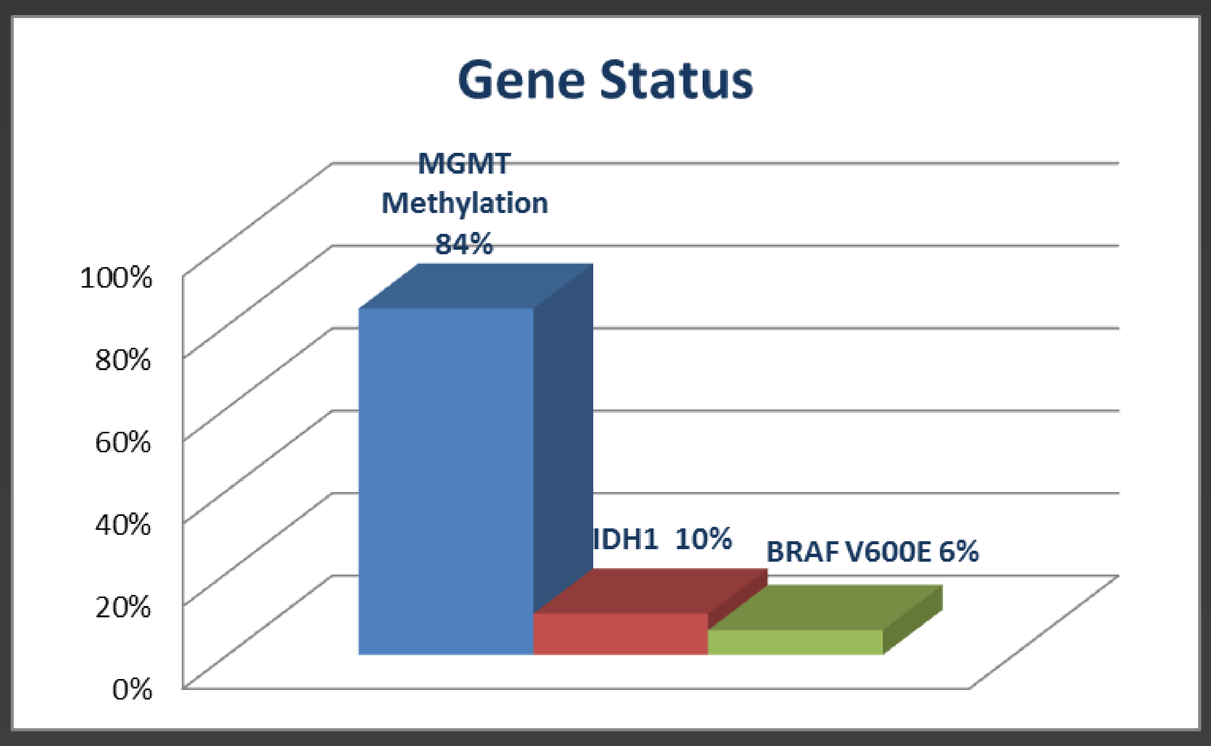
DNA was extracted from Formalin-Fixed Paraffin Embedded (FFPE) tissue using the Qiagen QIAmp DNA FFPE® tissue kit. Selective PCR amplification was carried out using specific primers for the *BRAF* gene.

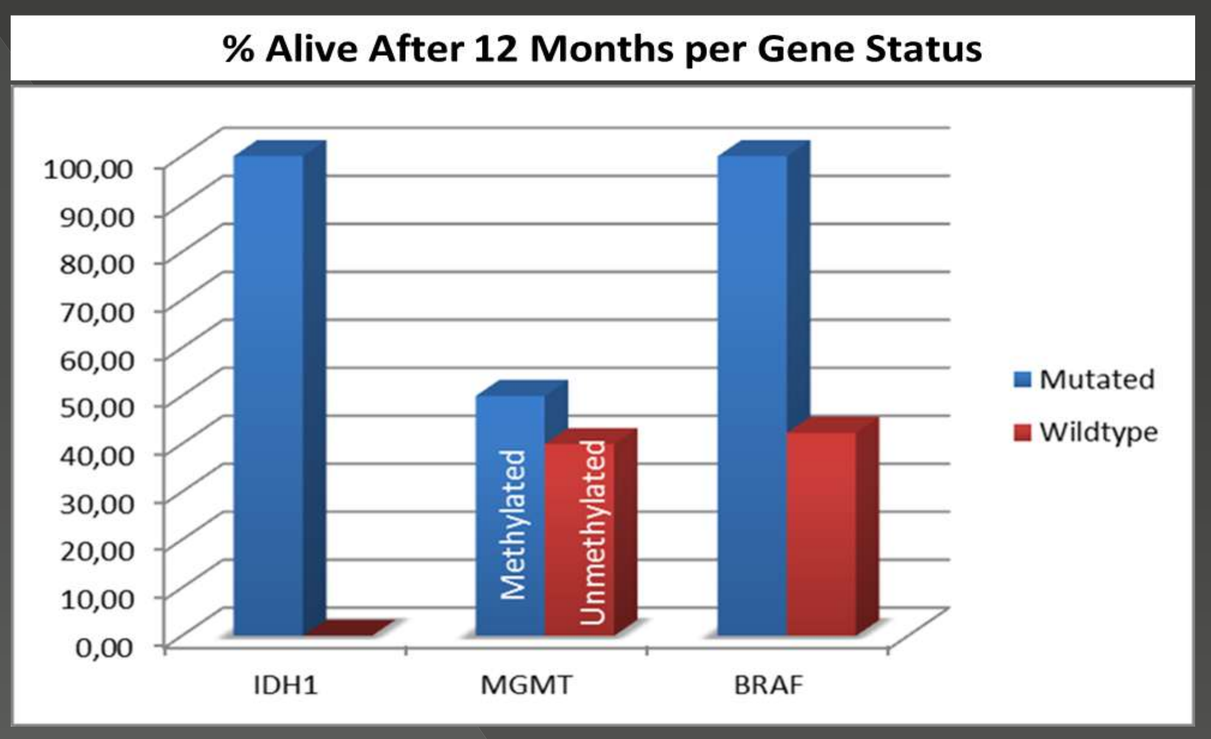
The methylation pattern in the CpG island of *MGMT* was determined by chemical modification of unmethylated, but not methylated, cytosine to uracil, using the EpiTect Bisulfite Kit (Qiagen). Exon 4 of the IDH1 genes was amplified by Polymerase chain reaction. Mutation detection was carried out by sequencing analysis.



Results

Among our patient population, 84% had MGMT methylation, 10% carried IDH1 mutations, and 6% had a BRAF V600E mutation. All of the IDH1 mutant patients had lower grade disease (Anaplastic Astrocytoma Grade III and Oligoderdroglioma Grade III) in accordance with the literature, while BRAF V600E mutations were assosiated with more agressive disease. Of the MGMT methylated patients with GBM, 10% had the V600E mutation in BRAF and none had a mutation in IDH1 or 2.





Conclusion

The use of molecular markers along with clinicopathological parameters can be helpful in determining the prognosis of patients with brain tumors. There is a definite need for prospective evaluation of these markers in a larger patient cohort.

References

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