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Molecular profile of diffuse lower-grade gliomas

Diffuse low- and intermediate-grade gliomas include World Health Organization grade II and III astrocytomas, oligodendrogliomas, and oligoastrocytomas. These lower-grade gliomas usually arise in the cerebral hemispheres of adults, and they are highly infiltrative and, therefore, cannot be completely resected. Residual tumor almost always results in recurrence, with a subset of tumors having the propensity to progress to highly malignant glioblastoma (WHO grade IV). The clinical course and survival outcome is highly variable, with some tumors progressing within months while others remain stable for years with a marked response to chemotherapeutic or radiation treatment. Histologic classification of the lower-grade gliomas suffers from high interobserver variability and does not adequately correlate with clinical outcome. In clinical practice, some molecular markers have been demonstrated to have independent prognostic information, with mutations in IDH being associated with a favorable prognosis and deletions of chromosomal arms 1p and 19q being associated with a favorable treatment effect. While these markers are being used to guide prognosis and treatment decisions, a comprehensive analysis of lower-grade gliomas has not been performed. In this study, conducted by The Cancer Genome Atlas Research Network, 293 previously untreated lower-grade gliomas were examined by complete exome sequencing, DNA copy-number profiling, messenger RNA sequencing, microRNA sequencing, DNA methylation profiling, TERT promoter sequencing, and reverse-phase protein lysate array profiling. These data were clustered and integrated using a variety of algorithms to identify distinct and robust molecular subtypes, and, interestingly, these subtypes correlated better with IDH mutation and 1p/19q codeletion status than with histologic subtype. The first group of tumors with IDH mutations and 1p/19q codeletions were associated with mutations activating the TERT promoter; mutations of CIC, FUBP1, and NOTCH1; and activating alterations in the PI3 kinase pathway. The second group of IDH-mutated tumors without the chromosomal codeletions often demonstrated TP53 and ATRX mutations, with TERT mutations being rare. The final group of tumors with wild-type IDH had more mutations than the tumors in the other molecular subtypes, and many of these mutations were similar to those seen in glioblastoma. These alterations included mutations in PTEN, EGFR, NF1, TP53, and PIK3CA, and copy-number alterations, such as gains of chromosome 7 and deletions of chromosome 10. Patients with lower-grade gliomas with wild-type IDH had significantly shorter overall survival (median survival, 1.7 years) than those in the mutated IDH with 1p/19q codeletion and mutated IDH without codeletion subtypes (median survival, 8.0 years and 6.3 years, respectively). Notably, patients with lower-grade gliomas with wild-type IDH had clinical outcomes similar to patients with glioblastoma, further demonstrating the biological similarities between the lower-grade gliomas with wild-type IDH and glioblastoma. Overall, these data demonstrate three molecular subtypes of lower-grade gliomas, each with distinct molecular features and clinical outcomes, and that the molecular subtypes potentially have greater significance than histological classification.

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