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Genetic and molecular epidemiology of adult diffuse glioma

Annette M. Molinaro[1,2], **Jennie W. Taylor**[1,3], **John K. Wiencke**[1,4], **Margaret R. Wrensch**[1,2,4]

[1]Department of Neurological Surgery, University of California, San Francisco (UCSF), San Francisco, Califonia, USA.

[2]Department of Epidemiology and Biostatistics, University of California, San Francisco (UCSF), San Francisco, Califonia, USA.

[3]Department of Neurology, University of California, San Francisco (UCSF), San Francisco, Califonia, USA.

[4]Institute of Human Genetics, University of California, San Francisco (UCSF), San Francisco, Califonia, USA.

Abstract

Previous glioma classification based primarily on tumour histology resulted in considerable inter-oberver variability and substantial variation in patient survival within grades. Furthermore, there were few known risk factors for glioma. Discoveries over the past decade have deepened our understanding of the molecular alterations underlying glioma and have led to the identification of numerous heritable genetic risk factors. The advances in glioma molecular characterization reframed our understanding of glioma biology and led the World Health Organization (WHO) to develop a new classification system for glioma. The WHO 2016 classification system comprises five glioma subtypes categorized by both tumour morphology and molecular genetic information, which led to reduced misclassification and more-uniform outcomes within glioma subtypes. To date, 25 risk loci for glioma have been identified and several rare inherited mutations that might cause glioma in some families have been discovered. This Review focuses on the two dominant trends in glioma science: the characterization of diagnostic and prognostic tumour markers and the identification of genetic and non-genetic risk factors. An overview of the many challenges still facing glioma researchers is also included.

Introduction

Every year, approximately 100,000 people worldwide are diagnosed as having diffuse gliomas[1]. Although they comprise less than 2% of all newly diagnosed cancers, diffuse glioma is associated with substantial mortality and morbidity[2]. Glioblastoma, the most lethal

Correspondence to A.M.M. annette.molinaro@ucsf.edu.

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glioma, accounts for 70–75% of all diffuse glioma diagnoses and has a median overall survival of 14–17 months. Globally, there are vast differences in glioma incidence between European and Asian populations[3], as discussed more below. In addition to geographic differences, glioma incidence varies by age, sex, ethnicity and tumour histology while glioma survival varies by age and sex.

Historically, gliomas were considered to originate from differentiated astrocytic and oligodendrocytic components of the central nervous system (CNS)[4]. As such, categorization of diffuse gliomas previously relied only on tumour histology based on the World Health Organization (WHO) 2007 glioma classification criteria[5]. Over the past decade, molecular studies in human tumours have provided important new insights into the complex genetic, chromosomal, and epigenetic changes within gliomas that accompany glioma formation and maintenance[6–11]. As a result, a new WHO integrated classification system was introduced in 2016 based on tumour morphology and molecular alterations[12]. Most recently, stem-like cells within the CNS are thought to be the cells of origin of several primary brain tumour types, including glioblastoma[13]. Data obtained in experimental animal models support the notion that neural stem cells[14], particularly in the subventricular zone, can give rise to at least a subset of glioblastomas[15]. Also, during the past 10 years, studies discovered many new genetic risk factors for gliomas including rare mutations confined to specific families and more common inherited variants in 25 independent genetic loci[16–19].

In this Review of adult diffuse gliomas, we focus on research advances that led from the previous WHO 2007 classification criteria to the WHO 2016 integrated classification system[12,20]. We present the latest incidence and survival data for adult diffuse glioma from several population based reports including that of the 2018 Central Brain Tumor Registry of the United States (CBTRUS)[21], which rely on the WHO 2007 classification system as the WHO 2016 system has not yet been used widely enough in population data sources. We also provide an update on clinical research and genetic and other risk factors for glioma and, where possible, relate these to the WHO 2016 glioma subgroups.

Classification of glioma

The 2007 WHO guidelines for classifying malignant gliomas were based on histologic criteria, in which several morphologic subtypes corresponded to the general appearance of the tissue of origin: astrocytoma, oligodendroglioma and mixed oligoastroctyoma. Tumour malignancy was graded II–IV according to morphological criteria. High-grade tumours generally had a poor prognosis. However, this classification system had high inter-observer variability[22–24] and survival varied substantially within grades. Thus, for many decades, neuropathologists and glioma biologists have been investigating markers to improve the characterization of clinically relevant subgroups[25].

In 2015, two research groups simultaneously published papers describing molecular and chromosomal subtypes that clarified glioma classification[26,27]. The first study included over 1,000 patients with WHO grade II–IV glioma from from three large studies in the United States[27]. These researchers focused on the presence or absence of three tumour markers: promoter mutations in *TERT (*which encodes telomerase reverse transcriptase); mutations in

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IDH1 (encoding isocitrate dehydrogenase [NADP] cytoplasmic) or *IDH2* (encoding isocitrate dehydrogenase [NADP], mitochondrial)[8,28–32], collectively referred to as *IDH* mutations, which had been shown to be common in some types of glioma and to be associated with survival[25]; and co-deletion of chromosome arms 1p and 19q, as observed in oligodendrogliomas[33]. These three markers classified patients with glioma into five groups that were distinguished by differences in survival (especially between patients with grade II or III tumours), age at diagnosis, germline risk alleles, and other tumour mutations and chromosome copy number changes. Notably, grade II or III astrocytomas with only *TERT* promoter mutations had outcomes very similar to glioblastoma. The second study included almost 300 patients with WHO grade II and III gliomas from the TCGA and found three distinct subgroups based on *IDH* mutation, *TP53* mutation, and 1p19q co-deletion status[26].

In 2016, building on data from these and other seminal studies[6], the WHO integrated tumour morphology, *IDH* mutation and 1p19q co-deletion status into a new classification system for adult diffuse glioma[12] (Figure 1). This classification system includes five primary designations of adult diffuse glioma: glioblastoma, *IDH*-wild type; glioblastoma, *IDH*-mutant; diffuse or anaplastic astrocytomas, *IDH*-wild type; diffuse or anaplastic astrocytomas, *IDH*-mutant; and oligodendroglioma or anaplastic oligodendroglioma, *IDH*-mutant and 1p19q co-deletion (Figure 1). Characterization of the third group was subsequently updated[20], as substantial evidence showed that many such tumours had WHO grade II or III histology but were associated with a clinical outcome similar to that of WHO grade IV tumours[8,27,34,35] (discussed below). A sixth group, based on histologic appearance in the absence of molecular determination, is designated malignant glioma not otherwise specified. A seventh group, diffuse midline glioma, H3 K27M-mutant (that is, with a histone 3 Lys27>Met amino acid substitution), is also discussed below. Two aspects of the new WHO integrated diagnosis are particularly important: oligoastrocytomas are no longer recognized as a separate entity and instead, via *IDH* mutation and 1p19q co-deletion status, reflect the genetic profile of either astrocytoma (1p19q intact) or oligodendroglioma (1p19q co-deletion)[36]; and when histology and molecular features are discordant, molecular features often become the primary determinant of classification.

The five new principal groups have accurately delineated ages at diagnosis and prognosis (Fig 1 and Table 1)[8,11,37–39]. Patients with glioblastoma, *IDH*-wild type have, on average, the highest age at diagnosis (median 59 years) and the worst prognosis (median overall survival 1.2 years). Patients with glioblastoma, *IDH*-mutant tend to be younger (median age at diagnosis 38 years) and have a better prognosis (median overall survival 3.6 years) than those with glioblastoma, *IDH*-wild type. Patients with astrocytoma, *IDH*-wild type, regardless of grade II or grade III histology, have a median age at diagnosis of 52 years; their median overall survival (only 1.9 years) is more similar to that of patients with glioblastoma, *IDH*-wild type than to that of patients with glioblastoma, *IDH*-mutant. By contrast, patients with astrocytoma, *IDH*-mutant have a median age at diagnosis of 36 years and median overall survival of 9.3 years[37,38]. Patients with oligodendroglioma, *IDH*-mutant and 1p19q co-deletion are also relatively young at diagnosis (median age 44 years) and have the longest median overall survival (17.5 years).

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As the WHO 2016 integrated diagnosis incorporates both *IDH* mutation and 1p19q co-deletion status, population-based incidence and survival data for the five WHO classes is not yet available. On the basis of calculations relating to the molecular subtypes (*IDH* and 1p19q status)[27,40] and the most recent CBTRUS data[21], we estimate that in 2019, approximately 71% of newly diagnosed diffuse gliomas will be classified as glioblastoma, *IDH*-wild type; 7% as glioblastoma, *IDH*-mutant; 5% as astrocytoma, *IDH*-wild type; 12% as astrocytoma, *IDH*-mutant; and 5% as oligodendroglioma, *IDH*-mutant and 1p19q co-deletion (Table 1).

Diffuse midline glioma, H3 K27M-mutant

The seventh group of the WHO 2016 integrated diagnosis (referenced above) is the diffuse midline gliomas, H3 K27M-mutant. According to the 2007 WHO classification system, these tumours could have met the histological criteria for any grade of astrocytoma, although their poor clinical outcomes more closely resemble those of patients with glioblastoma. First identified in paediatric intrinsic pontine gliomas, this subgroup is defined by gain-of-function mutations in genes encoding histone H3 (*H3F3A, HIST1H3B, HIST1H3C or HIST1H3I*) that result in a Lys>Met amino acid substitution at position 27.[41,42] This alteration, which appears early and homogeneously, was also identified in adults with diffuse glioma, predominantly those with young ages of onset and tumours in midline locations such as the spinal cord, thalamus, brainstem, and cerebellum. Although the histological classification of these tumours is typically low-grade, their clinical outcome is poor[42]. Consequently, the WHO 2016 classification identified diffusely infiltrating gliomas that arise in the midline and harbour the H3 K27M mutation as a separate entity regardless of the presence of anaplastic histologic features.[12,43]

Diffuse astrocytoma, *IDH*-wild type

Particular efforts have been made to further characterize tumours in the diffuse astrocytoma, *IDH*-wild type group according to the WHO 2016 classification, because patient outcomes in this group vary widely[20]. This group includes patients with very low grade tumours, such as glioneuronal tumours and pilocytic astrocytomas (not discussed in detail in this Review) that have a very favorable course, as well as patients who have a very poor prognosis similar to that of patients with glioblastoma, *IDH*-wild type. The inclusion of the latter group probably results from sampling of the tumour during resection being insufficient to show histological features of glioblastoma.

Other markers

The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) is a working group formed to incorporate advances in defining further subtypes of the WHO 2016 classification system into clinical practice[20,43,44]. For example, cIMPACT-NOW has recommended that diffuse astrocytoma, *IDH*-wild type tumours should undergo further characterization: testing for *EGFR* amplification; gain of chromosome 7 and loss of chromosome 10; and the presence of *TERT* promoter mutation. Regardless of tumour histology, if any of these molecular alterations are found, the patient is now considered to have diffuse astrocytic glioma, *IDH*-wild type, with molecular features of glioblastoma WHO grade IV[20].

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Similarly, several other tumour markers that are not incorporated into the formal WHO 2016 classification system are being used to fine-tune the prognosis of some categories of glioma. Below, we summarize the most promising additional markers. Additional genetic alternations and pathway abnormalities are reviewed elsewhere[6,45] and summarized in Table 1.

Telomerase alterations.—Numerous studies have shown the classification and prognostic importance of mutations in telomere maintenance genes, including *TERT* and *ATRX*[7,27,46–48]. Typically, *TERT* and *ATRX* alterations are mutually exclusive, probably because of functional redundancy[7,27,46]. A study of over 1,200 adult patients with diffuse glioma aimed to characterize the distribution and additional prognostic value of *TERT* and *ATRX* alterations within the five WHO 2016 groups[37] (Fig. 1). In the glioblastoma, *IDH*-wild type subgroup, over 75% of tumours had a *TERT* mutation. Approximately 3% of glioblastoma, *IDH*-wild type tumours had alterations in *ATRX*, which were associated with improved survival (adjusted HR 0.36; 95% CI 0.17–0.81). In the astrocytoma, *IDH*-wild type subgroup, over 60% of tumours had a *TERT* mutation whereas 12% had alterations in *ATRX*; *TERT*-wild type tumours were associated with improved survival (adjusted HR 0.48; 95% CI 0.27–0.87). Both the astrocytoma, *IDH*-mutant and glioblastoma, *IDH*-mutant subgroups showed high proportions of *ATRX* mutations (63% and 78%, respectively) and low proportions of *TERT* mutations (5% and 12%, respectively), although neither *TERT* nor *ATRX* alterations were associated with survival in these two groups. Among patients with oligodendroglioma, *IDH*-mutant and 1p19q co-deletion, *TERT* mutations were seen in 94% of tumours and *ATRX* alterations in 3%; *TERT*-wild type tumours were associated with markedly poor survival (adjusted HR 2.46; 95% CI 0.94–6.42). The authors concluded that in some subgroups, additional testing for *ATRX* and/or *TERT* mutations might be warranted.

Methylation signatures.—A tumour's methylome includes both somatically acquired DNA methylation changes and characteristics derived from the cell of origin. Distinct DNA-methylation signatures are associated with prognosis in glioma[9,11,46,49,50]. For example, mutations in *IDH* cause aberrant methylation of DNA and histones. Hypermethylation of CpG islands is referred to as the glioma CpG-island methylator phenotype (G-CIMP), which is associated with a favourable prognosis[11,25,51]. A study that used both methylation and gene expression analyses to examine over 1,100 newly diagnosed diffuse gliomas included in TCGA found six distinct pan-glioma DNA methylation and transcriptome subtypes, which they termed LGm1–LGm6 (Fig. 1)[46].

The *IDH*-mutant gliomas were separated into three groups: LGm1 with 1p19q co-deletion (18%); LGm2 (G-CIMP-high) with 1p19q-intact and highly methylated (25%); and LGm3 (G-CIMP-low) with 1p19q intact and low methylation levels (3%). Interestingly, the LGm1 and LGm2 groups had a similar prognosis; only the LGm3 group had distinctly better prognosis. The *IDH*-wild type gliomas were separated into four subgroups: LGm4 glioblastomas with classic gene expression profiles (18%); LGm5 glioblastomas with mesenchymal gene expression profiles (27%); and LGm6 glioblastomas with a distinct methylation pattern and stable telomeres (9%). A subset of low-grade gliomas in LGm6 that were similar to pilocytic astrocytoma (that is, with a young age at onset and favourable

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survival) were referred to as 'pilocytic astrocytoma -like'[46]. Of note, only the pilocytic astrocytoma-like subset showed a survival advantage. All other *IDH*-wild type tumours had indistinguishable survival.

DNA methylation profiling has repeatedly been shown to be a robust method of classifying tumours[23,52]. Accordingly, DNA methylation-based classification has been used to circumvent the interobserver variability highlighted in the methylation and gene expression study mentioned above and thereby to improve diagnostic precision[49]. The reference dataset comprised 2,800 CNS tumours including ~100 tumour types, which were divided into 82 CNS tumour methylation classes. Eight of these classes were subgroups of glioblastoma, which suggested a possible future role of DNA methylation profiling in differentiation of the two glioblastoma subgroups included in the WHO 2016 classification. The six TCGA pan-glioma methylation classes shown in Fig. 1 (LGm1–LGm6) overlap with nine of the 82 CNS tumour methylation classes (A IDH HG, A IDH, O IDH, GBM TRK II, GBM MES, GBM RTK I, DMG K27, GBM MID, and GBM MYCN). In the validation dataset, which included over 1,000 prospectively collected CNS tumours, the DNA methylation-based classifier was concordant with histopathology in 76% of tumours, and another 12% (129 tumours) were reclassified based on their methylation profile. In 70% of these 129 tumours, the WHO 2016 classification was either upgraded or downgraded, and several astrocytoma, *IDH*-wild type tumours were reclassified as glioblastoma, *IDH*-wild type. Thus, this DNA methylation classifier could substantially reduce tumour misclassification and decrease the subset of tumours for which diagnosis is difficult because the histology and molecular features are discordant.

MGMT: The DNA damage induced by temozolomide can be repaired by the enzyme methylated-DNA–protein-cysteine methyltransferase (MGMT, also known as 6-*O*-methylguanine-DNA methyltransferase). Accordingly, high levels of *MGMT* mRNA and MGMT protein have been linked to DNA alkylating agent resistance[53], whereas methylation of CpG islands in the promoter region of *MGMT* (which suppresses its transcription) increases chemosensitivity to these agents[54]. The importance of *MGMT* promoter methylation as both a prognostic and a predictive biomarker has been shown in multiple clinical trials and research studies[55–59]. A conclusion drawn from several of those studies is that patients with glioblastoma over 65–70 years of age whose tumour lacks *MGMT* promoter methylation clearly derive a reduced benefit from temozolomide.

Several studies have examined the interaction between *MGMT* promoter methylation and *IDH1* mutation status because *IDH1* mutation is associated with the globally hypermethylated G-CIMP phenotype[11,51]. Among patients with glioblastoma, *MGMT* promoter methylation rates range from ~40% in *IDH*-wild type tumours to ~90% in *IDH*-mutant tumours (a similar pattern is seen in the limited available data on non-glioblastoma astrocytomas[60,61]; Table 1). In grade III and IV gliomas, *MGMT* promoter methylation is a prognostic indicator of improved survival and decreased progression in patients with *IDH*-mutant glioma[62], and predicts a favourable therapeutic response to alkylating agents in *IDH*-wild type patients[63,64]. In a study that further explored the survival benefit associated with *MGMT* promoter methylation in patients with glioblastoma, *IDH1*-wild type, this benefit was only seen in the 75% of patients whose tumour also harboured a *TERT* promoter

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mutation (Figure 1)[65], which suggested that both markers should be included in future risk stratification. Thus, the research to date supports testing for *MGMT* promoter methylation in clinical practice, in particular for two groups: elderly patients with glioblastoma and those with a diagnosis of anaplastic (*IDH*-wild type) glioma[61]. Several studies in older patients (variably defined as age >60 or >65 years) have confirmed *MGMT* promoter methylation as a favourable prognostic factor and predictive of response to temozolomide[58,66,67]. Given the increased toxicity of combined radiotherapy and chemotherapy in elderly patients, individuals with *MGMT* promoter methylation might be treated with chemotherapy alone[67] or patients without *MGMT* promoter methylation might be treated with radiotherapy alone[58,66,67].

Historically, *MGMT* promoter methylation testing was not widespread owing to difficulties with the assays and their standardization as well as the existence of few therapeutic alternatives to the current standard of care[54]. However, a data set including over 4,000 patients with glioblastoma multiforme (GBM) pooled from the control arms of four large clinical trials, all of whom received radiation and temozolomide and underwent centralized *MGMT* promoter methylation testing using quantitative methylation-specific PCR, confirmed that patients without *MGMT* promoter methylation had a worse prognosis than patients with *MGMT* promoter methylation. This study also identified that 10% of patients had low *MGMT* promoter methylation. The outcome of these ‘grey zone’ patients was aligned more closely with the methylated than the nonmethylated group. These data support those from ongoing studies showing that both patients with *MGMT* promoter methylation and those with indeterminate *MGMT* promoter methylation status should receive treatment with temozolomide[68]. This agent should, therefore, only be withheld in patients who truly lack *MGMT* promoter methylation.

***CDKN2A* and/or *CDKN2B* deletion.—**Aberrations in signalling pathways affecting the cell cycle are a common mechanism of uncontrolled cell growth in glioma. In glioblastoma, this dysregulation most frequently manifests as homozygous deletions in *CDKN2A* and/or *CDKN2B* (50–60%), copy number alterations in other cyclin-dependent pathways (~20%), or mutations in the retinoblastoma-associated protein pathway (7–10%).[6,10]

Although 50–60% of patients with glioblastoma have loss of *CDKN2A* and/or *CDKN2B*, this mutation were not initially associated with prognosis[6–8]. However, homozygous deletions in *CDKN2A* and/or *CDKN2B* have now been identified as a histology-independent negative prognostic marker in *IDH*-mutant astrocytomas[69], including in glioblastoma, *IDH*-mutant[70,71]. The loss of *CDKN2A* and/or *CDKN2B*, regardless of WHO 2016 classification, was seen in 11–18% of all tested astrocytomas, *IDH*-mutant, and these patients clinical outcomes’ were similar to those of patients with glioblastoma, *IDH*-mutant. Although homozygous deletion of *CDKN2A* and/or *CDKN2B* was the strongest predictor of worse survival, the effect was diminished when combined with other aberrations in the cell cycle pathway, such as amplification of *CDK4* or *CDK6* or deficiency of *RB1*. The adverse effect of *CDKN2A* and/or *CDKN2B* deletion on prognosis might be unique to *IDH*-mutant astrocytomas with *TP53* mutations, and might not be seen in oligodendrogliomas or *IDH*-wild type astrocytomas, including glioblastoma[38,69].

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Incidence, Risk and Survival

Incidence and survival

Globally, the incidence of adult diffuse gliomas differs substantially between countries[72–78]. In older adults over 40, the age adjusted annual incidence rate of astrocytic tumors is 6.8/100,000 people[79]. Countries with predominantly Northern European populations have a higher rate (ranging from 7.8 in the USA to 9.6 in Australia/New Zealand) than countries with predominantly Asian or African populations (ranging from 1.9 in Southeast Asia to 3.3 in India)[79]. Similar patterns in incidence are seen in oligodendroglial tumors. The wide range of incidence values is confounded by differences in access to medical imaging, case ascertainment and surveillance. Nonetheless, the large difference in incidence between European and Asian populations is observed both when comparing different countries and within the USA and UK[79,80]. The fourfold higher incidence in Western Europe (8.5/100,000) compared to prosperous East Asian countries (such as Japan and Singapore) (1.9/100,000) suggests that ethnic, cultural and/or environmental differences might be more likely to explain the observed differences in incidence than reporting bias[3,78,79]. Future studies comparing genetic, environmental and regional lifestyle risk factors within and between countries will be important to understand these differences[78].

The latest incidence data in the USA for adult diffuse glioma are derived from the 2018 Central Brain Tumor Registry of the United States (CBTRUS) report[21], which relies on the WHO 2007 classification system as the WHO 2016 system has not yet been used widely enough in population data sources. As the CBTRUS definition of glioma includes pilocytic astrocytoma, unique astrocytoma variants, ependymal tumours, and malignant glioma not otherwise specified, when citing CBTRUS data, we have only included data on diffuse glioma in adults. However, other references cited contain variable definitions of glioma, which sometimes include paediatric patients. In this article, therefore, we differentiate between adult diffuse glioma and glioma. As noted above, the WHO 2016 classification does not include the prior histologic category of oligoastrocytoma. However, CBTRUS and other reporting registries retain that category and have not yet published population data based on the new classification. Therefore, in this section we use the older WHO 2007 classification used by registries for population statistics, and when available, limited data from studies that used the WHO 2016 subtypes.

In the United States, diffuse gliomas account for 72% of malignant brain tumours in adults and 21% of all primary brain and other CNS tumours in adults[21,81]. In adults, glioblastoma, the most rapidly fatal form, accounts for 73% of diffuse gliomas, 52% of malignant non-metastatic brain tumours, and 15% of all primary brain and other CNS tumours[21]. Although diffuse gliomas account for less than 1% of all new cancers[21,82], they are associated with considerable morbidity and mortality. Since 2000, the incidence of glioma has been relatively stable, with a small but statistically significant increase from 2000 to 2008 followed by a statistically significant decrease from 2008 to 2014[21,72,83,84]. In 2019, new cases of adult diffuse glioma in the USA are estimated to approach 17,000 whereas during 1990–1994 <10,000 cases annually were reported[85]. The large increase observed after 1994 is likely to be due to improved detection through advances in diagnostic imaging.

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Most population-based studies show that, in addition to the geographical differences, glioma incidence varies by age, sex, ethnicity and tumour histology (or WHO 2016 subtype), and that survival for patients with glioma also consistently varies by age, sex and tumour subtype.

Age and sex—Within diffuse glioma subtypes, population incidence varies according to age and sex (Figure 2). Astrocytoma (including glioblastoma and diffuse or anaplastic astrocytoma) incidence increases with age, and peaks between the ages of 75 years and 84 years. Men have a 40–50% higher incidence than women at all ages (Figure 2)[21,86]. In 2000–2014, 1-year and 5-year relative survival for adults with glioblastoma was 41% and 5%, respectively. Corresponding 1-year and 5-year relative survival for those with non-glioblastoma astrocytomas was 72% and 44%, respectively (Figure 2)[81]. In a large study using the WHO 2016 classification, the median age at diagnosis is lower for patients with *IDH*-mutant astrocytomas (36 years) and glioblastomas (38 years) than for those with *IDH*-wild type astrocytomas (52 years) and glioblastomas (59 years)[37] (Table 1). Median overall survival is better in patients with *IDH*-mutant astrocytomas (9.3 years) and *IDH*-mutant glioblastomas (3.6 years) than for those with *IDH*-wild type glioblastoma (1.9 years) and *IDH*-wild type astrocytoma (1.2 years)[37] (Table 1).

The population incidence of grade II oligodendrogliomas and oligoastrocytomas peaks at age 35–44 years (Figure 2). Men have a ~25–60% higher incidence than women depending on age. In 2000–2014, 1-year and 5-year relative survival for oligodendroglioma was 90% and 70%, respectively. The incidence of anaplastic oligoastrocytic tumours peaks between the ages of 55 years and 64 years; in this age group, men show a 20% higher incidence than women (range 20–40% across all age groups). The median age at diagnosis is 44 years for those with *IDH*-mutant and 1p19q co-deletion oligodendrogliomas and median overall survival is 17.5 years (Table 1)[37].

Similar age and sex patterns for astrocytomas (including glioblastoma) are also seen in Europe[87,88]. These age patterns may be related to the time needed to acquire the multiple genetic alterations required for malignant transformation. As the world population continues to grow and age, the incidence of diffuse glioma is expected to increase. As yet, no comprehensive explanations account for the peaks in glioma incidence observed in particular age groups nor for the increased incidence of glioma in men. The lack of definitive associations between hormone exposure and glioma risk in multiple large studies,[86,89–92] as well as the fact that most cancers show increased incidence in men, suggests the existence of unidentified risk factors.

Ethnicity—In the USA, the incidence of adult diffuse glioma is highest in non-Hispanic white individuals (versus Hispanic white, black, American Indian or Alaska Native, and Asian or Pacific Islander people). Non-Hispanic white people have over a twofold higher rate of glioblastoma than do black, Asian or Pacific Islander and American Indian or Alaska Native individuals, and a 30% higher rate than Hispanic white individuals[81]. This pattern is also consistently seen in other diffuse glioma subtypes, for which incidence rates are similarly highest in non-Hispanic white individuals. Data from the USA also suggest that the lifetime risk of developing a malignant brain tumour is 25% higher in non-Hispanic white

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than in Hispanic white individuals, and is twice as high as the risk in black individuals[81]. In glioblastoma, 5-year relative survival is lowest (5%) in non-Hispanic white individuals and highest (9%) in Asian or Pacific Islander individuals. For non-glioblastoma astrocytoma, the 5-year relative survival is lowest in non-Hispanic white people (43.2%) and higher in all other ethnic groups (44.1% to 50.8%), whereas for oligodendroglioma 5-year relative survival is lowest in black individuals (63.8%)[81].

Additional survival factors

Additional factors associated with survival are the extent of tumour resection, Karnofsky performance score and treatment. Multiple studies have indicated that complete resection is beneficial[93–95], even in low-grade tumours (for which early resection is preferable to watchful waiting or biopsy alone[96]). Although difficult to prove, the influence of extent of tumour resection on survival could be confounded by tumour location, whether it is resectable or non-resectable and/or by clinical judgement[97]. After 2005, when clinical trial results showing an increase in median overall survival from 12.1 months to 14.6 months were published, the standard of care for patients with newly diagnosed glioblastoma has been treatment with the DNA-alkylating agent temozolomide, radiotherapy and surgery (termed the Stupp protocol)[98]. Among patients with glioblastoma treated according to this protocol, median survival in contemporary clinical trials is 14–17 months[57,72,99–104]. In one trial, for which preliminary data were published in 2015[97] and the complete report in 2017[98], the addition of tumour-treating fields (an antimitotic treatment modality) to maintenance temozolomide resulted in median overall survival of 21 months, versus 16 months in the temozolomide-alone group, and 5-year overall survival of 13%. Although survival in glioblastoma remains poor, the conditional probability of surviving more than one year past 2 years has repeatedly been shown to be much more favourable than surviving more than one year past initial diagnosis[100,105,106].

Inherited genetic risk factors

Single-gene hereditary cancer syndromes such as Li–Fraumeni syndrome, neurofibromatosis, Lynch syndrome, melanoma–neural system tumour syndrome, Ollier disease, and tuberous sclerosis cause a small percentage of diffuse gliomas in adults[40,107]. Gliomagenesis in these familial cancer syndromes might differ from that in gliomas presumed to be spontaneous[108]. Gliomas arising in patients with neurofibromatosis type 1 lack mutations in *IDH1, IDH2* and the H3 K27M mutation. In addition, high-grade tumours in patients with neurofibromatosis type 1 often harbour loss of *ATRX* whereas low-grade tumours in these patients often show copy number gain of *TERT*. The methylation signature of these tumours falls into the LGm6 cluster and this subgroup can probably be subdivided further on the basis of *ATRX* status[109]. Gliomas in patients with germline *TP53* mutations and Li–Fraumeni syndrome show enrichment of the *IDH1* R132C mutation, which accounts for <5% of all *IDH* mutations, and suggests a pathologic relationship with the *TP53* mutation[110–112].

In the large majority of patients with glioma who do not have these familial cancer syndromes, 5–10% have a family history of glioma[113–115]. In fact, first-degree relatives of patients with glioma have a twofold increased risk of developing a primary brain tumour

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compared to first-degree relatives of people who do not have glioma[114–116]. Possible reasons for the observed familial clustering of glioma are shared genetic and/or environmental factors. Given the paucity of identified environmental risk factors (described below) and the likelihood that glioma familial aggregation is a polygenic effect[117,118], linkage analysis, whole-exome sequencing, and genome-wide association studies (GWAS) are ongoing to improve our understanding of how germline variants contribute to the risk of glioma. A potential risk locus for familial glioma was detected on chromosome 15 in an early, small linkage analysis study of a high-risk family[16]. A larger Gliogene Consortium study later identified a single locus on chromosome 17 and three other loci on chromosomes 6, 12, and 18[17,18]. Whole-exome sequencing of *POT1*, which modulates telomerase activity, identified germline DNA mutations linked to oligodendroglioma in multiply affected families[119].

A large GWAS including over 12,000 patients with glioma and 18,000 controls[19] identified or validated a total of 25 single nucleotide polymorphisms (SNPs) that were strongly associated with glioma risk in adults[17,19,120–122]. Of these 25 SNPs, 11 were associated with glioblastoma risk, 19 were associated with the risk of non-glioblastoma glioma, and five of these SNPs were associated with risk of both glioblastoma and non-glioblastoma gliomas. The strongest relative risk is for variants at 8q24.21, which confer more than a sixfold relative risk of developing astrocytoma, *IDH*-mutant or oligodendroglioma[40,123,124].

These 25 risk loci were subsequently included in a model to assess the relative risk and lifetime risk of developing glioma[125]. In another study, these 25 risk loci were studied in over 1,600 tumours for associations with the *IDH* mutation, *TERT* promoter mutation, and 1p19q co-deletion molecular subgroups[126]. The association of 8q24.21 variants with oligodendrogliomas was validated[126]. These same researchers also examined univariate and multivariate associations between these risk loci and the WHO 2016 glioma subtypes. The majority of the SNPs are in or near genes known to be involved in specific pathways, summarized in Fig. 3. For example, a SNP at 17p13.1 lies in the 3′ untranslated region of *TP53* (this SNP alters the polyadenylation signal of *TP53*, thereby impairing processing of *TP53* mRNA) and is associated with the risk of several types of cancer.

Telomere maintenance-related genes are important in glioma prognosis and classification. SNPs near *TERT* and *RTEL1* (encoding regulator of telomere elongation helicase 1), both of which genes encode proteins involved in telomere maintenance, were associated with gliomas that had *TERT* promoter mutations, reinforcing the relationship between SNP genotype and biology[126]. SNPs near *TERT*, *STN1* and *RTEL1* are associated with one to four of the five WHO 2016 groups of diffuse glioma (Fig. 3). Only glioblastoma, *IDH*-mutant is not associated with these SNPs, probably owing to small sample size (n=68) and, thus, lack of power[126]. One of these SNPs, in *TERT*, results in alternate splicing, which results in lack of telomerase activity[127].

Given the results of these GWAS as well as a Mendelian randomization study showing that genetically increased telomere length is associated with a fivefold increase in the risk of glioma[128], interference with telomere maintenance is clearly a hallmark of gliomagenesis. However, with the exceptions of the *TP53* SNP and the telomere-associated SNPs mentioned above, the reader should note that neither the actual functional effects of the glioma risk-

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associated SNPs nor the developmental window within which these SNPs act to increase glioma risk is known.

Non-genetic risk factors

Very few non-genetic risk factors for development of adult diffuse gliomas have been established despite decades of research[129]. Only ionizing radiation exposures are considered causal non-genetic risk factors for glioma, but they account for an overall small number of cases. Thus, the specific etiology of most diffuse gliomas remains unknown. Now that more is known about genetic risk factors, it eventually may be possible to understand the interplay between environmental exposures, developmental factors and genetic susceptibilities that may contribute to tumor formation[130]. Box 1 summarizes the evidence for and against several non-genetic risk factors, as discussed in more detail below.

Radiation—Exposure to ionizing radiation, particularly in childhood, remains the strongest environmental risk factor for developing diffuse glioma. Ionizing radiation is a known carcinogen that damages DNA which may lead to oncogenesis. This may occur as early as 7 – 9 years after radiation exposure[130] and is dose dependent. This is true for both lower dosage ionizing radiation exposures, such as in atomic bomb survivors[131], but also for higher therapeutic radiation used to treat childhood infections and cancers. For example, therapeutic radiation has been shown to increase glioma risk ranging from a 3- to 7-fold increase[129,132–134].

The roles of various types of non-ionizing radiation exposures for glioma risk including extremely low frequency exposures, microwaves and radiofrequencies used in cell phones have been widely studied, but results are not conclusive because of difficulties in establishing lifetime exposures to such radiation and lack of convincing biologic plausibility for the carcinogenic effects of these exposures[129,135–138].

Immune, allergic and atopic conditions—Numerous studies have suggested that history of allergies or other atopic conditions – defined as hay fever, eczema, and asthma – are associated with decreased glioma risk[139,140].

The largest study on this topic, from the Glioma International Case-Control (GICC) study confirmed a significant reduced risk of glioma with history of allergy[139]. Moreover, a recent Mendelian randomization study of 12,488 glioma cases and 18,169 controls reported SNPs associated with atopic dermatitis to be associated with a reduced risk of glioma[141]. However, the same study did not find correlations between glioma risk and SNPs which have been shown to be associated with other atopic conditions such as asthma, hay fever, and IgE levels[141]. These conflicting results highlight the complexity of elucidating the relationship between atopy and allergy with glioma risk.

One hypothesis put forth to explain this inverse association is that the atopic state translates into a heightened immunosurveillance, allowing the early detection and suppression of tumor growth[140,142,143]. Another hypothesis, supported by the inverse relationship seen between elevated immunoglobulin E (IgE) and glioma risk, is the ability of the overactive immune system to eradicate potential environmental toxins, particularly respiratory allergens

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that may lead to tumor formation[144]. However, since certain medications that brain tumor patients receive such as steroids and temozolomide affect IgE levels, the potential effects of these exposures on the relationships of IgE and glioma risk warrant further investigation[141,145].

In 1977, it was first noted that glioma patients have altered peripheral blood immune cell profiles[146]. Deficiencies in CD4 T cells, and other lymphocytes[147–149], as well as accumulation of myeloid cells[150–154] are observed in patients with glioma and is especially dramatic in patients with glioblastoma. Although glioma therapies including steroid, radiation and alkylating agents may adversely impact peripheral blood counts, glioma related immune cell defects can precede and be independent of therapies[155]. The prognostic importance of these changes is under study and is of obvious importance in the development of immunotherapies. Moreover, the etiologic significance of systemic immune profiles with respect to glioma risk is essentially unknown. New approaches for characterizing peripheral immune profiles based on archival DNA[156,157] may be useful to promote large scale epidemiologic exploration that address the etiologic role of systemic immune alterations in gliomagenesis.

Other non-genetic risk factors:

As shown in Box 1, a number of other non-genetic risk factors have not been linked to or not consistently linked to adult glioma risk including, pesticides or chlorinated solvent exposures[158–160], obesity/high BMI, cigarette smoking[161–165], alcohol consumption[164] traumatic brain injury[166,167168169].

Conclusions

Discoveries over the past 15 years have provided tremendous insight into the molecular pathways and inherited genetic risks associated with gliomagenesis, which have provided a solid foundation for future research. The integration of molecular data into the WHO 2016 classification system for diffuse glioma is critical for both improving prediction of prognosis and tailoring treatment. However, more work is needed to understand the interactions between genetic and non-genetic risk factors in gliomagenesis and to identify risk variants within specific molecular subtypes of adult diffuse glioma (as shown in Fig. 4). Furthermore, the role of patients' immune status at various stages of the disease process also remains to be elucidated. To address these critical efforts, future studies will need increased international collaboration and large databases of well-annotated biospecimens that include clinical outcome and imaging data as well as detailed exposure histories.

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Key points

- Glioma incidence differs by age, sex, ethnicity, and geography. Survival varies by tumour subtype, age, and sex.
- In the past decade, multiple discoveries have expanded our understanding of glioma biology and led to a new classification system (WHO 2016) that incorporates molecular alterations with histology for an integrated diagnosis.
- The WHO 2016 classification system defines five glioma subtypes that are more homogenous in their clinical outcomes.
- Twenty-five risk loci for glioma have been identified as well as several rare inherited mutations that may cause glioma in some families. However, only ionizing radiation is a confirmed environmental risk factor.

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Box 1.

Non-genetic risk factors for glioma

Association with increased risk

Ionizing radiation from atomic bombs

Therapeutic radiation exposure to the brain during childhood

- Radiation in childhood for treatment of tinea capitis
- Radiation for childhood leukaemia

CT scans in childhood to doses >50 mGy

Consistently reported association with decreased risk

Allergy and atopic conditions – asthma, hay fever, eczema

Possible but unconfirmed association with increased risk

Non-ionizing radiation such as radiofrequency electromagnetic fields

No clear association

Pesticide exposure

Obesity

Head injury

Cigarette use

Alcohol consumption

Non-genetic risk factors for adult glioma have been thoroughly reviewed in Ostrom et al. (2014)[72]

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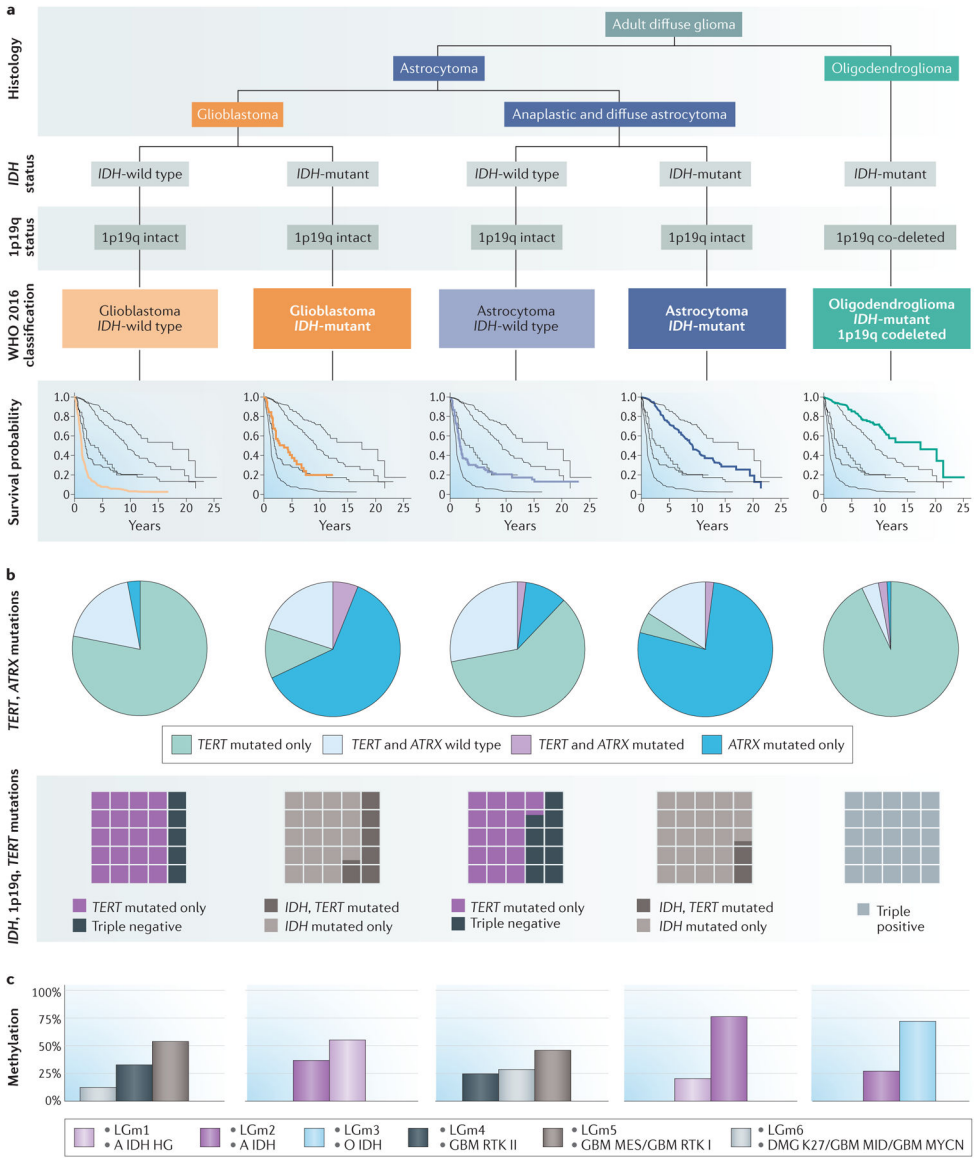


Figure 1. Overview of key molecular subtypes in the WHO 2016 classification of newly diagnosed adult diffuse glioma.

a | Histological assessment integrated with molecular diagnosis based on *IDH* mutation and 1p19q co-deletion status defines the five subtypes of adult diffuse glioma included in the WHO 2016 classification[12,26]. Kaplan–Meier survival curves for each type are based on data from 1989–2012[37]. b | For each WHO 2016 disease subtype, telomerase-related mutation frequencies are depicted in pie charts showing the proportion of tumours with mutations in *TERT* and/or *ATRX* (green, *TERT* mutations only; blue, *ATRX* mutations only; purple, mutations in both *TERT* and *ATRX*; light blue, wild type *TERT* and wild type *ATRX*)[37]. Waffle plots show the relative proportions of *IDH*-mutant, *TERT*-mutant and 1p19q co-deleted tumours in each WHO 2016 disease subtype[27]. c | Graphs showing methylation classifications for each WHO 2016 subtype. The methylation categories depicted[49] overlap to a great extent with those identified in a subsequent study[46] (pink, LGm1 and A IDH HG; purple, LGm2 and A IDH; light blue, LGm3 and O IDH; black, LGm4 and GBM RTK II;

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gray, LGm5 and GBM MES/GBM RTK I; brown-grey, LGm6 and DMG K27/GBM MID/GBM MYCN). WHO 2016 classification from REFS.[12,26]. Survival data and telomerase mutation data from REF.[37] with additional mutation data from REF.[27]. Methylation profile data from REFS.[46,49].

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Figure 2. Annual average age-adjusted incidence and relative survival data for non-glioblastoma and glioblastoma CNS tumours.

The Central Brain Tumor Registry of the United States (CBTRUS) and other global reporting registries have not yet published glioma statistics based on the WHO 2016 classification system. Accordingly, this Figure presents the latest available published CBTRUS statistics from 2011–2015 as well as data accessed directly from CBTRUS, both based on the WHO 2007 classification system. Data from REF.[21] Note that different axes are used for incidences of glioblastoma versus the other types of glioma.

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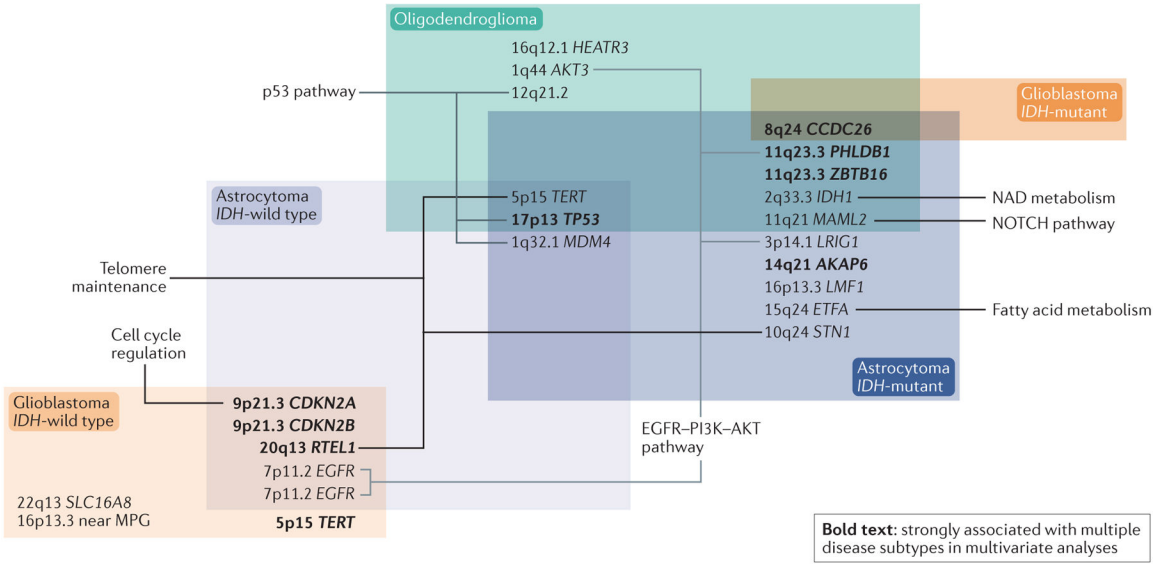


Figure 3. Heritable germline risk factors for the WHO 2016 subtypes of adult glioma.

Summary of the relationship between heritable germline risk factors and WHO 2016 classification. Overlapping boxes contain alterations shared by different diffuse glioma tumour subtypes. Involved genes are known to be relevant to the indicated biological pathways, but with a few exceptions the functional consequences of individual single-nucleotide polymorphisms (SNPs) are unknown. SNPs and gene names in bold were strongly associated with more than one WHO 2016 glioma subgroup in multivariant analyses. Data from REFS.[19,126].

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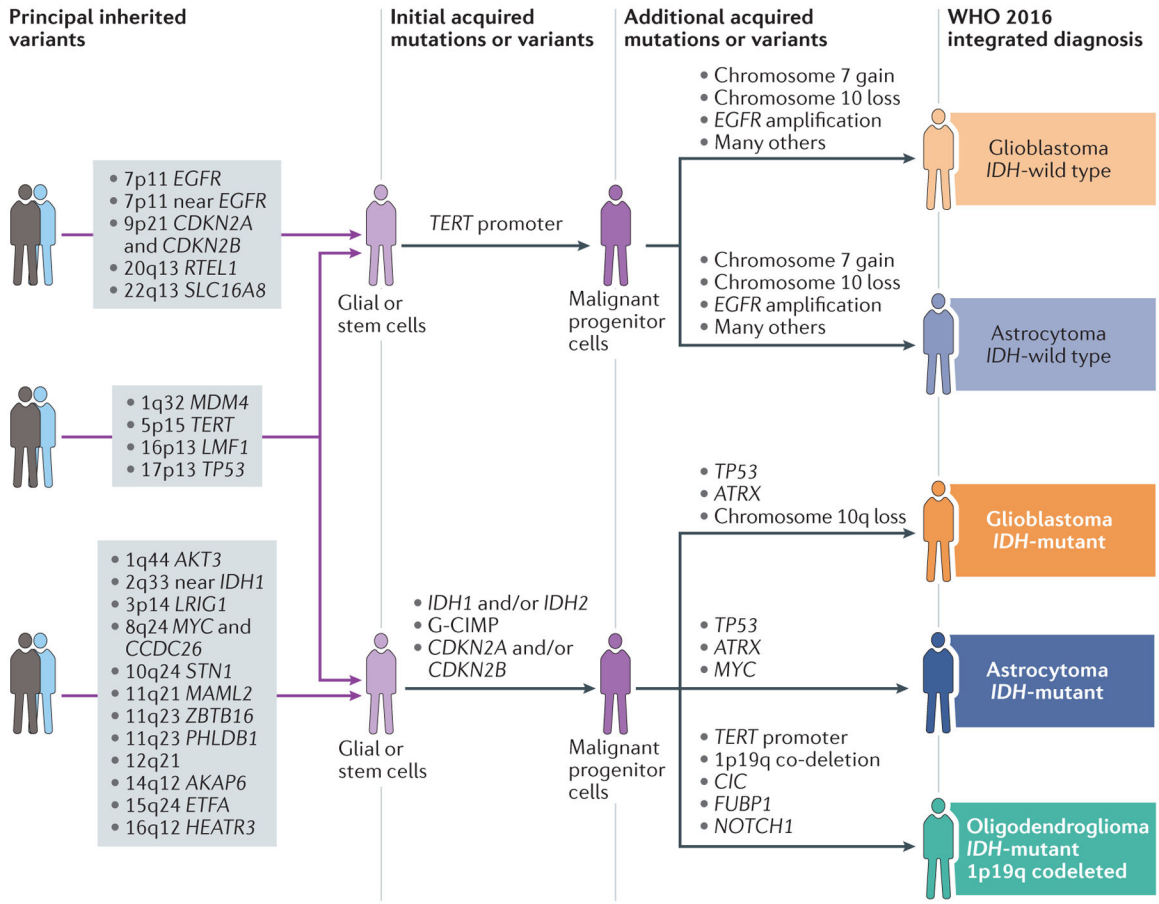


Figure 4. Hypothesized pathways of glioma development.

Our current understanding of gliomagenesis involves an interplay of inherited risk variants and acquired alterations. Additional SNPs associated with glioma not included in the figure are: 1p31 (RAVER2); 10q25 (VTI1A); 11q14 (11p14); 16p13 (near MPG); and 16p13 (LMF1). Data from REFS.[17,19,120,122,126].

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Table 1 –

Additional frequent tumor alterations in and information about the five WHO 2016 subtypes of adult diffuse glioma.

WHO 2016 classification	Frequent molecular aberrations[a]	*MGMT* promoter methylation (%)[b]	Median age at diagnosis (years)[c]	Median overall survival (years)[c]	Proportion of 2019 diagnoses (%)[d]
Glioblastoma, *IDH*-wild type	• *EGFR* amplification • *CDKN2A* or *CDKN2B* deletion • *PTEN* mutation • *PDGFRA1* mutation • *TP53* mutation • *NF1* mutation • Chromosome 7 gain • Chromosome 10 loss • *MDM2* amplification	~40	59	1.2	71
Glioblastoma, *IDH*-mutant	• *TP53* mutation • Chromosome 10q loss • *CDKN2A* or *CDKN2B* deletion	~90	38	3.6	7
Astrocytoma, *IDH*-wild type	• *PTEN* loss • *EGFR* amplification • *NF1* mutation • *TP53* mutation • *PIK3CA* **mutation**	55	52	1.9	5
Astrocytoma, *IDH*-mutant	• *TP53* mutation • *CDKN2A* or *CDKN2B* deletion • *MYC* **amplification** • *RTK* or *RIS* **mutation**	~85	36	9.3	12
Oligodendroglioma, *IDH*-mutant and 1p19q co-deletion	• *CIC* mutation • *FUBP1* mutation • *NOTCH1* **mutation** • *PI3K* **mutation** • *CDKN2A* or *CDKN2B* deletion	~65–100	44	17.5	5

[a] Data from REFs.[6,8,20,45,46].

[b] Data from REFs.[45,60–62].

[c] Data fromREF.[37] and in agreement with REFs.[8,11,38,39].

[d] Data from CBTRUS (2011–2015)[21] and REFs[27,40].