Nature Reviews Clinical Oncology **12**, 502 (2015); published online 14 July 2015; doi:10.1038/nrclinonc.2015.111

CNS CANCER

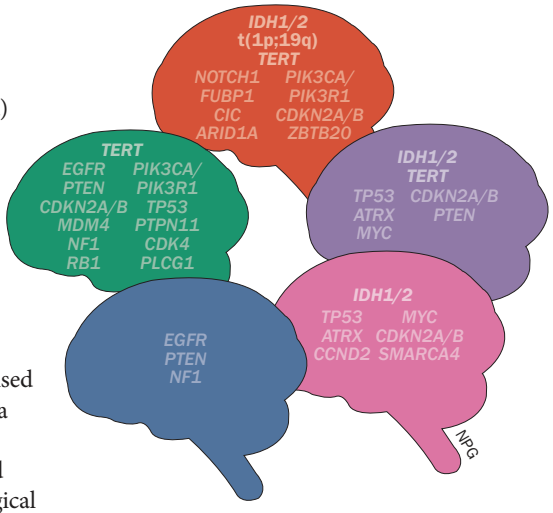
Molecular classification of glioma

The clinical characteristics and prognosis of patients with grade II–III glioma and glioblastoma (grade IV glioma) are not accurately reflected by histological classifications. Two recent studies support the development of a new molecular classification.

The Cancer Genome Atlas (TCGA) have identified three nonoverlapping disease subgroups based on unsupervised clustering of diverse omics data from 293 grade II–III gliomas. "These molecular subtypes did not correlate well with histological class, but correlated extremely well with biomarkers used clinically to characterize these tumours," states Daniel Brat, who led the study. Two subgroups comprised gliomas with *IDH* (*IDH1/2*) mutations, but could be distinguished by the presence of either the t(1p;19q) chromosomal translocation (1p/19q codeletion), or *TP53* mutations; the third disease subset was *IDH* wild-type.

The TCGA study found *TERT* alterations in 64% and 90% of *IDH*-wild-type and *IDH*/t(1p;19q)-mutant gliomas, respectively, but only 4% of *IDH*/*TP53*-mutated tumours. In the second study, these differences in *TERT* status, considered together with *IDH* and t(1p;19q) status, enabled Jeanette Eckel-Passow *et al*. to develop a classification that stratified 97.4% of 1,087 grade II–IV gliomas into five subtypes: tumours with *IDH*/t(1p;19q)/*TERT* alterations; *IDH*/*TERT* mutations; *IDH* mutations only; *TERT* mutations only; or triple-negative gliomas.

In both studies, the subgroups identified differed in terms of age at diagnosis and somatic alterations (see image), and the patterns observed were mostly consistent between the studies. Importantly, the glioma subtypes identified had prognostic significance. "The *IDH*-wild-type gliomas had genetic characteristics and an aggressive clinical behaviour similar to that of primary glioblastoma," Brat explains. By contrast, *IDH*-mutated, 1p/q19 codeleted gliomas had a predominantly oligodendroglial histology—typically associated with a good response to chemoradiotherapy—and the most favourable outcome.



The studies also provided information on the process of glioma tumorigenesis, and linked molecular subgroups with specific germline mutations. "For example, while it is the rarest of the five molecular groups, *IDH*/*TERT*-mutant glioma (without 1p/19q codeletion) is the only group that is associated with *TP53* germline variants," says Eckel-Passow.

"Incorporating our molecular classification schema into a patient's diagnosis will more-accurately predict their prognosis and help determine how they should be treated," Eckel-Passow concludes. Brat adds, "enrolment and stratification of future clinical trials based on these molecular subsets should advance the development of effective therapies and uncover further predictive markers."

David Killock

Original articles The Cancer Genome Atlas Research Network. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. *N. Engl. J. Med*. **372**, 2481–2498 (2015) | Eckel-Passow, J. E. *et al*. Glioma groups based on 1p/19q, *IDH*, and *TERT* promoter mutations in tumors. *N. Engl. J. Med*. **372**, 2499–2508 (2015)