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Review Article

Molecular Biology of the most Conventional Gliomas -An Essential Review

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Abstract

Malignant brain tumors are one of the most important causes of morbidity and mortality in a wide range of individuals. Malignant brain tumors, gliomas mainly are the most conventional primary intracranial tumors in adult individuals. They appear in the brain and concern the glial tissue. The World Health Organization (WHO) grade II tumors, known as low-grade tumors incline to progress to grade III high-grade gliomas and, eventually, to grade IV glioblastoma multiforme (GBM), which is the most conventional glioma, with a period of 12-15 months median survival after definitive diagnosis. Progress in cancer research regarding the genetics and molecular biology of GBM has been substantially increased in the past decades, leading to classification methods that could contribute to management and classification of GBM patients into different groups. The WHO grading system for glial tumors classifies the distinct neoplasms of astrocytic or oligodendroglial origin, as diffuse astrocytoma or GBM, oligodendroglioma, oligoastrocytoma, astrocytoma, and ependymoma, which constitute molecularly, genetically and clinically distinctive unique entities. The human glioma molecular biology is a complicated and fast-developing field in which basic research is necessary to meet clinical expectations in terms of anti-tumor effectiveness. Many researches contributed to advancement in the knowledge of gliomas pathogenesis and biology and to the detection of new agents for personalized targeted molecular therapy. Despite the progress in molecular biology, significant contribution to the overall survival and life quality still lacks. Unluckily, the fundamental literature concerning gliomas molecular biology remains indistinct. The current article presents a comprehensive review of current knowledge regarding the molecular characteristics of glioma tumorigenesis from the molecular biology perspective, focused on the major intracellular signaling pathways implicated in glioma pathogenesis, genomic and epigenetic relevant characteristics of glioma, the predictive values of molecular indices according to the WHO classification of glial neoplasms, and the implication of molecular and cellular heterogeneity in gliomas, responsible for its therapy resistance.

Key Words: glioma, glioblastoma, astrocytoma, oligodendroglioma, epemdymoma, molecular biology, genetics, epigenetics

Introduction

Gliomas constitute the most frequent malignant brain tumors in adult individuals. They can appear in any location in the Central Nervous System (CNS); however, they arise mainly in the brain, come from glial cells and can be either astrocytic, oligodendrocytic or oligoastrocytic [1]. More than 75 % of the diffuse gliomas in adult individuals are astrocytic, approximately two-thirds of those are represented by the most malignant form, Glioblastoma Multiforme (GBM). Oligoastrocytomas (OAs) and Oligodendrogliomas (ODs) have been, in general, gathered together as

oligodendroglial neoplasms and represent less than 10% of the diffuse gliomas. It must be noted that, glioma variations with a more circumscribed growth pattern are more common than diffuse gliomas in children, whereas oligodendroglial neoplasms are rare, less than 4 % of the primary CNS tumors [2].

Glioma's ratio ranges from 4.67 to 7.73 cases per 100,000 individuals, whereas in a recent research its incidence ranges from 0.59 to 5 cases per 100,000 individuals [3]. The WHO categorizes gliomas in grades varying from I to IV according to their aggressiveness (Table 1), with GBM being a grade IV astrocytic glioma [4], which is the fast-growing and the most aggressive tumor and frequently spreads out the surrounding brain tissues, and constitutes the deadliest tumor type in the brain [5,6], with an incidence of 0.59 to 3.69 cases per 100,000 individuals. The mentioned incidence increases with age, getting a maximum between 75 and 84 years, and is greater in white males [7]. GBM is the most conventional malignant primary brain neoplasm [8], represents more than 50,0% of all primary CNS malignant tumors [8,9], 50-60% of astrocytic tumors, 12-15% of all intracranial tumors [10], and has a poor prognosis despite the remarkable progress in knowledge about its molecular pathogenesis and biology, since a rate of less than10% of patients survive more than 5 years, with an average survival period of 12-15 months after the eventual diagnosis [10], whereas the median survival of almost 15 months [11] and a 5-year relative survival rate of 6.8%, although this depends on the age at diagnosis and the patient's gender [12].

Type of Glioma [4] (modified)	Central Nervous System WHO Grade
Adult-type diffuse gliomas	
Glioblastoma, IDH-wildtype	IV
Astrocytoma, IDH-mutant	II, III, IV
Oligodenroglioma, IDH-mutant, and 1p/19q-co-deleted	II, III
Circumscribed astrocytic gliomas	
Pilocytic astrocytoma	I
Pleomorphic xanthoastrocytoma	II, III
High-grade astrocytoma with piloid features	-
Sub-ependymal giant cell astrocytoma	I
Ependymal tumors	

Table 1: WHO (2021) Gliomas classification (more common types)

The great majority of GBMs cases, 90% appear *de novo* in elderly individuals, without previous histopathological or clinical evidence of a less malignant precursor lesion, also known as primary GBMs. Secondary GBMs come from lower grade gliomas, known as anaplastic or diffuse astrocytomas. They develop in younger individuals, are characterized by a lower necrosis degree, are commonly discovered in the frontal lobe and have significantly favorable prognosis than that of primary GBMs. The mentioned GBM forms, histologically, are practically indiscernible, however, they are different in their molecular aspects that concern genetic and epigenetic profiles [13]. GBM is further divided into different subgroups and each one of those is linked with a different molecular signature. The WHO in 2016, announced a brain neoplasms classification update which comprises GBM in the oligodendroglial and diffuse astrocytic neoplams group and divides it into three subgroups according to isocitrate dehydrogenase (IDH) mutations, as 1) GBM, IDH-wild type, clinically recognized as *de novo* or primary GBM and predominant in individuals over 55 years of age, which represents 10% of GBM cases, 2) GBM, IDH-mutant, clinically recognized as secondary GBM and more conventional in younger individuals, which represents 90% of GBM cases,and 3) GBM NOS, which is not otherwise specified, does not match into the previous classes and is not well determined. Moreover, GBM IDH-wild type is able to be divided into different subtypes according to histologic elements, as 1) gliosarcoma, which shows a metaplastic mesenchymal ingredient, 2) giant cell GBM, which identified by the existence of multi-nucleated cells, and 3) epithelioid GBM, which constitutes a temporary new GBM variant added to the WHO 2016 classification in 2016 which contains large epithelioid cells and variably present rhabdoid cells [14].

GBM is a complicated and heterogeneous disease and the classification methods are essential for the establishment of personalized targeted therapies for the discrete subtypes. GBM molecular classification has been extended over the years in order to acquire a better understanding of the molecular processes that lead to oncogenesis and tumor progression [15]. GBM gene expression profiling permitted the recognition of various molecular subgroups [16-18]. Growingly, surveys have detected that GBM is a notably heterogeneous group of neoplasms, and its pathogenesis implicates complicated changes in genetics, epigenetics, and transcriptomics, which eventually result in remarkable alterations in substantial signaling pathways [16,19-21].

Oligodendroglial tumors, comprising ODs and OAs, account for between 5% and 18% of all primary human brain neoplasms [22]. OD is a type of diffusely infiltrating glioma type and constitutes approximately 5% of primary intracranial tumors [23]. Mixed OA and OD account for 5%-20% of all glial neoplasms [24]. ODs are, generally, low-grade WHO grade II neoplasms, are slow-growing and have a promising therapy response when compared with other glioma types. Grade III anaplastic OD is a more malignant form of the neoplasm that portends a less favorable prognosis and may appear *de novo* or as degeneration from the lower grade OD [25]. ODs are uncommon, have an incidence of 0.2 cases per 100,000 patients and are the 3rd most conventional primary brain neoplasm after GBM and diffuse astrocytoma. ODs comprise approximately 5% of all primary CNS neoplasms [26]. They have a light male predominance, recorded from 1.1-2: 0.92 male to female ratio [27]. ODs are predominantly an adult neoplasm with a peak incidence in the 4th and 5th decades and a smaller peak of tumor incidence that occurs in children 6 to 12 years of age, whereas the low-grade ODs incline to appear in slightly younger individuals [24].

OAs display both astrocytic and oligodendroglial morphologic characteristics [28]. Because of the rather indistinct criteria for determining OA, OA incidence diversifies substantially between different studies. According to molecular findings, OAs possess an intermediate place between astrocytomas and ODs [29].

Astrocytoma is an invasive intracranial neoplasm, a severe form of brain cancer characterized by the worst prognosis and a marginally higher survival rate by established therapy. Those tumors are categorized based on their grade, the aberrant development and behavior of their cells. Low-grade astrocytomas, also acquainted as grade I and II, are slow-growing neoplasms, less aggressive than high-grade astrocytomas, and are classified as grade III or IV. Grade III astrocytomas are regarded anaplastic ones, which denotes that their cells have more aberrant alterations and show a higher development rate than grade II astrocytomas. Grade IV astrocytomas, also known as GBM, are the most conventional and aggressive brain cancer form, as already mentioned [30]. According to the WHO updated classification for 2016-2021, OAs are considered as polymorphic neoplasms that may can induce ODs or astrocytic neoplasms according to their molecular components. ODs which are located in the frontal, occipital, and lobes parietal revealed a

higher allelic loss possibility than ODs which are located in the temporal lobes. Even though 30% to 70% of OAs have LOH 1p and LOH 19q [30,31] showing a genetic similarity to ODs, only 30% of OAs carry mutations in the TP53 gene or LOH 17p [32] suggesting an association with astrocytomas. Particularly, LOH1p and LOH 19q are negatively associated with TP53 mutations [33]. Ependymoma is the 3rd most conventional pediatric brain neoplasm, following astrocytoma and medulloblastoma, and more than 50% of cases concern children less than 5 years of age [1,34]. Based on the Central Brain Tumor Registry of the United States (CBTRUS) report (2014), ependymomas represent 5.2% of CNS, and all brain neoplasms and in children and adolescents 0-19 years of age compared to 1.9% of adult individuals. Based on the same source, the overall 10-year survival rate was estimated to be 79.2% [2]. Generally, the survival rate was the highest for individuals aged 20-44 years and reduces with increasing age at the time of diagnosis. Actually, the 10-year survival rate was 28.1% in individuals aged 75 years whereas, the same survival rate in children and adolescents aged 0-19 years was 66% [35,36].

Based on the CBTRUS report in 2020, ependymal neoplasms account for approximately 1.6% of all primary CNS neoplasms. Ependymal tumors incidence varies from 0.29 to 0.6 per 100,000 individual-years and is lowest in the first two decades of life and highest in the 65-74 years old individuals [37].

Tumor position is substantially dependent on the individual age, with almost 90% of pediatric ependymal neoplasms appearing intracranially, and almost 65% of adult neoplasms appearing in the spine. A remarkable morbidity and mortality has been estimated amongst individuals with intracranial ependymomas [38]. Ependymomas are primary CNS neoplasms originated from the ventricular system ependymal lining [14,39], affect children and adults and are located every-where in the CNS, including the infratentorial (IT) space, the spinal (SP) compartment, and the supra-tentorial (ST) space, and, derive from the cerebral ventricles lining, as mentioned or the central canal of the spinal cord. However, recent data suggests that the origin cells concern radial glial stem cells [40].

The Classification of Tumors of the Nervous System, reported by WHO classifies ependymomas as grades I, II, and III according to their anaplasia grade. The objective of the mentioned classification was to predict the different clinical prognoses for the different histological grades [1]. However, an increasing number of surveys challenging the hypothesis that histological grades are able to predict prognosis, particularly in different age groups and at different CNS positions [34]. That observation suggests that genetic heterogeneity within the same histological grade imposes the biological behavior of ependymomas [41].

The aim of the current article was to review the molecular characteristics of glioma tumorigenesis from the molecular biology perspective, and the molecular biomarkers that can play possible clinical roles as future directions for detecting new biomarkers and therapeutic targets.

GBM molecular biology

The great majority of GBMs are developed de novo (90%), whereas secondary ones are unusual (10%). IDH mutations are rarely observed in primary GBMs (5%), are common in secondary GBMs (85%), are responsible for neoplasm progression in early stages, and are associated with other genetic aberrations detected in low-grade gliomas, such as ATRX and TP53 mutations and 1p/19q co-deletion. GBMs also present a reverse association with gene amplification of EGFR and monosomy of chromosome 10, which are usual events in primary GBMs [42]. The recognition of IDH1 as a molecular index was critical for those two subtypes separation. They were first identified when it was detected that those mutations incurred in most secondary GBM patients [42]. In this day and age, after similar surveys concerning this issue, it has been accepted that IDH 1 mutation is the most valid secondary GBMs diagnostic molecular index [43]. In 2010, was carried out a survey regarding the genetic expression profiles of 200 GBM samples in order to provide a novel and more accurate classification form according to molecular characteristics. They were identified four clinically relevant GBM subtypes characterized by abnormalities in IDH1, PDGFRA, EGFR, and Fibronectin1 (NF1). Those are classical, neural, proneural, and mesenchymal subtypes [44].

Regardless of the mentioned differences, the TCGA report revealed, in 2008, three important genetic events in humans GBMs, a) growth signaling dysregulation via mutational activation and amplification of RTK genes, b) activation of the phosphatidylinositol-3-OH-kinase (PI (3)K) pathway, and c) inactivation of p53 and retinoblastoma (RB) tumor suppressor pathways. The mentioned events result in GBM malignant transformation; however, neoplasms require many genetic and metabolic adaptations in order to retain proliferation and spreading, comprising alterations in energetic metabolism, invasive ability, angiogenesis and migration [43].

Amplification of MDM2 oncogene has also been detected, especially, in neoplasms without TERT and TP53 mutations. In the TCGA report have also been described several GBM genetic aberrations which concern FN1mutations and PI3KR1 homozygous deletion [43]. On the contrary to primary GBMs, TP53 mutations, associated with MGMT methylation promoter, have been detected in most secondary GBMs, along with 10q, 13q, 19q, heterozygosity and partial loss of 22q [44].

In a recent study, Neftel *et al.* [45] revealed four heterogeneous cellular conditions using single-cell RNA-sequencing and confirmed the GBM intra-tumoral heterogeneity and the coherence of this subtyping. The authors classified the neural signatures growth into OD-progenitor-like, neural-progenitor-like, astrocyte-like, and mesenchymal-like conditions [46]. The neural subtype originates from ODs and astrocytes and expresses neuron-related genes, the pro-neural subtype exhibits oligodendroglial cells characteristics and is developed in young individuals [47]. The classical subtype has astrocytic characteristics and expresses stem cell and neuron precursor markers, whereas the mesenchymal subtype has characteristics of cultured astrocytic gliomas [10] Jankowska *et al.* [48] categorized GBM subtypes according to immunochemical expression and observed the classical subtype of GBM is characterized by mutation of TP53, which makes that subtype greatly sensitive to classical chemotherapy with adjuvant temozolomide (TMZ) and radiotherapy.

The mesenchymal subtype is characterized by mutations of MET, AKT, PTEN, FN1, and TRADD. Moreover, characteristic of the proneural subtype is IDH1, TP53PDGFRA, HIF, and OLIG2 mutations. Another report recorded the neuronal markers for recognizing and profiling neural GBM, such as NEFL, GABRA1, SLC12A5, and SYT1 (Table 2) [49].

Type of Adult Gliomas [4,14] (modified)	Genetic/Molecular Profiles Alterations
Glioblastoma, IDH-wildtype	IDH-wildtype, EGFR amplification, TERT promoter mutation concurrent gain of chromosome 7, loss of chromosome 10
Astrocytoma, IDH-mutant	IDH1/ IDH2 mutation, TP53 mutation, ATRX mutation, CDKN2A/B mutation
Pleomorphic xanthoastrocytoma	BRAF mutation, CDKN2A/B homozygous deletion
Pilocytic astrocytoma	KIAA1549-BRAF fusion, NF1 mutation, BRAF mutation

High-grade astrocytoma with piloid features	NF1 mutation, BRAF mutation, ATRX mutation, CDKN2A/B homozygous deletion
Sub-ependymal giant cell astrocytoma	TSC1 mutation, TSC2 mutation
Oligodendroglioma, IDH-mutant, and 1p/19q-co-deleted	IDH1/ IDH2 mutation, TERT promoter mutation, CIC mutation, FUBP1 mutation, NOTCH1 mutation, 1p/19q co-deletion
Supratentorial ependymoma	ZFTA-RELA fusion, YAP1-MAML2 fusion
Spinal ependymoma	MYCN amplification, NF2 mutation
Posterior fossa ependymoma	H3K27methylation, EZHIP over-expression

Table 2. Genetic/Molecular alterations in more common gliomas

Similar to the mentioned categorization, Herrera-Oropeza *et al.* [50] carried out a driver genes multi-omics analysis. They observed that mesenchymal subtype growth was associated with the up-regulation of the MGMT promoter and the down-regulation of ATRX, TP53, EGFR, and H3 F3A. More data was recorded for the proneural subtype, which is characterized by the overexpression of MKI67 and OLIG2, and the classical subtype by the overexpression of TP53, EGFR, VIM, and NES [50].

Cai *et al.* [51] examined the glioma reclassification according to the Gβ/γ genes expression levels using the TCGA and the Chinese Glioma Genome Atlas (CGGA) datasets. The outcomes showed that Gβ/γ heterodimer is able to activate the Erk1/2 pathway by inducing the overexpression of the guanine nucleotide-binding protein beta 4 (GNB4), which leads to the transformation of epithelial and mesenchymal cells into glioma cells. After clustering, three subgroups were obtained, GNB2, GNB3, and GNB5. GNB2 seemed to be the best malignant neoplasms indicator, particularly in individuals with IDH-mutated, non-co-deleted 1p/19q low-grade gliomas (LGGs). The same subgroup was characterized by high M0/M2 cell infiltration levels and was greatly associated with the immunosuppressive phenotype, consequently exhibiting increased PI3K-Akt/JAK-STAT pathways and tumor-associated macrophages (TAMs) and M2 macrophages high levels. It is obvious that the mentioned subgroup would display the immunosuppressive phenotype in gliomas. Each subgroup has a monadic neoplasm-related pathway that can contribute to the chemotherapeutic drug selection and increase the prognosis of glioma by selecting the proper target [51].

Two models have been suggested to explain the heterogeneity of the tumor. During tumor progression, the genomic instability enhances, and new genetic variants arise. The neoplasm heterogeneity could be explained by the presence of the mentioned genetic variants. The mentioned model is based on the conventional mutations in G1/S cell cycle checkpoint, RTK/MAPK/PI3K and TP53, occurrence [52]. Cancer Stem Cell (CSC) model suggests a hierarchical arrangement of cells within the tumor, in which only Glioblastoma Stem Cells (GSCs) are able to maintain tumor development and give rise to phenotypically various malignant cells. The mentioned models are not mutually exclusive, as GSCs themselves undergo clonal progress and obtain more growth or aggressive self-renewal properties [53].

Diverse genes seem to be important on GBM cell proliferation and invasion. In GBM samples B4GALT3 expression is increased, particularly in the proneural subtype, and this increased expression predicts poor survival for glioma individuals. B4GALT3 exhaustion decreases U251 GBM cells viability and invasion, possibly due to the β-catenin, vimentin, and matrix metalloproteinase-2 (MMP-2) reduced expression, along with an increased expression of E-cadherin. In GBM samples, expression of GBP2 is also elevated, especially in mesenchymal GBM, and this overexpression promotes, *in vitro*, cell migration and invasion [54]. FN1is an extracellular glycoprotein implicated in cell migration, and its exhaustion avoids GBP2-induced invasiveness in the examined cell lines. STAT3, which contributes to the mesenchymal subtype maintenance of the GBM's, is also implicated in expression of GBP2-promoted FN1 and other genes expression are induced by overexpression of GBP2 in U251 and U87 GBM cell lines [55]. PHIP is another gene that is implicated in motility of GBM thru its regulatory activity on the focal adhesion complex. Moreover, in melanoma cases, promotes cell invasion which shares its neuroectodermal origin with GBM. PHIP interacts with VCL, which is localized to the focal adhesions force transductor domain. PHIP down-regulation remarkably suppresses the migratory potential of the U251 cells, an expected result regarding the focal adhesions role in cell migration. The mentioned gene expression has also been proposed to be a biomarker of glioma progression [56]. The essential genetic alterations that are characteristic in GBM concern mutation of TERT promoter, deletion of PTEN tumor suppressor gene, proto-oncogene EGFR amplification, ATRX mutation high-level gene amplification, and mutation of TP53 [4,18,21]. PTEN deletion, TERT promoter mutation, and amplification of EGFR are more commonly present in primary GBM (IDH wild-type GBM), whereas mutation of ATRX and TP53 are much more usual in secondary GBM (IDH mutant-type GBM) [18]. Other essential genetic alterations recorded in GBM concern MDM4, PIK3CA, RB1, CDKN2A/B, and CDK4 [16,20]. In general, the genetic aberrations in GBM are characterized by three crucial biological processes, beginning tumor growth, evading senescence, and immortal development. Genetic deficiencies in each of the mentioned processes are necessary for gliomagenesis through the essential signaling pathways [5,18].

Epigenetic alterations, including histone modification, DNA methylation, and chromatin remodeling, have been considered as a GBM tumorigenesis hallmark [57]. MGMT promoter methylation status is one of the better examined instances, which was detected to predict the alkylating chemotherapy benefit and has clinical significance in GBM patient prognosis [58]. Epigenetic modifications have been largely observed in a genome-wide scale in GBM and showed some interesting aspects [59]. For instance, by describing promoter DNA methylation changes in 272 GBM tumors from TCGA, a special samples subset with concerted hyper-methylation at a wide number of CpG island loci (G-CIMP) have been detected. Moreover, G-CIMP phenotype patients inhibited distinct clinical characteristics and prognoses, showing the possible role of epigenetic modifications in clarifying patient classification [60]. In a similar way, a DNA methylation-based profile could categorize CNS tumors, and GBM, into different cancer entities, showing again the epigenetic alterations possibility in cancer diagnosis [61].

It has been found that the DNA methylation environment showed expansive heterogeneity in time and space during GBM progression [62]. Recently, it was observed that epigenetic remodeling was also associated with tumor microenvironment as it could influence the activity of immune cells and regulate antitumor immune response within the GBM neoplasm microenvironment [63]. Mechanistically, epigenetic modifications could result in transcriptional aberrations and influence diverse biological processes, such as cell cycle, cell differentiation, angiogenesis, apoptosis, and eventually regulate GBM proliferation and development of neoplasm cells [57]. GBM molecular pathogenesis, and the crucial signaling pathways implicated in GBM tumorigenesis and development, concern three key signaling pathways that are constantly and frequently modified in GBM, namely RTK, TP53, and RB pathway [16,19,20,64], that interact with each other and have some degree of overlap as some genes that are implicated in one pathway may also be involved in other pathways (Figure 2).

The signaling of receptor tyrosine kinase (RTK) is the most commonly changed signaling pathway in GBM, particularly in IDH-wild-type GBM tumors. RTK is a cell-surface receptor that binds growth factors [65], the family of which contains TGFR, EGFR, FGFR, PDGFR, VEGFR, and MET, and consists a substantial element of signal transduction pathways that mediate cell-to-cell communication. In GBM cases, the RTK signaling activation through the PI3K/AKT/ m TOR pathway induces cell survival, proliferation, differentiation, and migration [66,67]. The most usual RTK pathway targets are PTEN and EGFR, the former acts as a tumor suppressor gene whereas the second has oncogenic role. In GBM cells, the signaling activation of the EGFR and PI3K/AKT/mTOR pathways could be affected either through EGFR amplification, leading to EGFR overexpression, and/or EGFR mutation. PTEN as a pathway negative regulator, could be inactivated through deletion or mutation, and thus expedites the pathway activation and induces cell survival, invasion, and migration. Ras pathway (Ras/BRAF/MEK), is another usually changed RTK pathway in GBM. Active Ras (Ras-GTP) promotes cell cycle progression, cell survival, and migration through a downstream effectors cascade [66,67]. RTK has been proposed as a druggable target in GBM and is expansive examined in clinical trials [67-70].

TP53 is a tumor suppressor gene and a DNA-binding transcription factor, which plays crucial roles in tumor prevention by regulating an extensive diversity of cellular processes, such as invasion, proliferation, apoptosis evasion, and migration. The TP53/MDM2/CDKN2A signaling pathway is deregulated in 94% of GBM cell lines and 84% of GBM cases [71]. TP53 inactivation by mutation, which is found in almost 2/3 IDH-mutant GBM and 1/3 IDH-wild-type GBM results in its tumor suppressive functions loss and, consequently, leads in tumorigenesis. MDM2, a p53 inhibitor, mediating p53 degradation and therefore promotes tumorigenesis. The amplification of MDM2 is commonly mutually exclusive with the mutation of TP53 and is more regularly observed in primary GBMs that lack the mutation of TP53. CDKN2A is another TP53 pathway regulator and its homozygous deletion, which is dominant in 22-35% of all GBM cases (58% of IDH-wild-type GBM and 16-47% IDH-mutant GBM), results in TP53 pathway inactivation and is related with lower overall survival in GBM cases [64,71]. CDKN2A has presently been comprised into the WHO classification for gliomas, indicating its essential potential as a landmark marker in the clinical management of GBM [21]. The RB protein pathway is also frequently modified in GBM and plays a critical role in regulating GBM tumorigenesis [64,67]. The phosphorylation of RB protein, which is caused by the CDK4/Cyclin D1complex, is able to inhibit the progress of cell cycle from the G1 to S phase by binding with the E2F transcription factor. RB pathway could be connected with the TP53 pathway through CDKN2A, which encodes Arf and Ink4a proteins and plays an essential role in activating TP53and, RB respectively. The RB pathway development inhibition function is frequently deranged in GBM, most frequently due to RB1 and CDKN2A/CDKN2B inactivation and amplification of CDK4 and CDK6 [72,73]. RB1 promoter methylation, which is frequent in secondary GBM (IDH-mutant), can also lead to decreased expression of RB1 and cell-cycle check-point function and eventually results in abnormally regulated cell cycle and uncontrolled cell proliferation [73]. CDK4 and CDK6 inhibitors have demonstrated hopeful antitumor effectiveness in GBM and are being investigated in clinical trials [74].

Astrocytoma molecular biology

Astrocytoma is one of severe and invasive brain malignant tumors with the worst prognosis and a slightly higher survival rate by conventional management. They are categorized based on their grade, according to the abnormal emergence and behavior of their cells. Low-grade astrocytomas also known as grade I and II (or diffuse astrocytoma), are slow-growing tumors less aggressive than high-grade ones, classified as grade III or IV. Diffuse astrocytoma has a chance to progress in a more dangerous tumors over time. Grade III astrocytomas are regarded anaplastic astrocytomas, which means that the cells display more anomalous alterations and have a higher development rate than grade II astrocytomas. Grade IV astrocytomas, known as GBMs, are the most severe and aggressive brain cancer form [75]. The tumor can be further categorized based on the genetic variety, such as the IDH1 or IDH2 mutation [76,77].

Various molecular genetic events resulted in astrocytoma differentiation from grades I-IV. Three critical events, the gene deletion that operates as a tumor suppressor gene on chromosome 22q, PDGF gene proliferation, and TP53 gene inactivation, have been linked with grade II astrocytoma appearance with enhanced cellular proliferation and reduced apoptosis. At loci of chromosomes 9p, 11p, 13q, and 19q, CDK4 and tumor suppressor gene suppression are related with the appearance of anaplastic astrocytomas (AAs) [75].

Low grade astrocytomas, classified as grade II, are characterized by several molecular genetic alterations and mutations. IDH mutations and the 1p/19q co-deletion, are the two features which distinguish ODs, also known as diffuse gliomas, from other gliomas types [78]. The IDH mutation seems to play a critical role in appearance of several types of gliomas, according to the WHO [7]. The IDH mutation has been observed in approximately 80% of grade II-III gliomas and subsequent GBM cases [42,79]. In gliomas the IDH1 mutation influences amino acid residue 132, and the mutation major segment (more than 85%) contains a heterozygous alteration from arginine to histidine (R132H) [80]. That amino acid residue is localized in the active site of the enzyme, which is essential for the binding of isocitrate [81]. The mentioned mutation terminates the regular catalytic activity of the protein by inhibiting the protein's capacity to bind isocitrate. Consequently, some concentrations of crucial cofactors, such as like-KG and NADPH, are decreased, however the IDH 2 role in diffuse astrocytoma remains unclear [82].

AA, or grade III high-grade astrocytoma, originates from star-shaped glial cells, known as astrocytes [83]. The tumor comes from the low-grade precursor's progression or by *de novo* synthesis, representing 1% to 2% of all primary brain neoplasms. It occurs in the brain cerebral hemisphere however it may arise in the CNS [84,85]. AA can be further divided into subgroups according to IDH mutation and 1p/10q co-deletion. The presence of the mentioned events leads to a better prognosis, whereas the worst prognosis is observed in the wild type [86]. Typical events of OD and OA concern somatic deletions on the chromosome 1 short arm, heterozygosity (LOH) 1p loss, and LOH 19q loss [87-89]. So far, however, neither the 1p nor 19q gene has been recognized. Although LOH 19p is also commonly observed in AAs and may be related to tumor growth LOH1p is more substantially related to oligodendroglia gliomas [90]. The LOH1p and LOH 19q combination has been found only scarcely in gliomas other than OD and OA [89].

The mitogen-activated protein kinase (MAPK) signaling pathway is responsible for various cellular functions in the brain, such as memory formation, cortical neurogenesis, pain perception, and midbrain and cerebellum growth [91]. ERK transcription factor is essential for development and its hyper-activation is a crucial component in the appearance and spread of cancer. The most important signaling pathway, the Ras/Ras/MAPK (MEK)/ERK, is crucial for the tumor cells survival and development [92]. The MAPK extracellular signal-regulated kinase pathway results in astrocytoma development [93]. To be more specific, the mentioned signaling pathway may be changed in most astrocytoma cases. For instance, p38 MAPK activation is considered to be a possible oncogenic factor that promotes brain neoplasm development and chemotherapy resistance in glioma cells by promoting invasion and metastasis and is significantly related to the grade of the tumor [94]. The most supposed cause is the 2 Mb fragment of 7q tandem duplication, which leads to the fusion of two genes and the production of transforming fusion protein which contains the KIAA1549 N-terminus and the BRAF kinase domain [95]. Many genetic abnormalities, most especially gene fusions between KIAA1549 and BRAF, have been shown to be responsible for MAPK pathway dysregulation [96]. Various MAPK

pathway phosphorylation events and essential signaling features play an essential role in carcinogenesis. Human cancer normally displays a RAS-RAF-MEK/ERK/MAPK pathway alteration as an abnormal RTK activation result or function mutations gain, mainly in the RAF or RAS genes [97]. The MAPK signaling pathway is started by activating a trans-membrane RTK and the phosphate molecule to Raf kinase binding, which in turn activates the intracellular serine/threonine kinase BRAF. BRAF fusions have been detected in almost 70% of pilocytic astrocytomas (PAs), in 80% of cerebellar PAs, and in 50%-55% of non-cerebellar PAs [98]. Even though BRAF fusion genes are the genetic abnormalities that most commonly derange the Ras/ERK/MAPK pathway in sporadic PAs, other mutations are also able to activate that pathway [99]. MAPK is activated in PAs through two special pathways. The tandem duplication at 3p25 is the first, which is, impressively similar to the typical BRAF fusion, which is responsible for an oncogenic in-frame fusion between RAF1 and SRGAP3.The Raf1 kinase domain is implicated in the fusion, which shows higher kinase activity than the wild type [100], in which the auto-inhibiting RAF1 domain is substituted by the SRGAP3 gene beginning, the SRGAP3-RAF1 fusion gene is established. In contrast to KIAA1549-BRAF, SRGAP3-RAF1 does not have a trans-membrane domain code, but comprises the Fes/CIP4 (cell division control 42 protein-interactive protein 4) homology domain [98,101]. The genes HRAS, NRAS, KRAS, and PTPN11 are activated and somatic G12A KRAS mutations have been detected in PAs [102]. The BRAFV600E mutation and KIAA1549-BRAF fusions are BRAF gene alterations that display a variable standard between different age-groups in the majority of circumscribed astrocytomas [103]. In sporadic circumscribed astrocytomas, KIIA1549-BRAF is an evidenced hereditary alteration leading to the BRAF protein combination (f-BRAF) and increased BRAF mobility [104].

NF1 is a predominant condition which leads to neoplasia different types in humans, 15%-20% leads to astrocytoma development, especially circumscribed astrocytoma, which are categorized as WHO grade I. NF1-associated PAs (NF1-PAs) scarcely act as aggressive neoplasms. It is considered that a combination of germline and acquired physical NF1 tumor silencer quality modifications lead to circumscribed astrocytoma development in NF1 acquired malignancy condition [95,105].

The O6-methylguanine-DNA methyl-transferase (MGMT) is essential for DNA damage control from alkylating chemicals [106]. The MGMT gene, which codes for O6-alkylguanine-DNA- alkyl transferase, has been detected in the chromosomal band 10q26. The O6 position of guanine, a critical target of methylating and alkylating chemicals, is where methyl- and chloroethyl-groups are removed by the AGT repair enzyme. MGMT repair capacity deficiency is responsible for accumulation of DNA mutations and chromosomal instability, and contributes to human malignancies appearance and growth [107]. In diffuse astrocytoma, the TP53 gene mutation and the MGMT gene alteration are dominant [108].

OAs exhibit both oligodendroglia and astrocytic morphologies. As the criteria for determining of OA are inconsistent, OA incidence varies remarkably between different reports. According to molecular features, OAs possess an intermediate position between astrocytomas and ODs. A rate between 30% and 70% of OAs showed LOH 1p and LOH 19q8-12 [90] consequently, genetically are similar to ODs, whereas 30% carry mutations in the TP53 gene or LOH 17p10, indicating an association with astrocytomas. LOH 1p and LOH19q are reversely related to TP53 mutations [28].

Historically, OA has been determined as an infiltrating glioma constituted of two definite neoplastic cell types, with oligodendroglia and astrocytic features, respectively [1]. Based on to the CNS WHO classification, in 2016, OA diagnosis essentially must not be based on the efficiency of molecular testing to distinguish between those glioma types [14]. Even though "OA, dual genotype" has been described by the mentioned classification, it is not regarded a variant of gliomas or a distinct entity. TP53 and ATRX variants characterization with 1p/19q co-deletion testing leads approximately all IDH-mutant gliomas cases to be diagnosed definitely as astrocytomas or ODs, with TERT promoter, FUBP1and CIC variants confirming further definition [109-111]. Similar genetic alterations have been detected, on micro-dissection, in oligodendroglia and astrocytic segments, suggesting an OAs clonal origin [112]. Even though in OAs the astrocytic ingredient entails a lesser positive prognosis, many reports did not confirm differences in clinical outcomes between OA and OD [29,113].

According to an updated WHO classification in 2016-2021 OAs are polymorphic tumors that may lead to astrocytic tumors or ODs based on their molecular characteristics. The BRAF proto-oncogene is responsible for the most dominant genomic distortion. Cancers which are characterized by BRAF duplication exhibited BRAF mRNA increased mRNA levels and a down-stream target, CCND1, compared to tumors without such a duplication [114]. The mutation of TP53 seems to play a predominant role in the development of brain neoplasms [115,116]. That specific mutation comprises oncogenic features, making it more appropriate for cell invasion, immortalization, proliferation, and metastasis. (Table 2).

Oligodendrogliomas molecular biology

Oligodendrogliomas (ODs) are the 2nd most conventional intra-parenchymal brain tumor in adult individuals [117]. According to neuropathologic criteria, WHO classifies those as low-grade, grade II, or anaplastic, grade III ODs [1]. ODs were identified as a special histological entity of the family of diffuse gliomas [118], and were determined as the prototypic 'molecularly determined' brain tumor. Those gliomas sub-category molecular identification is described by the long arm of chromosome 1whole-arm loss and the chromosome 19 short arm loss (1p/19q-codeletion) of their genome. Concurrently with 1p/19q-codeletion, repeated molecular genetic changes have been detected comprising mutations in IDH1/2, CIC, FUBP1, TERT promoter, and the absence of TP53 and ATRX changes. Those alterations are essential for OD consequent diagnosis [119], as the mentioned mutations have been identified in the majority of ODs. On the contrary, other mutations such as TP53 and ATRX are characteristic features of diffuse gliomas, such as astrocytomas [120].

The lower-grade astrocytomas and ODs, regardless of their distinct histologic differences, have high IDH gene mutations rates, showing a rate of 80% in most cases. ODs that do not have IDH1 mutations comprise IDH2 mutations [121]. Genomic investigation has recorded that the 1p/19q whole-arm-lost ODs vast majority carry mutations of the IDH gene [122], whereas their absence may imitate alternative histologic types, such as dysembryoplastic neuroepithelial tumors or clear-cell ependymoma [123]. On the contrary, it has been found that TP53 mutations are usually detected in grade II and III astrocytic gliomas, but are scarcely revealed in oligodendroglia neoplasms [27].

1p/19q-co-deleted ODs which were analyzed by the genomic sequencing technology led to the identification of inactivating mutations in the FUBP gene on chromosome 1p and in CIC gene on chromosome 19 [124,125]. CIC, the most commonly mutated gene in ODs, is regarded to function downstream of growth factor receptor signaling pathways by binding to DNA regulatory segments as a reversible repressor of target genes [126].

Specifically, CIC missense mutations in ODs are enclosed in the supposed DNA binding domain. The mentioned CIC mutational inactivation tumor-suppressor spectrum indicates that ODs may have a fundamental level of those signaling pathways 'released' activation, which may explicate why amplification events of growth factor receptor are scarcely found in ODs, as they may not offer additional eclectic growth advantage for the malignant cells. Recently, TERT promoter somatic mutations in IDH-mutant, CIC-mutant ODs were identified [127]. Those mutations are related to TERT over-expression. Moreover, somatic TERT promoter mutations have also been observed in the IDH wild-type GBMs great majority, whereas they are practically never detected in IDH-mutant

TP53-mutant ATRX mutant astrocytic gliomas. Therefore, ATRX and TERT mutations for the diffuse gliomas are mutually exclusive, and ODs comprise no less than four different repeated molecular genetic interactions, namely,1p/19q loss, IDH, TERT promoter and CIC mutations [128].

Epigenetic alterations influence cell function in a different way than direct DNA sequence alterations such as amplifications and mutations. A small number of researches have investigated the epigenetic alterations role in ODs pathogenesis. The promoter methylation of MGMT has been revealed in many ODs [129], and promoter regions hyper-methylation can be observed in many tumor-associated genes in ODs [130]. An ODs subset has extensive alterations in DNA methylation to G-CIMP [131]. Since IDH mutations are almost general events in ODs, in those tumors wide-spread methylation abnormalities may be associated with their mutant IDH status. Consequently, it is possible that some of the genetic affections reflected in 1p/19q loss and the related molecular genetic changes, such as IDH1 mutation, originate from changes in epigenetic regulatory mechanisms, similar to what has been observed in other tumor types in which pathologic alterations may be associated with regulatory enhancers, promoters, and long intergenic non-coding RNAs (Linc RNAs) [132].

Compared to low-grade ODs, anaplastic ODs (AODs) commonly show additional chromosomal deletions, LOH of 9p and/or gene deletion of CDKN2A, mainly [133]. Those abnormalities appear in 33%-50% of AODs and are related to tumor development. Inevitably, other chromosomal anomalies have been detected in low- and in high-grade ODs with aberrant morphological characteristics, are conventionally related to astrocytomas and are commonly mutually exclusive with 1p/19q co-deletion [29,133,134]. In 19%-25% of anaplastic oligodendroglia tumor cases have been observed deletions on chromosome 10 [133].

EGFR gene amplification on chromosome 7p appears in 20%-30% of oligodendroglia tumor cases, but never revealed in those with 1p and 19q deletion, and is associated with a poor prognosis [133,135]. Similarly, a prospective EORTC study on anaplastic oligodendroglia tumors molecular analysis identified more frequent loss of chromosome 10 and amplification of EGFR gene in tumors diagnosed as mixed OAs with necrosis [136]. Those molecular aberrations were conversely associated with the 1p/19q co-deletion, finding indicating that those tumors are generated from different precursor cells. That suggestion is contended by the considerable differences in clinical outcome and prognosis, with a favorable outcome in the presence of 1p and19q loss, and with poor survival in AODs characterized by 10q loss and/or EGFR amplification [134]. In pure AODs the existence of EGFR amplification or 10q loss is remarkably rare to propose an alternate diagnosis, such as small cell GBM [133]. Anaplastic oligoastrocytomas (AOAs) are not a constant category of malignant tumors, but rather a morphological continuity between astrocytomas and pure ODs. Only in special cases mixed tumors show genetically special clones of tumor in histologically distinct regions [137].

Several other mutations have been detected in 1p/19q co-deleted ODs, and concern inactivating mutations in the Drosophila capicua (CIC) homolog, and FUBP1 gene, considered to appear secondary to the unbalanced translocation and observed to be present in almost 50-70 % and 15-30 % of 1p/19q co-deleted tumors, respectively. Those genes are localized on the 1p (FUBP1) and 19q (CIC) chromosomal arms, supporting their hypothesized roles as tumor suppressor genes [124]. In tumors without 19q loss have been detected no mutations that concern CIC. CIC mutations appear with IDH mutations mainly, and are extremely rare in other brain neoplasms. CIC is a receptor kinase (RTK) pathways (RTK-RAS-RAF-MAPK) downstream ingredient and prevents transcription through binding to a regulatory district. It is also negatively regulated by RTK signaling pathway that prevents the CIC function through MAPK-mediated phosphorylation, event that leads to CIC degradation. Mutations of FUBP1gene may lead to MYC activation or ribosomes biogenesis. The extra influence of those changes on the patients outcome with 1p/19q co-deleted glioma is currently unknown [125, 138].

In gliomas two mutually exclusive mutations seem to play an essential role in the maintenance telomeres. TERT mutations in hot spot promoter locations C228T, C250T lead to increased expression of telomerase. Incredibly, those mutations are present in IDH wild type high-grade gliomas and in1p/19q co-deleted ODs [127, 128]. Almost all 1p/19q co-deleted neoplasms have TERT mutations. Gliomas in the presence of 1p/19q co-deletion with TERT mutations, as occurs in ODs, have a very favorable clinical outcome where the same TERT mutations in the absence of 1p/19q co-deletion or IDH mutations suggest an extremely poor prognosis comparable to GBM [139]. Amplifications of EGFR are almost mutually exclusive with 1p/19q co-deletion and IDH mutations, observation which suggests that oligodendroglia tumors follow a different oncogenic pathway from the beginning. The gene amplification of EGFR and the chromosome 7 polysomy existence are related to TERT mutations and show similar prognosis to primary GBM, generally. In histologically pure AODs, EGFR amplification appearance is indicative of GBM [133]. The GBM variant which is characterized by small cell has morphological similarities to AOD but the EGFR amplification is present in70 % of cases [140]. Anaplastic oligodendroglia tumors commonly have extra genetic abnormalities, especially 9pLOH and/or CDKN2A gene, PIK3CA mutations deletion, and polysomies [124,133,141]. The TCGA regarding lower grade gliomas, WHO grade II and III, stated that IDH mutations in those tumors were almost mutually exclusive with EGFR amplification and CDKN2A homozygous deletion [109,142]. As already stated, the amplification of EGFR mainly appears in 1p/19q intact, IDH wild type gliomas and demonstrates GBM diagnosis. Previous reports suggested decreased recurrence free survival times or poorer prognosis for oligodendroglia tumors with 1p and 19q polysomy, however the exact importance of that finding it still remains unclear [143,144].

Ependymomas molecular biology

Ependymoma is the 3rd most conventional pediatric brain tumor, following astrocytoma and medulloblastoma, with over 50% of cases appearing in children less than 5 years of age [145]. Ependymomas are primary CNS tumors come from the ependymal lining of ventricular system. Those tumors are located everywhere in the CNS, comprising the infratentorial (IT) space, the supratentorial (ST) space, and the spinal (SP) section, however they are most usually locating in the parenchyma, and in the ventricular system [14,39].

Spinal ependymoma (SPE), classified as WHO grade II or III, is a well-circumscribed neoplasm comprised of monomorphic glial cells with round to oval nuclei with stigmatic chromatin. The tumor is regarded to be WHO grade III and is characterized by hypercellularity, frequent mitoses, cellular atypia, great endothelial proliferation and/or palisading necrosis. The tumors express GFAP, S100, EMA protein, and NHERF1/EBP50 [145,146]. SPE is related to neurofibromatosis type 2 (NF2) deletions or mutations as it has been found that 90.5% of samples classified into the SPE group revealed chromosome 22q copy number variations [147]. Myelocytomatosis-N (MYCN), a member of MYC oncogenes family, plays a crucial role in neurogenesis and has been involved in several CNS malignancies pathogenesis such as medulloblastoma, neuroblastoma, and pediatric GBM, and in other malignancies such as prostate cancer and leukemia [148,149]. SPE with amplification of MYCN (SPE-MYCN) has recently been regarded as a novel ependymoma molecular class according to the 2021 CNS WHO categorization, which was based on diverse surveys that have revealed the appearance of that molecular signature in a highly aggressive SPEs subgroup. MYCN gene which is localized on chromosome 2p24.3 encodes a proto-oncogene transcription factor in the cell nucleus which is essential for normal growth of CNS [150]. Another report, based on DNA methylation analyses, also confirmed the amplification of MYCN in a

cohort of 13 neoplasms, of which10 were classified as WHO Grade III and three were classified as WHO Grade II SPE [151]. (Table 1).

Many of those tumors, especially those that are appeared intracranially, do not have NF2 mutations. Consequently, despite that NF2 gene may be essential for the formation of some SPEs, it is possibly not the critical tumor suppressor gene on chromosome 22q that is implicated in sporadic intracranial ependymoma tumorigenesis [147,152]. Ependymoma has also been observed in patients with Li-Fraumeni syndrome, and concern TP53 tumor suppressor gene germline mutation, however, such incidences and TP53 somatic mutations in sporadic ependymomas are rare events, thus reducing p53 role in ependymoma tumorigenesis [153].

The c-myeloblastosis gene (c-MYB), a proto-oncogene encoding a transcription regulator is localized on chromosome 6q23.3, and plays a critical role in hematopoiesis regulation, is being investigated as a driver in ependymoma oncogenesis [154]. In another study multiple ependymomas located intracranially and spinally were observed in a patient with Turcot syndrome, i.e., adenomatous polyposis coli (APC) gene germline mutation, whose function loss activates the Wnt signaling pathway and predisposes to colorectal cancer [155,156]. Intracranial and SP ependymomas have also been revealed in multiple endocrine neoplasia type I (MEN1) syndrome cases **[**157**].** However, the gene/Wnt signaling activation and the MEN1 role in sporadic ependymoma tumorigenesis remains still unknown.

Three remarkable genes are under investigation regarding its possible role in ependymomas appearance, and as possible future molecular targets. The overexpression of Homeobox B13 (HOXB13), a gene encoding a transcription factor that regulates skin development, has been found to be implicated by previous studies [158,159]. The crucial implication of the HOX gene in developmental pathways has led researchers to suggest its essential role in myxopapillary ependymoma (MPE) tumorigenesis. The weak point of that suggestion is that the up-regulated HOX genes usually observed in MPE are HOXB13, HOXC10, HOXA13, and HOXD10. Those genes are overexpressed in lumbar spine developing [152,160]. Neuro-filament light chain (NEFL) gene, encoding a Class IV intermediate neuro-filament expressed in neurons and localized on chromosome 8p21.2 in close proximity to HOX genes transcription factor binding, and PDGFRA, a gene which encodes a tyrosine kinase are over-expressed in MPE [158,159,161]. A recent survey estimating DNA methylation and pediatric SPEs gene expression profiles also revealed HOXB13 over-expression, giving further evidence regarding the significance of that gene [161].

It has also been revealed an important overexpression of genes implicated in the mitochondrial oxidative phosphorylation respiratory chain, such as cyclooxygenase-2 (COX2), a gene that encodes for cyclooxygenase, which is involved in inflammatory response and has been found to be overexpressed in diverse cancer types, such as gliomas, as is implicated in neovascularization, cell proliferation, and metastasis **[**162**].**

A microarray-based study of gene expression profiling, was used to compare ependymoma with normal brain controls, revealed 112 abnormally expressed genes in ependymoma. Genes with increased expression concern the WNT5A oncogene, TP53 homologue TP63, and several cell cycle, adhesion, proliferation, and extracellular matrix genes such as the transcription factor ZIC1, VEGF, and FN1. Other supposed oncogenes that have been implicated in diverse cancer types are HOX7, IBP2, COL4A1, GAC1, and WEE1. Genes that were found to be down-regulated comprised the NF2-interacting gene SCHIP-1, the APC-associated gene EB1, and genes that are implicated in vesicle trafficking and recycling such as RAB40B, TJ2, NPC1, and SH3GL3 [163].

Among the supposed oncogenes in ependymoma are NOTCH1, NOTCH4, and JAG1, which are Notch signaling pathway members, suggesting the Notch signaling implication in ependymoma tumorigenesis [40,164]. NOTCH1, the first oncogene found to be mutated in ependymomas, and those missense mutations cause the Notch1 receptor to be constitutively active in a ligand independent manner [159]. (Table 2).

Supra-tentorial ependymomas also found to be associated with EphB-Ephrin (EPHB2/3/4 and EPHRI NA3/4) signaling pathways, and genes implicated in the regulation of cell cycle (Cyclin B2/D1/G2, CDKN1C/2C, and CDK2/4). On the other hand, the highly expressed genes that discerned posterior fossa ependymomas were differentiation inhibitors (ID1/24) and members of multiple homeobox (HOX) family members (HOXA7/9, HOXB6/7, and HOXC6/10) and insulin-like growth factor (IGF1) [159]. Previous studies found that supra-tentorial ependymomas expressed remarkably increased levels of Notch (JAGGED1/2) members [40,152]. Deregulated Notch signaling, which is critical for neural development, seems to play an essential role in ependymoma tumorigenesis, mainly at the supra-tentorial location, since oncogenesis is thought to mirror normal development gene amiss [164]. Despite the overexpression of the Notch ligands JAGGED 1/2 shown by Taylor *et al.,* [40], there is consistent up-regulation of the Notch receptors (NOTCH 1/2), ligands (JAGGED1/2 and DLL1/3), and target genes (HES1/5, HEY2, c-MYC, and ERBB 2), whereas FBXW7, the major repressor of the Notch pathway, is consistently down-regulated [40,159,165,166]. Gilbertson *et al.* [166] further displayed the ERBB receptors high level expression (ERBB2/4), which are direct Notch signaling targets, could be observed in more than 75% of pediatric ependymomas and were significantly associated with tumor proliferative activity as expressed by the Ki-67 index. Moreover, the up-regulation of sonic hedgehog (SHH) and bone morphogenetic protein (BMP) pathway members were also distinct in intra-cranial ependymomas [152].

In grade III ependymomas Wnt signaling activation is displayed by the Wnt ligand (WNT11), over-expression of Frizzled receptors (FZD2/5/8), and its related transcription factor TCF3 and the Wnt target genes c-MYC, FOSL1, CCND1, BIRC5, and TP54. The same report also showed that WHO grade III anaplastic ependymomas were differed from grade II tumors by the genes involved in overexpression of Wnt/β-catenin signaling activation, regulation of cell cycle/proliferation (cyclin--dependent kinases CDK2/4 , proteins of cell cycle CDC25A/25B/25C/2, and minimal chromosome maintenance proteins MCM2/3/5/6/7), apoptosis (tumor necrosis factor superfamily members TNFRSF11A/21 and caspases (CASP1/4), angiogenesis (VEGF,VEGFR2, VEGFB, TNIP2 and DOC2), and adherents junctions remodeling through E-cadherin destruction (MET, MN23H1, caveolin, RAB5/7 GTPases) as well as transcription factors E2F1 and DP1 (TFDP1) up-regulation [159].

Suarez Merino *et al*. recorded that SCHIP-1 gene expression was significantly down-regulated in pediatric ependymomas [163], whereas Modena *et al.,* [152] by integrating the genomic and ex-pression profiles of 24 primaries intracranial ependymomas, found SULT4A1 gene down-regulation which is located at 22q13.3. Candidate oncogenes suggested by analyzing recurrent gains on chromosome 7 concern EGFR at 7p11.2, ARHGEF5 at 7q34, and TWIST1 and HDAC9 at 7p21.1. EGFR especially exhibits frequent gains and high level amplifications in intra-cranial ependymomas, and its over-expression results in poor prognosis [152,167].

RGCs (Retinal ganglion cells) is of vital importance cell type for developing of CNS and are a particular neural stem cells group. They are responsible for production of neurons and glia, as guide cells for subsequent neuronal migration, and as basic segments in standardizing and location specific differentiation of the CNS [168]. It has also been found that ependymal cells, from which ependymoma appears, are come from RGCs during embryogenesis [169]. Genetic mutations in RGCs may consequently result in their transformation into cancer stem cells of pediatric ependymomas [145,170]. Since supra-tentorial ependymomas are characterized by Notch and EphB Ephrin signaling pathways members increased expression, it is possible that those pathways over-activation may induce RGCs neoplastic transformation in the cerebral

sub-ventricular zone. In a similar way, up-regulation of the transcription factors HOX family may be involved in SPE growth by transforming RGCs in the spinal region. There is also evidence that RG-like cells are present not only during CNS development but also persist in the adult CNS, especially in the sub-ventricular zone and the spinal cord. Consequently, those RG-like cells may act as the cells of origin for adult ependymomas [170,171].

Additionally, a small number of families with increased ependymoma incidence but without any currently known familial cancer syndromes have been stated. Such families have loss of 22q but do not carry mutations, further indicating the presence of another crucial tumor suppressor gene at that chromosomal location [163]. CBX7 allelic loss, located at 22q13.1, could be detected in 55% of ependymoma cases. CBX7 controls cellular lifetime through regulating the Arf/p53 and the p16Ink4a/Rb pathways [172]. The role of the mentioned pathways in ependymoma pathogenesis is unclear, though their deregulation is pivotal to many types of cancer, comprising gliomas [40,173]. In addition, CDKN2A/P16 at 9p21.3 and RB at 13q14.2 deletion and hyper-methylation have been observed in ependymomas **[**174]. Chromosome 6q loss has been found mostly in infra-tentorial tumors, whereas chromosome 9 deletions appear more frequently in supra-tentorial tumors [175,176]. The most frequently deleted locus concerned 6q25.3, which contains the SNX9 and SYNJ2 genes. Nevertheless, loss of 6q25.3 was a favorable prognostic index for overall survival in anaplastic intracranial ependymomas, as the deletion of the SNX9 and SYNJ2 genes which are known to regulate invasion and cell migration could inhibit tumor progression [176,177]. Chromosome 9 is also frequently deleted in patients with ependymomas, whereas on the sam chromosome homozygous deletion extending the CDKN2A locus at 9q21.3 has been observed in anaplastic supra-tentorial tumors [173,177,178].

Promoter DNA (CpG) hyper-methylation as an epigenetics type is an important event in carcinogenesis, possibly plays a crucial role in silencing tumor suppressor genes implicated in ependymoma appearance. However, epigenetic studies on ependymoma have been limited to candidate gene and their possible role as tumor suppressor genes and their methylation status. The hypermethylated in cancer1 (HIC-1) supposed tumor suppressor gene methylation status, which displays hyper-methylation and expression loss in diverse tumors such as medulloblastoma and gliomas, has been examined. Additionally, the HIC-1 locus at chromosome 17p13.3 is commonly lost in ependymoma [179,180]. It has been observed hyper-methylation and down-regulation in 83% and 81% of ependymomas, respectively, and that hyper-methylation was significantly associated with non-spinal localization [179].

The Ras association domain family 1 isoform A (RASSF1A) gene has also been found to be frequently silenced by methylation in ependymoma, with an incidence of 86% [181]. It is a recently well recognized tumor suppressor gene whose inactivation through promoter methylation is implicated in many human cancer's development [182,183]. Other genes that are methylated in ependymoma concern the TRAIL apoptosis pathway-related genes CASP8, TFRSF10C, TFRSF10D, and TNFRSF10C, with incidences of 30%, 9.5%,36.4%, and 9.5%, respectively [183]. Methylated genes in ependymoma are also DAPK, THBS1, TIMP3, TP73, MGMT, GSTP1, CDKN2A, FHIT, RARB, BLU, and MCJ with incidence ranging from 10% to 57% [152,183]. (Table 3).

Putative oncogenes	Putative tumor suppressor genes
MYCN (2p24), hTERT (5p15.33), EGFR (7p11.2), NOTCH1 (9q34.3), NOTCH4 (6p21.32), DUSP12 (1q23.3), CDC6 (17p13.3), TNC (9q33.1), MDK (11p11.2), DNASE1L3 (3q25.2), EDG3 (9q22), MTA1 (14q32.33), PRM1 (16q12.2), VAV1 (19p13.3), BIRC2 (11q22), BIRC3 (11q22), JAG1 (20p12.2), SHC3 (9q22), TYR (11p13), YAP1 (11q22), ARHGEF5 (7q34), EDG3 (9q22), HOXC4 (12q13.13), SLC6A10 (16p11.2), STK32C (10q26.3)	CDKN2A (9p21.3), GRID1 (10q23.2), MINPP1 (10q23.31), TACC2 (10q26.13), AJAP1 (1p36. 32), PRKCA (17q24.2), FOXD4 (9p24.31), ZNF262(1p34.3), TUBGCP2 (10q26.3), SULT4A1 (22q13.3)

Table 3: Molecular genetics of ependymoma pathogenesis

Conclusions

Many researches have been carried out in an effort to contribute to decode the genetics and molecular biology and underlying the appearance of gliomas. This has resulted in alterations in CNS tumors categorization and management of patients, contributing to personalized therapy. However, gliomas are responsible for the death of thousands of people worldwide annually, with no probabilities to inhibit the disease progression. A large amount of promising therapeutic strategies has displayed no clinical benefit in glioma patients. Although a great body of knowledge regarding the gliomas molecular basis has been acquired, this knowledge has not led to efficient treatments for individuals who suffer from such diseases. To reach efficient treatments against gliomas, must be dominated various of their hallmarks such as tumor invasion potential, metabolic heterogeneity, medication and immune resistance, and poor pharmacokinetics. The comprehension of genetic, molecular, and metabolic characteristics of gliomas is crucial for the identification of new possible targets and the establishment of novel therapeutic strategies. Glioma's heterogeneity can influence response to treatments. The current interaction between different cell types and molecular and metabolic pathways indicates that single-agent therapeutic strategies may lead to short term success, whereas, the development of combination *therapeutic strategies could be more beneficial.*

References

1. Louis DN, Ohgaki H, Wiestler OD, et al., (2007) The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*;114(2):97-109.
2. Ostrom QT, Gittleman H, Liao P, et al. (2014) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. *Neuro Oncol;* 16 (Suppl 4):1-63.
3. Grech N, Dalli T, Mizzi S, et al. (2020) Rising incidence of glioblastoma multiforme in a well-defined population. *Cureus*; 12(5): e8195.
4. Louis DN, Perry A, Wesseling P, et al. (2021) The 2021 WHO Classification of Tumors of the Central Nervous System: A summary. *Neuro Oncol*; 23: 1231-1251.
5. Wen PY, Weller M, Lee EQ, et al. (2020) Glioblastoma in adults: A Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro Oncol*;2 2: 1073-1113.
6. Oronsky B, Reid TR, Oronsky A, et al. (2021) A Review of Newly Diagnosed Glioblastoma. *Front Oncol* ;10: 574012.
7. Tan AC, Ashley DM, López GY, et al. (2020) Management of glioblastoma: State of the art and future directions. *CA Cancer J Clin* ;70(4):299-312.

8. Miller KD, Ostrom QT, Kruchko C, et al. (2021) Brain and other central nervous system tumor statistics. *CA Cancer J Clin* ;71: 381-406.
9. Ostrom QT, Price M, Neff C, et al. (2023) CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2016-2020. *Neuro Oncol*; 25, iv1-iv99.
10. Soomro SH, Ting LR, Qing YY, et al. (2017) Molecular biology of glioblastoma: classification and mutational locations. *J Pak Med Assoc*; 67(9):1410-1414.
11. Stupp R, Mason WP, Van Den Bent MJ, et al. (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* ;352(10): 987-996.
12. Ostrom QT, Cioffi G, Gittleman H, et al. (2019) CBTRUS Statistical Report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. *Neuro Oncol*; 21(Suppl 5): v1-v100.
13. Ohgaki H, Kleihues P. (2013) The definition of primary and secondary glioblastoma. *Clin Cancer Res*; 19(4): 764-772.
14. Louis DN, Perry A, Reifenberger G, et al. (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A summary. *Acta Neuropathol* ;131: 803-820.
15. Lee E, Yong RL, Paddison P, et al. (2018) Comparison of glioblastoma (GBM) molecular classification methods. *Semin Cancer Biol*; 53:201-211.
16. Verdugo E, Puerto I, Medina MA. (2022) An update on the molecular biology of glioblastoma, with clinical implications and progress in its treatment. *Cancer Commun* ;42, 1083-1111.
17. Zhang P, Xia Q, Liu LQ, et al. (2020) Current Opinion on Molecular Characterization for GBM Classification in Guiding Clinical Diagnosis, Prognosis, and Therapy. *Front Mol Bio-sci*; 7: 562798.
18. del Pilar Guillermo Prieto M, de La Fuente MI. (2021) The Role of Molecular Genetics of Glioblastoma in the Clinical Setting. In Precision Molecular Pathology of Glioblastoma; Springer: Berlin/Heidelberg, Germany, 2021; pp. 21-33.
19. Esemen Y, Awan M, Parwez R, et al. (2022) Molecular Pathogenesis of Glioblastoma in Adults and Future Perspectives: A Systematic Review. *Int J Mol Sci*; 23: 2607.
20. Ludwig K, Muthukrishnan SD, Alvarado AG, et al. (2021) Overview of glioblastoma biological hallmarks and molecular pathology. In Glioblastoma Resistance to Chemotherapy: Molecular Mechanisms and Innovative Reversal Strategies; Academic Press: Cambridge, MA, USA, Volume 15, pp. 1-15.
21. Delgado-Martin B, Medina MA. (2020) Advances in the Knowledge of the Molecular Biology of Glioblastoma and Its Impact in Patient Diagnosis, Stratification, and Treatment. *Adv Sci*; *7*: 1902971.
22. Schiffer D. (1997) Brain Tumors. Biology, Pathology, and Clinical References. Berlin, Springer, pp. 109-131.
23. Ostrom QT, Gittleman H, Liao P, et al. (2017) CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. *Neuro Oncol* ;19(suppl 5): v1-v88.
24. Cairncross G, Macdonald D, Ludwin S, et al. (1994) Chemotherapy for anaplastic oligodendroglioma. National Cancer Institute of Canada Clinical Trials Group.*J Clin Oncol*; 12:2013-2021.
25. Anderson MD, Gilbert MR. (2013) Treatment recommendations for anaplastic oligodendrogliomas that are codeleted. *Oncology (Williston Park)*; 27(4):315-20, 322.
26. Wesseling P, van den Bent M, Perry A. (2015) Oligodendroglioma: pathology, molecular mechanisms and markers. *Acta Neuropathol*; 129(6): 809-827.
27. Ohgaki H, Kleihues P. (2005) Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. *J Neuropathol Exp Neurol*; 64(6):479-489.
28. Hart MN, Petito CK, Earle KM. (1973) Mixed gliomas. *Cancer*; 33:134-140.
29. Maintz D, Fiedler K, Koopmann J, et al. (1997) Molecular genetic evidence for subtypes of oligoastrocytomas. *J Neuropathol Exp Neurol*; 56:1098-1104.
30. Louis DN. (1997) A molecular genetic model of astrocytoma histopathology. *Brain Pathol*; 7:755-764.
31. Hirtz A, Rech F, Dubois-pot-schneider H, et al. (2020) Astrocytoma: a hormone-sensitive tumor? *Int J Mol Sci*; 21(23);1-23.
32. Sohel M, Aktar S, Biswas P, et al. (2023) Exploring the anti-cancer potential of dietary phytochemicals for the patients with breast cancer: a comprehensive review. *Cancer Med*; 12:14556-14583.
33. Mueller W, Hartmann C, Hoffmann A, et al. (2002) Genetic signature of oligoastrocytomas correlates with tumor location and denotes distinct molecular subsets. *Am J Pathol*; 161(1). 313-319
34. Godfraind C. (2009) Classification and controversies in pathology of ependymomas. *Childs Nerv Syst*; *25*(10):1185-1193.
35. Gatta G, Botta L, Rossi S, et al. (2014) Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5-a population-based study. *Lancet Oncol*;15(1):35-47.
36. Visser O, Ardanaz E, Botta L, et al. (2015) Survival of adults with primary malignant brain tumours in Europe; Results of the EUROCARE-5 study. *Eur J Cancer* ;51(15):2231-2241.
37. Ostrom QT, Patil N, Cioffi G, et al. (2020) CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2013-2017. *Neuro Oncol*; 22: IV-IV96.
38. McGuire CS, Sainani KL, Fisher PG. (2009) Incidence patterns for ependymoma: A Surveillance, Epidemiology, and End Results study-Clinical article. *J Neurosurg*; 110: 725-729.
39. Wu J, Armstrong TS, Gilbert MR. (2016) Biology and management of ependymomas. *Neuro Oncol*; 18: 902-913.
40. Taylor MD, Poppleton H, Fuller C, et al. (2005) Radial glia cells are candidate stem cells of ependymoma. *Cancer Cell*; 8(4): 323-335.
41. Mack SC, Taylor MD. (2009) The genetic and epigenetic basis of ependymoma. *Childs Nerv Syst*; 25(10):1195-1201.
42. Yan H, Parsons DW, Jin G, et al. (2009) IDH1 and IDH2 mutations in gliomas. *N Engl J Med*;360(8):765-773.
43. The Cancer Genome Atlas Research Network. (2008) *Nature*; 455:1061.
44. Crespo I, Vital AL, Gonzalez-Tablas M, et al. (2015) Molecular and Genomic Alterations in Glioblastoma Multiforme. *Am J Pathol*; 185(7): 1820-1833.
45. Neftel C, Laffy J, Filbin MG, et al. (2019) An integrative model of cellular states, plasticity, and genetics for glioblastoma. *Cell*; 178(4):835-849.e21.
46. Tang Y, Qazi MA, Brown KR, et al. (2021) Identification of five important genes to predict glioblastoma subtypes. *Neurooncol Adv*; 3(1): vdab144.
47. Verhaak RG, Hoadley KA, Purdom E, et al. (2010) Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*; 17(1):98-110.
48. Jankowska S, Lewandowska M, Masztalewicz M, et al. (2021) Molecular classification of glioblastoma based on immune-histochemical expression of EGFR, PDGFRA, NF1, IDH1, p53 and PTEN proteins. *Pol J Pathol*; 72(1):1-10.

49. Kan LK, Drummond K, Hunn M, et al. (2020) Potential biomarkers and challenges in glioma diagnosis, therapy and prognosis. *BMJ Neurol Open*; 2(2): e000069.
50. Herrera-Oropeza GE, Angulo-Rojo C, Gástelum-López SA, et al. (2021) Glioblastoma multiforme: a multi-omics analysis of driver genes and tumor heterogeneity. *Interface Focus*;11(4):20200072.
51. Cai Z, Yu C, Li S, et al. (2021) A novel classification of glioma subgroup, which is highly correlated with the clinical characteristics and tumor tissue characteristics, based on the expression levels of G*β* and G*γ* genes. *Front Oncol*; 11:685823.
52. Brennan CW, Verhaak RGW, McKenna A, et al. (2013) The Cancer Genome Atlas Research Network. *Cell*; 155: 462.
53. Visvader JE, Lindeman GJ. (2008) Cancer stem cells in solid tumor's: accumulating evidence and unresolved questions. *Nat Rev Cancer*; 8(10): 755-768.
54. Wu T, Li Y, Chen B. (2020) B4GALT3 promotes cell proliferation and invasion in glioblastoma. *Neurol Res*; 42(6):463-470.
55. Yu S, Yu X, Sun L, et al. (2020) GBP2 enhances glioblastoma invasion through Stat3/ fibronectin pathway. *Oncogene*; 39(27):5042-5055.
56. de Semir D, Bezrookove V, Nosrati M, et al. (2020) PHIP drives glioblastoma motility and invasion by regulating the focal adhesion complex. *Proc Natl Acad Sci* USA; 117(16):9064-9073.
57. Montella L, Cuomo M, Del Gaudio N, et al. (2023) Epigenetic alterations in glioblastomas: Diagnostic, prognostic and therapeutic relevance. *Int J Cancer;* 153, 476-488.
58. Mansouri A, Hachem LD, Mansouri S, et al. (2019) MGMT promoter methylation status testing to guide therapy for glioblastoma: Refining the approach based on emerging evidence and current challenges. *Neuro-Oncology*; 21: 167-178.
59. Della Monica R, Cuomo M, Buonaiuto M, et al. (2022) MGMT and Whole-Genome DNA Methylation Impacts on Diagnosis, Prognosis and Therapy of Glioblastoma Multiforme. *Int J Mol Sci*; 23: 7148.
60. Noushmehr H, Weisenberger DJ, Diefes K, at al. (2010) Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer Cell*; 17: 510-522.
61. Capper D, Jones DTW, Sill M, et al. (2018) DNA methylation-based classification of central nervous system tumours. *Nature;* 555: 469-474.
62. Klughammer J, Kiesel B, Roetzer T, et al. (2018) The DNA methylation landscape of glioblastoma disease progression shows extensive heterogeneity in time and space. *Nat Med* ;24: 1611-1624.
63. McClellan BL, Haase S, Nunez FJ, et al. (2023) Impact of epigenetic reprogramming on antitumor immune responses in glioma. *J Clin Investig*; 133: e163450.
64. Khabibov M, Garifullin A, Boumber Y, et al. (2022) Signaling pathways and therapeutic approaches in glioblastoma multiforme (Review). *Int J Oncol*; 60: 69.
65. Alexandru O, Horescu C, Sevastre AS, et al. (2020) Receptor tyrosine kinase targeting in glioblastoma: Performance, limitations and future approaches. *Wspolczesna Onkol*; 24:55-66.
66. Li XM, Wu CJ, Chen NC, et al. (2016) PI3K/Akt/mTOR signaling pathway and targeted therapy for glioblastoma. *Oncotarget*; 7: 33440-33450.
67. Dewdney B, Jenkins MR, Best SA, et al. (2023) From signaling pathways to targeted therapies: Unraveling glioblastoma's secrets and harnessing two decades of progress. *Signal Transduct Target Ther*; 8: 400.
68. Qin A, Musket A, Musich PR, et al. (2021) Receptor tyrosine kinases as druggable targets in glioblastoma: Do signaling pathways matter? *Neuro Oncol Adv*; 3: vdab133.
69. Kim G, Ko YT. (2020) Small molecule tyrosine kinase inhibitors in glioblastoma. *Arch Pharm Res*; 43: 385-394.
70. Tilak M, Holborn J, New LA, et al. (2021) Receptor Tyrosine Kinase Signaling and Targeting in Glioblastoma Multiforme. *Int J Mol Sci*; 22: 1831.
71. Zhang Y, Dube C, Gibert M, et al. (2018) The p53 Pathway in Glioblastoma. *Cancers*; 10: 297.
72. Chkheidze R, Raisanen J, Gagan J, et al. (2021) Alterations in the RB Pathway with Inactivation of Characterize Glioblastomas with a Primitive Neuronal Component. *J Neuropathol Exp Neurol*; 80: 1092-1098.
73. Suwala AK, Stichel D, Schrimpf D, et al. (2021) Glioblastomas with primitive neuronal component harbor a distinct methylation and copy-number profile with inactivation of TP53, PTEN, and RB1. *Acta Neuropathol*; 142: 179-189.
74. Tien AC, Li J, Bao X, et al. (2019) A Phase 0 Trial of Ribociclib in Recurrent Glioblastoma Patients Incorporating a Tumor Pharmacodynamic- and Pharmacokinetic-Guided Expansion Cohort. *Clin Cancer Res*; 25: 5777-5786.
75. Chowdhury Lutfun Nahar Metu, Sunita Kumari Sutihar, Md Sohel, et al. (2023) Unraveling the signaling mechanism behind astrocytoma and possible therapeutics strategies: A comprehensive review. *Cancer Reports*; 6: e1889
76. Foote MB, Papadopoulos N, Diaz LA. (2015) Genetic classification of gliomas: refining histopathology. *Cancer Cell*; 28:9-11.
77. Ceccarelli M, Barthel FP, Malta TM, et al. (2016) Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. *Cell*; 164:550-563.
78. Louis DN, Perry A, Burger P, et al. (2014) International Society of Neuropathology-Haarlem consensus guidelines for nervous system tumor classification and grading. *Brain Pathol* (Zurich, Switzerland); 24:429-435.
79. Balss J, Meyer J, Mueller W, et al. (2008) Analysis of the IDH1 codon 132 mutation in brain tumors. *Acta Neuropathol*; 116:597-602.
80. Mi RK, Min Sung Kim, Ji Eun Oh, et al. (2009) Mutational analysis of IDH1 codon 132 in glioblastomas and other common cancers. *Int J Cancer*; 125:353-355.
81. Cohen AL, Holmen SL, Colman H. (2013) IDH1 and IDH2 mutations in gliomas. Curr *Neurol Neurosci Rep*; 13:345.
82. Yan H, Bigner DD, Velculescu V, et al. (2009) Mutant metabolic enzymes are at the origin of gliomas. *Cancer Res*; 69:9157-9159.
83. Caccese M, Padovan M, D'Avella D, et al. (2020) Anaplastic astrocytoma: state of the art and future directions. *Crit Rev Oncol Hematol*; 153:1-7.
84. Bui KM, Farooq AV, Valyi-Nagy T, et al. (2013) Parenchymal anaplastic astrocytoma presenting with visual symptoms due to bilateral optic nerve sheath involvement. *J Neuro-ophthalmol*; 33:3.
85. Grimm SA, Chamberlain MC. (2016) Anaplastic astrocytoma. *CNS Oncol*; 05:145-157.
86. Ruff MW, Uhm J. (2018) Anaplastic glioma: treatment approaches in the era of molecular diagnostics. *Curr Treat Options Oncol*; 19:61.
87. von Deimling A, Louis DN, von Ammon K, et al. (1992) Evidence for a tumor suppressor gene on chromosome 19q associated with human astrocytomas, oligodendrogliomas and mixed gliomas. *Cancer Res*; 52:4277-4279.
88. Bello MJ, Vaquero J, de Campos JM, et al. (1994) Molecular analysis of chromosome 1 abnormalities in human gliomas

reveals frequent loss of 1p in oligodendroglial tumors. *Int J Cancer*; 57:172-175.
89. Kraus JA, Koopmann J, Kaskel P, et al. (1995) Shared allelic losses on chromosomes 1p and 19q suggest a common origin of oligodendroglioma and oligoastrocytoma. *J Neuropath Exp Neurol*; 54:91-95.
90. von Deimling A, Bender B, Jahnke R, et al. (1994) Loci associated with malignant progression in astrocytomas: a candidate on chromosome 19q. *Cancer Res*; 54:1397-1401.
91. Salles D, Santino SF, Ribeiro DA, et al. (2022) The involvement of the MAPK pathway in pilocytic astrocytomas. *Pathol Res Pract*; 232:1-13.
92. Guo Y, Pan W-W, Liu S-B, et al. (2020) ERK/MAPK signaling pathway and tumorigenesis. *Exp Ther Med*; 19(7):1997-2007.
93. Sadighi Z, Slopis J. (2013) Pilocytic astrocytoma: a disease with evolving molecular heterogeneity. *J Child Neurol*; 28:625-632.
94. Grave N, Scheffel TB, Cruz FF, et al. (2022) The functional role of p38 MAPK pathway in malignant brain tumors. *Front Pharmacol*; 15:1-19.
95. Collins VP, Jones DTW, Giannini C. (2015) Pilocytic astrocytoma: pathology, molecular mechanisms and markers. *Acta Neuropathol*; 129:775-788.
96. Vaitkiene P, Skiriute D, Steponaitis G, et al. (2014). Gene expression and function-based identification of biomarkers for diagnosis of glioma malignancies. *Int J Mol Med*;34: S55-S55
97. Santarpia L, Lippman SM, El-Naggar AK. (2012) Targeting the MAPKRAS-RAF signaling pathway in cancer therapy. Expert Opin Ther Targets; 16:103-119.
98. Cin H, Meyer C, Herr R, et al. (2011) Oncogenic FAM131B-BRAF fusion resulting from 7q34 deletion comprises an alternative mechanism of MAPK pathway activation in pilocytic astrocytoma. *Acta Neuropathol*; 121:763-774.
99. Tatevossian RG, Lawson ARJ, Forshew T, et al. (2009) MAPK pathway activation and the origins of pediatric low-grade astrocytomas. *J Cell Physiol*; 222(3): 509-514.
100. Jones DTW, Kocialkowski S, Liu L, et al. (2009) Oncogenic RAF1 rearrangement and a novel BRAF mutation as alternatives to KIAA1549: BRAF fusion in activating the MAPK pathway in pilocytic astrocytoma. *Oncogene*; 28:2119-2123.
101. Ryall S, Tabori U, Hawkins C. (2020) Pediatric low-grade glioma in the era of molecular diagnostics. *Acta Neuropathol Commun*; 8:30.
102. Janzarik WG, Kratz CP, Loges NT, et al. (2007) Further evidence for a somatic KRAS mutation in a pilocytic astrocytoma. *Neuropediatrics*; 38:61-63.
103. Kurani H, Gurav M, Shetty O, et al. (2019) Pilocytic astrocytomas: BRAFV600E and BRAF fusion expression patterns in pediatric and adult age groups. *Childs Nerv Syst*; 35:1525-1536.
104. Chen R, Keoni C, Waker CA, et al. (2019) KIAA1549-BRAF expression establishes a permissive tumor microenvironment through NFκB-mediated CCL2 production. *Neoplasia* (United States)' 21:52-60.
105. Gutmann DH, McLellan MD, Hussain I, et al. (2013) Somatic neurofibromatosis type 1 (NF1) inactivation characterizes NF1-associated pilocytic astrocytoma. *Genome Res*; 23: 431-439.
106. Nakasu S, Fukami T, Jito J, et al. (2007) Prognostic significance of loss of O6-methylguanine-DNA methyl-transferase expression in supratentorial diffuse low-grade astrocytoma. *Surg Neurol*; 68: 603-608.
107. Kaina B, Christmann M, Naumann S, et al. (2007) MGMT: key node in the battle against genotoxicity, carcinogenicity and apoptosis induced by alkylating agents. *DNA Repair* (Amst); 06:1079- 1099.
108. Gerson SL. (2004) MGMT: its role in cancer aetiology and cancer therapeutics. *Nat Rev Cancer*; 04:296-307.
109. Groenendijk FH, Taal W, Dubbink HJ, et al. (2011) MGMT promoter hyper-methylation is a frequent, early, and consistent event in astrocytoma progression, and not correlated with TP53 mutation. *J Neurooncol*; 101:405-417.
110. Brat DJ, Verhaak RG, Aldape KD, et al. (2015) Cancer Genome Atlas Research Network Comprehensive, integrative genomic analysis of diffuse lower-grade Gliomas.*N Engl J Med*; 372:2481-2498.
111. Sahm F, Reuss D, Koelsche C, et al. (2014) Farewell to oligoastrocytoma: in situ molecular genetics favor classification as either oligodendroglioma or astrocytoma. *Acta Neuropathol*; 128:551-559.
112. Wiestler B, Capper D, Sill M, et al. (2014) Integrated DNA methylation and copy-number profiling identify three clinically and biologically relevant groups of anaplastic gliomata. *Acta Neuropathol*; 128:561-571.
113. Smith JS, Alderete B, Minn Y, et al. (1999) Localization of common deletion regions on 1p and 19q in human gliomas and their association with histological subtype. *Oncogene*; 18:4144-4152.
114. Kyritsis AP, Yung WKA, Bruner J, et al. (1993) The treatment of anaplastic oligodendrogliomas and mixed gliomas. *Neurosurgery*; 32:365-371.
115. Pfister S, Janzarik WG, Remke M, et al. (2008) BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. *J Clin Invest*; 118:1739-1749.
116. Taylor AM, Shih J, Ha G, et al. (2018) Genomic and functional approaches to understanding cancer aneuploidy. *Cancer Cell*; 33:676-689.
117. Okamoto Y, Di Patre P-L, Burkhard C, et al. (2004) Population-based study on incidence, survival rates, and genetic alterations of low-grade diffuse astrocytomas and oligodendrogliomas. *Acta Neuropathol*; 108:49-56.
118. Ostrom QT, Gittleman H, Farah P, et al. (2013) *CBTRUS* statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro-Oncol*; 15(Suppl. 2), ii1–ii56 (2013).
119. Burger PC, Rawlings CE, Cox EB, et al. (1987) Clinicopathologic correlations in the oligodendroglioma. *Cancer*; 59(7): 1345-1352.
120. Cahill DP, Louis DN, Cairncross JG. (2015) Molecular background of oligodendroglioma:1p/19q, IDH, TERT, CIC and FUBP1. *CNS Oncol*; 4(5): 287-294.
121. Appin CL, Brat DJ. (2015) Biomarker-driven diagnosis of diffuse gliomas. *Mol Aspects Med*; 45:87-96.
122. Hartmann C, Meyer J, Balss J, et al. (2009) Type and frequency of *IDH1* and *IDH2* mutations are related to astrocytic and oligodendroglia differentiation and age: a study of 1,010 diffuse gliomas. *Acta Neuropathol*; *118*(4): 469-474.
123. Labussiere M, Idbaih A, Wang XW, et al. (2010) All the 1p19q co-deleted gliomas are mutated on *IDH1* or *IDH2*. *Neurology;* 74(23): 1886-1890.
124. Capper D, Reuss D, Schittenhelm J, et al. (2011) Mutation-specific *IDH1* antibody differentiates oligodendrogliomas and oligoastrocytomas from other brain tumors with oligodendroglioma-like morphology. *Acta Neuropathol*; *121*(2): 241-252.
125. Bettegowda C, Agrawal N, Jiao Y, et al. (2011) Mutations in CIC and FUBP1 contribute to human oligodendroglioma. *Science*; 333:1453-1455.
126. Sahm F, Koelsche C, Meyer J, et al. (2012) CIC and FUBP1 mutations in oligodendrogliomas, oligoastrocytomas and astrocytomas. *Acta Neuropathol*; 123:853-860.

127. Ajuria L, Nieva C, Winkler C, et al. (2011) Capicua DNA-binding sites are general response elements for RTK signaling in drosophila. *Development*; 138(5): 915-924.
128. Killela PJ, Reitman ZJ, Jiao Y, et al. (2013) TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. *Proc Natl Acad Sci USA*; 110:6021-6026.
129. Arita H, Narita Y, Fukushima S, et al. (2013) Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total 1p19q loss. *Acta Neuropathol*; 126:267-276.
130. Kuo LT, Kuo KT, Lee MJ et al. (2009) Correlation among pathology, genetic and epigenetic profiles, and clinical outcome in oligodendroglial tumors. *Int J Cancer*; 124(12):2872-2879.
131. Hong C, Bollen AW, Costello JF. (2003) The contribution of genetic and epigenetic mechanisms to gene silencing in oligodendrogliomas. *Cancer Res*; *63*(22): 7600-7605.
132. Van Den Bent MJ, Gravendeel LA, Gorlia T, et al. (2011) A hypermethylated phenotype is a better predictor of survival than MGMT methylation in anaplastic oligodendroglial brain tumors: a report from EORTC study 26951. *Clin Cancer Res*; 17(22): 7148-7155.
133. Suva ML, Riggi N, Bernstein BE. (2013) Epigenetic reprogramming in cancer. *Science*; 339 (6127): 1567-1570.
134. Fallon KB, Palmer CA, Roth KA, et al. (2004) Prognostic value of 1p, 19q, 9p, 10q, and EGFR-FISH analyses in recurrent oligodendrogliomas. *J Neuropathol Exp Neurol*; 63:314-322.
135. Hoang-Xuan K, Huguet S, Mokhtari K, et al. (2002) Molecular heterogeneity of oligodendrogliomas suggests alternative pathways in tumor progression. *Neurology*; 57:1278-1281.
136. Idbaih A, Crinière E, Marie Y, et al. (2008) Gene amplification is a poor prognostic factor in anaplastic oligodendrogliomas. *Neuro Oncol*; 10:540-547.
137. Kouwenhoven MCM, Gorlia T, Kros JM, et al. (2009) Molecular analysis of anaplastic oligodendroglia tumors in a prospective randomized study: A report from EORTC study 26951. *Neuro Oncol*; 11(6): 737-746.
138. Qu M, Olofsson T, Sigurdardottir S, et al. (2007) Genetically distinct astrocytic and oligodendroglia components in oligoastrocytomas. *Acta Neuropathol*; 113:129-136.
139. Jiao Y, Killela PJ, Reitman ZJ, et al. (2012) Frequent ATRX, CIC, FUBP1 and IDH1 mutations refine the classification of malignant gliomas. *Oncotarget*; 3:709-722.
140. Labussiere M, Di Stefano AL, Gleize V, et al. (2014) TERT promoter mutations in gliomas, genetic associations and clinicopathological correlations. *Br J Cancer*; 111:2024-2032.
141. Perry A, Aldape KD, George DH, et al. (2004) Small cell astrocytoma: an aggressive variant that is clinicopathologically and genetically distinct from anaplastic oligodendroglioma. *Cancer*; 101:2318-2326.
142. Broderick DK, Di C, Parrett TJ, et al. (2004) Mutations of PIK3CA in anaplastic oligodendrogliomas, high-grade astrocytomas, and medulloblastomas. *Cancer Res*; 64:5048-5050.
143. Agnihotri S, Aldape KD, Zadeh G. (2014) Isocitrate dehydrogenase status and molecular subclasses of glioma and glioblastoma. *Neurosurg Focus*; 37: E13.
144. Snuderl M, Eichler AF, Ligon KL, et al. (2009) Polysomy for chromosomes 1 and 19 predicts earlier recurrence in anaplastic oligodendrogliomas with concurrent 1p/19q loss. *Clin Cancer Res*; 15(20) :6430-6437.
145. Wiens AL, Cheng L, Bertsch EC, et al. (2012) Polysomy of chromosomes 1 and/or 19 is common and associated with less favorable clinical outcome in oligodendrogliomas: fluorescent in situ hybridization analysis of 84 consecutive cases. *J Neuropathol Exp Neurol*; 71:618-624.
146. Kilday JP, Rahman R, Dyer S, et al. (2009) Pediatric ependymoma: biological perspectives. *Mol Cancer Res*; 7(6):765- 786.
147. Georgescu MM, Yell P, Mobley BC, et al. (2015). NHERF1/EBP50 is an organizer of polarity structures and a diagnostic marker in ependymoma. *Acta Neuropathol Commun*; 3: 11.
148. von Haken MS, White EC, Daneshvar-Shyesther L, et al. (1996) Molecular genetic analysis of chromosome arm 17p and chromosome arm 22q DNA sequences in sporadic pediatric ependymomas. *Genes Chromosomes Cancer*; 17(1): 37-44.
149. Astolfi A, Vendemini F, Urbini M, et al. (2014). MYCN is a novel oncogenic target in pediatric T-cell Acute Lymphoblastic Leukemia. *Oncotarget*; 5: 120-130.
150. Barone G, Anderson J, Pearson ADJ, et al. (2013). New strategies in neuroblastoma: Therapeutic targeting of MYCN and ALK. *Clin. Cancer Res*; 19: 5814-5821.
151. Ruiz-Pérez MV, Henley AB, Arsenian-Henriksson M. (2017) The MYCN protein in health and disease. *Genes*; 8(4): 113.
152. Ghasemi DR, Sill M, Okonechnikov K, et al. (2019). MYCN amplification drives an aggressive form of spinal ependymoma. *Acta Neuropathol*; 138: 1075-1089.
153. Modena P, Lualdi E, Facchinetti F, et al. (2006) Identification of tumor-specific molecular signatures in intracranial ependymoma and association with clinical characteristics. *J Clin Oncol*; 24(33):5223-5233.
154. Albright AL, Adelson PD, Pollack IF. (2008) Principles and practice of pediatric neurosurgery. Second edition. New York: Thieme, 2008.
155. George OL, Ness SA. (2014). Situational awareness: Regulation of the myb transcription factor in differentiation, the cell cycle and oncogenesis. *Cancers*; 6: 2049-2071.
156. Mullins KJ, Rubio A, Myers SP, et al. (1998). Malignant ependymomas in a patient with Turcot's syndrome: case report and management guidelines. *Surg Neurol*; 49(3):290-294.
157. Torres CF, Korones DN, Pilcher W. (1997) Multiple ependymomas in a patient with Turcot's syndrome. *Med Pediatr Oncol*; 28 (1):59-61.
158. Al-Salameh A, Francois P, Giraud S, et al. (2010) Intracranial ependymoma associated with multiple endocrine neoplasia type 1. *J Endocrinol Invest*; 33(5):353-356.
159. Barton VN, Donson AM, Kleinschmidt-Demasters BK, et al. (2010). Unique molecular characteristics of pediatric myxopapillary ependymoma. *Brain Pathol*; 20: 560-570.
160. Palm T, Figarella-Branger D, Chapon F, et al. (2009) Expression profiling of ependymomas unravels localization and tumor grade-specific tumorigenesis. *Cancer* ;115: (17):3955- 3968.
161. Wellik DM. (2007) Hox patterning of the vertebrate axial skeleton. *Dev Dyn*; 236: 2454-2463.
162. Takahashi Y, Hamada JI, Murakawa K, et al. (2004) Expression profiles of 39 HOX genes in normal human adult organs and anaplastic thyroid cancer cell lines by quantitative real-time RT-PCR system. *Exp Cell Res*; 293: 144-153.
163. Schonthal AH. (2012) Exploiting Cyclooxygenase-(in) Dependent Properties of COX-2 Inhibitors for Malignant Glioma Therapy. *Anticancer Agents Med Chem*; 10: 450-461.
164. Suarez-Merino B, Hubank M, Revesz T, et al. (2005) Microarray analysis of pediatric ependymoma identifies a cluster of 112 candidate genes including four transcripts at 22q12.1-q13.3 [J]. *Neuro Oncol*; 7(1):20-31.
165. Louvi A, Artavanis Tsakonas S. (2006) Notch signaling in vertebrate neural development. *Nat Rev Neurosci*; 7(2):93-102.
166. Puget S, Grill J, Valent A, et al. (2009) Candidate genes on chromosome 9q33-34 involved in the progression of childhood ependymomas. *J Clin Oncol*; 27(11):1884-1892.

167. Gilbertson RJ, Bentley L, Hernan R, et al. (2002) ERBB receptor signaling promotes ependymoma cell proliferation and represents a potential novel therapeutic target for this disease. *Clin Cancer Res*; 8(10):3054-3064.
168. Zhang XM, Dormady SP, Chaung W, et al. (2000) mVH1, a dual-specificity phosphatase whose expression is cell cycle regulated. *Mamm Genome*; 11(12):1154-1156.
169. Campbell K, Gotz M. (2002) Radial glia: multi-purpose cells for vertebrate brain development. *Trends Neurosci*; 25(5): 235-238.
170. Spassky N, Merkle FT, Flames N, et al. (2005) Adult ependymal cells are postmitotic and are derived from radial glial cells during embryogenesis. *J Neurosci*; 25(1):10-18.
171. Poppleton H, Gilbertson RJ. (2007) Stem cells of ependymoma. *Br J Cancer*; 96(1):6-10.
172. Barry D, McDermott K. (2005) Differentiation of radial glia from radial precursor cells and transformation into astrocytes in the developing rat spinal cord. *Glia*; 50(3): 187-197.
173. Gil J, Bernard D, Martinez D, et al. (2004) Polycomb CBX7 has a unifying role in cellular lifespan. *Nat Cell Biol*; 6 (1): 67-72.
174. Korshunov A, Witt H, Hielscher T, et al. (2010) Molecular staging of intracranial ependymoma in children and adults. *J Clin Oncol*; 28(19): 3182-3190.
175. Rajaram V, Leuthardt EC, Singh PK, et al. (2004) 9p21 and 13q14 dosages in ependymomas. A clinicopathologic study of 101 cases. *Mod Pathol*; 17(1):9-14.
176. Hirose Y, Aldape K, Bollen A, et al. (2001) Chromosomal abnormalities subdivide ependymal tumors into clinically relevant groups. *Am J Pathol*; 158(3): 1137-1143.
177. Monoranu CM, Huang B, Zangen IL, et al. (2008) Correlation between 6q25.3 deletion status and survival in pediatric intracranial ependymomas. *Cancer Genet Cytogenet*; 182(1):18-26.
178. Huang B, Starostik P, Schraut H, et al. (2003) Human ependymomas reveal frequent deletions on chromosomes 6 and 9. *Acta Neuropathol*; 106(4): 357-362.
179. Schneider D, Monoranu CM, Huang B, et al. (2009) Pediatric supratentorial ependymomas show more frequent deletions on chromosome 9 than infratentorial ependymomas: a micro-satellite analysis. *Cancer Genet Cytogenet*; 191 (2): 90-96.
180. Waha A, Koch A, Hartmann W, et al. (2004) Analysis of HIC-1 methylation and transcription in human ependymomas. *Int J Cancer*; 110(4):542-549.
181. Mack SC, Taylor MD. (2009) The genetic and epigenetic basis of ependymoma. Childs *Nerv Syst*; 25(10):1195-1201.
182. Hamilton DW, Lusher ME, Lindsey JC, et al. (2005) Epigenetic inactivation of the RASS F1A tumor suppressor gene in ependymoma. *Cancer Lett*; 227(1):75-81.
183. Donninger H, Vos MD, Clark GJ. (2007) The RASSF1A tumor suppressor. *J Cell Sci*; 120 (Pt 18):3163-3172.
184. Michalowski MB, de Fraipont F, Michelland S, et al. (2006) Methylation of RASSF1A and TRAIL pathway-related genes is frequent in childhood intracranial ependymomas and benign choroid plexus papilloma. *Cancer Genet Cytogenet*; 166 (1):74-81.

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