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EDITORIAL

Update of the 2021 WHO classification of tumors of the central nervous system: adult diffuse gliomas

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Introduction

The fifth edition of the WHO classification of tumors of the central nervous system (CNS) [17], published in 2021, has become more reliant on molecular testing for the diagnosis and grading of diffuse gliomas, compared to the 2016 WHO revised 4th edition [6, 9] that adopted molecular information to define tumor entities for the first time. Under the 2021 revision, only three primary tumor types remained in the group of diffuse gliomas in adults (termed "adult-type diffuse gliomas"), namely, "astrocytoma, IDH-mutant," "oligodendroglioma, IDH-mutant and 1p/19q codeleted," and "glioblastoma, IDH-wildtype," all of which are solely defined by canonical molecular alterations regardless of morphological features.

The 2021 revision further demarcated adult-type diffuse glioma from its pediatric counterpart, "pediatric-type diffuse gliomas." Pediatric-type diffuse gliomas are molecularly distinctive from the adult-type in the absence of IDH mutation and 1p/19q codeletion; the presence of RAS-MAPK pathway alteration in the low-grade group and H3 alterations in the high-grade group typifies them, respectively. Although the adult and pediatric types represent the gliomas that occur primarily in adults and children, the pediatric type may occur in adults, and the adult type may more rarely occur in children [5].

Being the adult type restrictedly defined by the molecular signature of this type, the remaining IDH-wildtype and 1p/19q non-deleted are supposed to be categorized within the pediatric type. Nonetheless, the distinction between the IDH-wild adult and pediatric types is sometimes unclear, causing diagnostic difficulties in routine daily practice.

Subtypes of IDH-mutant gliomas

After the publication of the 2021WHO CNS, a few subtypes of IDH-mutant gliomas were added to this group of tumors (Table 1). The rare infratentorial variant [1] often harbors non-canonical mutations of either *IDH1* or *IDH2*. The primary mismatch repair deficient type [16], which shares the identical IDH genotype with "astrocytoma, IDH-mutant," carries mismatch repair deficiency germline mutations in DNA mismatch repair genes (*MLH1*, *MSH6*, *MSH2*) that can be detected by immunohistochemistry demonstrating the loss of mismatch repair proteins. This subtype exhibits a highly aggressive behavior than other IDH-mutant gliomas. Oligosarcoma [15] is a recently described subtype of "oligodendroglioma, IDH-mutant and 1p/19q codeleted," which derives from prior oligodendroglioma or develops de novo, carrying *CDKN2A/B* homozygous deletion. The above four subtypes of IDH-mutant gliomas are exclusively clustered in DNA methylation-based t-SNE from known methylation classes, supporting that each type is epigenetically distinctive.

Other rear phenomena in IDH-mutant gliomas are somatic IDH mosaicism [8, 11] and concurrent *IDH1* and *IDH2* mutations [18]. Intertumoral, somatic IDH mosaicism has been described in patients with Ollier and Maffucci syndrome [12], which are rare non-hereditary enchondromatosis. The mosaicism can be demonstrated by sub-threshold peaks at the position where *IDH1* R132H mutations are expected, indicating that the mutant allele is present in a small subpopulation of the tumor cells. Some researchers consider IDH mosaicism a possible alternative mechanism of cancer preposition [8] or a determinant of recurrence and resistance to therapy [11].

Concurrent *IDH1* and *IDH2* mutations are rare but have been reported in acute myeloid leukemia (AML) [13] and

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Table 1 Subtypes of IDH-mutant gliomas

Tumor type	Molecular hallmarks (mutations and homozygous deletion)
Astrocytoma, IDH-mutant	*IDH1* or *IDH2* mt, ATRX loss > 90% *CDKN2A/B* HD
Infratentorial astrocytoma, IDH-mutant [1]	*IDH1* (< 25% *IDH1*R132H) or *IDH2*, ATRX loss < 50% *CDKN2A/B* HD
Primary mismatch repair deficient IDH-nutant astrocytoma (PMMRDIA) [16]	*IDH1* or *IDH2* mt, ATRX loss > 90% *CDKN2A/B* HD MLH1 or MSH6 or MNH2 loss
Oligodendroglioma, IDH-mutant and 1p/19q codeleted	*IDH1* or *IDH2* mt, 1p/19q codeletion, *TERT* promoter mt
Oligosarcoma, IDH-mutant [15]	*IDH1* or *IDH2* mt, 1p/19q codeletion, *TERT* promoter mt *CDKN2A/B*
Somatic IDH mosaicism [8, 11]	*IDH1*R132H mt (the mutant allele is present in a small subpopulation of the tumor cells)
Concurrent *IDH1* and *IDH2* mutations [18]	*IDH1* R132H mt, *IDH2* R172G *TP53* mt, *CDKN2A/B* HD, *MYC* copy number gain

HD homozygous deletion, *mt* mutation

chondrosarcoma [10]. Precise incidences of the concurrent are unknown; one study identified 5.7% in AML [13], the other 3.0% in chondrosarcoma [10], and the other four tumors (0.7%) out of 579 diffuse gliomas [4]. A single case report described a patient with "astrocytoma, IDH-mutant, CNS WHO grade 3," who remained well for ten years without recurrence after subtotal resection with chemo-radiotherapy [18]. Although the significance of concurrent *IDH1/2* mutations, which are probably underestimated due to the use of *IDH1* R132H antibody, is currently unknown, it might be a hint for elucidating the role of IDH mutations in glioma cell metabolism.

Controversial issues in IDH-wildtype gliomas

One of the most challenging diagnostic issues in diffuse gliomas in the adult population is that of IDH-wildtype gliomas [3]. As mentioned earlier, the 2021 revision certified only one tumor type, "glioblastoma, IDH-wildtype," as an adult IDH-wildtype. Nonetheless, considering pediatric-type gliomas may occur in adults, all the adult- and pediatric-IDH-wildtype gliomas should always be included in the differential diagnosis. The ambiguity of the diagnostic criteria of "diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype" makes the case more complicated. For example, "diffuse pediatric-type high-grade glioma RTK2" is enriched for *EGFR* amplifications (~ 50%) and *TERT* promoter mutations (~ 64%) [7] (Table 2), both of which are ones of essential diagnostic criteria for "glioblastoma, IDH-wildtype [14]." Therefore, a DNA methylation array might be necessary to distinguish the adult type RTK2 from the pediatric type.

Such ambiguity also lies in lower-grade IDH-wildtype gliomas. One study, which analyzed 724 adult patients with gliomas, identified 151 patients with IDH-wildtype, H3-wildtype diffuse glioma WHO grade II and III in 2016WHO criteria [2]. Among them, methylation array analysis was performed for 54 lower-grade gliomas (LGG)

Table 2 Comparison between adult and pediatric RTK2 gliomas

	GBM RTK2 [14]	Pediatric HGG RTK [7]
p*TERT* mutation	82%	64%
EGFR amplification	63%	50%
Combined Chr 7 gain/Chr 10 loss	79%	–
Chr 7 gain/Chr 10 losses	–	28%/50%

GBM glioblastoma, *HGG* high-grade glioma, *pTERT TERT* promoter, *Chr* chromosome

without poor prognostic predicters, i.e., *TERT* promoter mutations, *EGFR* amplification, *PDGFRA* gain/amplification, and *PTEN* deletion. Thirty-one of 54 LGG did not match any known methylation class and had significantly better prognoses than those clustered with glioblastoma, suggesting the existence of a heterogeneous group of gliomas that did not fall into any categories in the current WHO classification.

The latest version of the DNA methylation profiling classifier, version 12.5, of the German cancer research center (DKFZ), has added more than ten novel methylation class subtypes in pediatric and adult groups (www.molecularneuropathology.org). Representative examples of the novel methylation class include "anaplastic neuroepithelial tumor with condensed nuclei," "adult-type diffuse high-grade glioma, IDH-wildtype, subtype B, E, and F," and "diffuse pediatric-type high-grade glioma, H3 wildtype and IDH wild type, Subtype A and B."

In summary, the classification of adult and pediatric diffuse gliomas remains an ongoing process, and diagnosing IDH-wildtype could be challenging even with a DNA methylation array and DKFZ profiling classifier. Further data acquisition and risk stratification are needed for optimal classification to diagnose and treat diffuse gliomas.

Data availability All the data is available upon request.

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