Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas.

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Public Summary:
Diffuse low and intermediate-grade gliomas (World Health Organization grades II and III gliomas) are cancerous brain tumors that typically occur in younger adults. These diseases have highly variable clinical behavior that is not adequately predicted on the basis of state-of-the-art diagnostic methods, which include looking at the tumor cells under the microscope to classify the diseases into astrocytomas, oligodendrogliomas and oligoastrocytomas. This diagnostic strategy can be subjective and can vary depending on the observer, contributing to the uncertainty during diagnosis. Some gliomas grow slowly; others quickly progress to very aggressive glioblastomas, and it is often unclear which patient will have which course of the disease. For the current study, members of The Cancer Genome Atlas Analysis Working Group took a crack at categorizing lower-grade gliomas using an integrated profile DNA and RNA sequences, along with other genomic analyses on samples from almost 300 individuals with lower-grade gliomas. The approach established more reliable classifications than the traditional microscopy approach. In particular, this combined molecular data classified low and intermediate forms of astrocytoma, oligoastrocytoma, and oligodendroglioma into three main molecular groups, largely defined by genetic features, including the IDH1/2 gene mutations, chromosome 1 and 19 co-deletion, and TP53 mutations. These results point to the possibility of classifying lower-grade gliomas in the clinic using a small set of informative biomarkers that can be examined using tumor DNA. Integrated molecular profiles for tumor and matched normal samples from 293 individuals with grade II and grade III glioma also provided a clearer look at molecularly defined subtypes containing these alterations. In particular, tumors containing IDH mutations could further be sub-classified depending on the presence or absence of the chromosome 1 and 19 co-deletion. Oligodendrogliomas almost always contained both IDH mutations and the 1p/19q deletion, suggesting that these mutations may molecularly define that subtype. The most commonly mutated genes in that subtype included NOTCH1, FUBP1, and CIC. The IDH-mutant, 1p/19q-deleted tumors also tended to contain alterations that affected the region that regulates the amount of the telomerase-coding gene TERT, boosting expression and activity of this molecule, important for cancer cell divisions. On the other hand, tumors from the astrocytoma subtype frequently carried IDH mutations in combination with TP53 and the ATRX gene glitches, while tumors lacking IDH mutations defined an aggressive subtype with some genetic and clinical similarities to the most aggressive brain tumor, glioblastoma. The study will inform how doctors define and treat grade II and grade III gliomas.

Scientific Abstract:
BACKGROUND: Diffuse low-grade and intermediate-grade gliomas (which together make up the lower-grade gliomas, World Health Organization grades II and III) have highly variable clinical behavior that is not adequately predicted on the basis of histologic class. Some are indolent; others quickly progress to glioblastoma. The uncertainty is compounded by interobserver variability in histologic diagnosis. Mutations in IDH, TP53, and ATRX and codeletion of chromosome arms 1p and 19q (1p/19q codeletion) have been implicated as clinically relevant markers of lower-grade gliomas. METHODS: We performed genomewide analyses of 293 lower-grade gliomas from adults, incorporating exome sequence, DNA copy number, DNA methylation, messenger RNA expression, microRNA expression, and targeted protein expression. These data were integrated and tested for correlation with clinical outcomes. RESULTS: Unsupervised clustering of mutations and data from RNA, DNA-copy-number, and DNA-methylation platforms uncovered concordant classification of three robust, nonoverlapping, prognostically significant subtypes of lower-grade glioma that were captured more accurately by IDH, 1p/19q, and TP53 status than by histologic class. Patients who had lower-grade gliomas with an IDH mutation and 1p/19q codeletion had the most favorable clinical outcomes. Their gliomas harbored mutations in CIC, FUBP1, NOTCH1, and the TERT promoter. Nearly all lower-grade gliomas with IDH mutations and no 1p/19q codeletion had mutations in TP53 (94%) and ATRX inactivation (86%). The large majority of lower-grade gliomas without an IDH mutation had genomic aberrations and clinical behavior strikingly similar to those found in primary glioblastoma. CONCLUSIONS: The integration of genomewide data from multiple platforms delineated three molecular classes of lower-grade gliomas that were more concordant with IDH, 1p/19q, and TP53 status than with histologic class. Lower-grade gliomas with an IDH mutation either had 1p/19q codeletion or carried a TP53 mutation. Most lower-grade gliomas without an IDH mutation were molecularly and clinically similar to glioblastoma. (Funded by the National Institutes of Health.).
