Glioma biomarker

1p/19q co-deletion.

ATRX.

BRAF.

CDKN2A.

Chromosome 7 Gain and Chromosome 10 Loss

EGFR

H3F3A.

H3K27M

IDH1 and IDH2.

MAPK Pathway

MGMT

MN1

MYB.

PTRF

TERT.

TP53.

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see Glioblastoma biomarker.

Diffuse gliomas exhibits different molecular and genetic profiles with a wide range of heterogeneity and prognosis. Recently, molecular parameters including ATRX gene mutation, P53, and IDH mutation status or absence or presence of 1p/19q co-deletion have become a crucial part of diffuse glioma diagnosis. Shabanzadeh Nejabad et al. tried to analyze the routine practice of the above-mentioned molecular markers focusing on the IHC method in cases of adult diffuse gliomas to evaluate their utility in the integrated diagnosis of adult diffuse gliomas. Totally, 134 cases of adult diffuse glioma were evaluated. Using the IHC method, 33,12, and 12 cases of IDH mutant Astrocytoma grade 2, 3, 4, and 45 cases of glioblastoma, IDH wild type, were molecularly diagnosed. By adding the FISH study for 1p/19q co-deletion, 9 and 8 cases of oligodendroglioma grades 2 and 3 also were included. Two IDH mutant cases were negative for IDH1 in IHC but revealed a positive mutation in further molecular testing. Finally, we were not able to incorporate a complete integrated diagnosis in 16/134(11.94%) of

cases. The main molecularly unclassified group was histologically high-grade diffuse glial tumors in patients less than 55 years old and negative IDH1 immunostaining. P53 was positive in 23/33 grade 2, 4/12 grade 3, and 7/12 grade 4 astrocytomas, respectively. Four out of 45 glioblastomas showed positive immunostain, and all oligodendrogliomas were negative. In conclusion, a panel of IHC markers for IDH1 R132H, P53, and ATRX significantly improves the molecular classification of adult diffuse gliomas in daily practice and can be used as a tool to select limited cases for co-deletion testing in the low resources area [1)].

Nakae et al., previously investigated IDH1/2 and TP53 mutations via Sanger sequencing for adult supratentorial gliomas and reported that PCR-based sequence analysis classified gliomas into three genetic subgroups that have a strong association with patient prognosis: IDH mutant gliomas without TP53 mutations, IDH and TP53 mutant gliomas, and IDH-wildtype gliomas. Furthermore, this analysis had a strong association with patient prognosis. To predict genetic subgroups prior to initial surgery, we retrospectively investigated preoperative radiological data using CT and MRI, including MR spectroscopy (MRS), and evaluated positive 5-aminolevulinic acid (5-ALA) fluorescence as an intraoperative factor. We subsequently compared these factors to differentiate each genetic subgroup. Multiple factors such as age at diagnosis, tumor location, gadolinium enhancement, 5-ALA fluorescence, and several tumor metabolites according to MRS, such as myo-inositol (myo-inositol/total choline) or lipid20, were statistically significant factors for differentiating IDH mutant and wild type, suggesting that these two subtypes have totally distinct characteristics. In contrast, only calcification, laterality, and lipid13 (lipid13/total Choline) were statistically significant parameters for differentiating TP53 wild-type and mutant in IDH mutant gliomas. In this study, we detected several pre- and intraoperative factors that enabled us to predict genetic subgroups for adult supratentorial gliomas and clarified that lipid13 quantified by MRS is the key tumor metabolite that differentiates TP53 wild-type and mutant in IDH mutant gliomas. These results suggested that each genetic subtype in gliomas selects the distinct lipid synthesis pathways in the process of tumorigenesis [2)].

Glioma grading and classification, today based on histological features, is not always easy to interpret and diagnosis partly relies on the personal experience of the neuropathologists. The most important feature of the classification is the aimed correlation between tumor grade and prognosis. However, in the clinical reality, large variations exist in the survival of patients concerning both glioblastomas and low-grade gliomas. Thus, there is a need for biomarkers for a more reliable classification of glioma tumors as well as for prognosis.

Sorting and grading of glial tumors by the WHO grade classification provide clinicians with guidance as to the predicted course of the disease and choice of treatment. Nonetheless, histologically identical tumors may have very different outcome and response to treatment. Molecular biomarkers that carry both diagnostic and prognostic information add useful tools to traditional classification by redefining tumor subtypes within each WHO category. Therefore, molecular markers have become an integral part of tumor assessment in modern neurooncology and biomarker status now guides clinical decisions in some subtypes of gliomas. The routine assessment of IDH status improves histological diagnostic accuracy by differentiating diffuse glioma from reactive gliosis. It carries a favorable prognostic implication for all glial tumors and it is predictive for chemotherapeutic response in anaplastic oligodendrogliomas with 1p/19q co-deletion chromosomes. Glial tumors that contain chromosomal codeletion of 1p/19q are defined as tumors of oligodendroglial lineage and have favorable prognosis. MGMT promoter methylation is a favorable prognostic marker in astrocytic high-grade gliomas and it is predictive for chemotherapeutic response in anaplastic gliomas with wild-type

IDH1/2 and in elderly glioblastoma [3].

The growing awareness that histologically indistinguishable tumors can be divided into more precise and biologically relevant subgroups has demanded a more global routine approach to biomarker assessment. These considerations have begun to intersect with the decreasing costs and availability of genome-wide analysis tools and, thus, incorporation into routine practice [4].

The Metabolomics profiling of glioma tissue as well as serum may be a valuable tool in the search for latent biomarkers for future characterization of malignant glioma [5].

In a article, Li et al. from Nanjing provided an overview of how Long non-coding RNAs (lncRNAs) regulate cellular processes in glioma, enumerated the lncRNAs that may act as glioma biomarkers, and showed their potential clinical implications [6].

see also Glioma diagnosis.

Glioma shed extracellular vesicles (EVs), which invade the surrounding tissue and circulate within both the cerebrospinal fluid and the systemic circulation. These tumor-derived EVs and their content serve as an attractive source of biomarkers.

In a review, Hochberg et al., discuss the current state of the art of biomarkers for glioma with emphasis on their EV derivation [7].

A study identified an 18-cytokine signature for distinguishing glioma sera from normal healthy individual sera and also demonstrated the importance of their differential abundance in glioma biology [8].

Shi et al., from Hangzhou, Department of Neurosurgery, Changhai Hospital, Second Military Medical University, Shanghai. Department of Neurosurgery, Huai'an Second People's Hospital, The Affiliated Huai'an Hospital of Xuzhou Medical University, Huai'an, China, extracted data sets from the Gene Expression Omnibus data set by using “glioma” as the keyword. Then, a coexpression module was constructed with the help of Weighted Gene Coexpression Network Analysis software. Besides, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed on the genes in these modules. As a result, the critical modules and target genes were identified. Eight coexpression modules were constructed using the 4,000 genes with a high expression value of the total 141 glioma samples. The result of the analysis of the interaction among these modules showed that there was a high scale independence degree among them. The GO and KEGG enrichment analyses showed that there was a significant difference in the enriched terms and degree among these eight modules, and module 5 was identified as the most important module. Besides, the pathways it was enriched in, hsa04510: Focal adhesion and hsa04610: Complement and coagulation cascades, were determined as the most important pathways. In summary, module 5 and

the pathways it was enriched in, hsa04510: Focal adhesion and has 04610: Complement and coagulation cascades, have the potential to serve as glioma biomarkers [9].

Eckel-Passow et al., defined five glioma molecular groups with the use of three alterations: mutations in the telomerase reverse transcriptase TERT promoter, mutations in IDH, and codeletion of chromosome arms 1p19q (1p/19q co-deletion). They tested the hypothesis that within groups based on these features, tumors would have similar clinical variables, acquired somatic alterations, and germline variants.

They scored tumors as negative or positive for each of these markers in 1087 gliomas and compared acquired alterations and patient characteristics among the five primary molecular groups. Using 11,590 controls, they assessed associations between these groups and known glioma germline variants.

Among 615 grade II or III gliomas, 29% had all three alterations (i.e., were triple-positive), 5% had TERT and IDH mutations, 45% had only IDH mutations, 7% were triple-negative, and 10% had only TERT mutations; 5% had other combinations. Among 472 grade IV gliomas, less than 1% were triple-positive, 2% had TERT and IDH mutations, 7% had only IDH mutations, 17% were triple-negative, and 74% had only TERT mutations. The mean age at diagnosis was lowest (37 years) among patients who had gliomas with only IDH mutations and was highest (59 years) among patients who had gliomas with only TERT mutations. The molecular groups were independently associated with overall survival among patients with grade II or III gliomas but not among patients with grade IV gliomas. The molecular groups were associated with specific germline variants.

Gliomas were classified into five principal groups on the basis of three tumor markers. The groups had different ages at onset, overall survival, and associations with germline variants, which implies that they are characterized by distinct mechanisms of pathogenesis [10].

Long non-coding RNA in glioma

see Long non-coding RNA in glioma.

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