Molecular pathology of paediatric central nervous system tumours

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Abstract

Advances in our understanding of the biology of paediatric central nervous system (CNS) tumours have encouraged pathologists to use molecular markers alongside histopathological analysis for disease classification or prognostication and treatment stratification. In this article, we review molecular genetic alterations in paediatric CNS tumours, including those in low-grade and high-grade gliomas, ependymomas, and embryonal tumours. Some of these molecular changes with clinicopathological utility have been used for the first time in the most recent edition of the World Health Organization (WHO) classification of CNS tumours to define entities like ependymoma, RELA fusion–positive or diffuse midline glioma, H3 K27M–mutant. The classification of paediatric CNS tumours is entering a new era when histopathologists must work with molecular genetic data and their molecular pathology colleagues to provide an optimal diagnostic evaluation for their patients and clinical colleagues.

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Introduction

Central nervous system (CNS) tumours are the leading cause of cancer-related death in children [1]. The overall average annual age-adjusted incidence rate is about 5.5 per 100 000. While meningiomas and glioblastomas are more common in adults, the most common paediatric brain tumours are low-grade gliomas, such as pilocytic astrocytoma (15%), and embryonal tumours (12%), most of which are medulloblastomas. Embryonal tumours are the most common CNS tumour type in children aged 0–4 years. Supratentorial tumours account for about 25% of paediatric CNS tumours, followed by tumours arising in the cerebellum (20%), brainstem (12%), suprasellar region (8%), cranial nerves (7%), ventricles (6.4%), and spinal cord (4.3%).

Until recently, the diagnosis of paediatric CNS tumours was based on histopathological features, and their classification generally followed that of adult tumours with similar appearances. However, advances in our understanding of tumour biology have provided opportunities to use molecular markers alongside histopathological analysis for disease classification, prognostication, and predicting therapy response. The pace of discovery has increased to such an extent, with the advent of high-throughput sequencing strategies, that molecular studies are becoming an essential part of the diagnostic workup. Furthermore, genomic discoveries have redefined relationships between tumours with similar and dissimilar histopathological features, and the distinction between adult and paediatric disease in related tumour types. Many molecular changes, from dominant-negative histone mutations and the hijacking of distal enhancer elements to new oncogenic gene fusion products and mutations, have been identified. Epigenetic dysregulation has also been revealed as a common theme across several tumour subtypes.

The new 2016 World Health Organization (WHO) classification of tumours of the central nervous system will have a fundamental impact on clinical practice [2]; for the first time, molecular alterations are used in the classification of several entities. Major restructuring has occurred for adult diffuse gliomas, medulloblastomas, and other embryonal tumours in light of recent molecular discoveries. New entities defined by both histology and molecular signatures have emerged, including IDH-wild type and IDH-mutant glioblastomas, H3 K27M-mutant diffuse midline glioma, RELA fusion–positive ependymoma, WNT-activated and SHH-activated medulloblastomas, and C19MC-altered embryonal tumour with multilayered rosettes. These more homogeneous and narrowly defined entities are expected to facilitate patient stratification and precision therapy and to improve the design of clinical trials and experimental models.

Paediatric gliomas and glioneuronal tumours

About 55% of paediatric CNS tumours are gliomas [1]. Paediatric gliomas are heterogeneous, encompassing...
low-grade tumours such as the cerebellar pilocytic astrocytoma, which is generally curable, WHO grade II diffuse gliomas, which resemble those that present in adults but are genetically and biologically distinct, and aggressive high-grade tumours such as the incurable diffuse pontine glioma, which would now be classified as diffuse midline glioma, H3 K27M-mutant [2].

**Paediatric low-grade gliomas (LGGs)**

Paediatric LGGs are dominated by the pilocytic astrocytoma (PA; WHO grade I) and WHO grade II tumours, the diffuse astrocytoma (DA) or oligodendroglioma [2]. Two autosomal-dominant hereditary tumour syndromes, tuberous sclerosis complex (TSC) and neurofibromatosis type 1 (NF-1), are associated with the subependymal giant cell astrocytoma (SEGA) and optic pathway PA, respectively [3]. Unlike diffuse LGGs in adult patients, paediatric LGGs rarely harbour IDH1 or IDH2 mutations or undergo malignant transformation to higher-grade neoplasms [4].

Alterations of genes involved in the mitogen-activated protein kinase (MAPK) pathway are frequently found in paediatric LGGs, especially PAs [5,6], and BRAF alterations, particularly the KIAA1549–BRAF fusion–duplication and the V600E mutation, are most common (Table 1) [7–10]. Other alterations that activate the MAPK pathway, such as mutations in NF1, RAF, RAS, and FGFR1, have also been identified in paediatric LGGs [5,11]. These molecular alterations are mutually exclusive, except in rare instances, as most paediatric LGGs and low-grade glioneuronal tumours harbour only one somatic genetic alteration that affects protein coding [5,12]. Patients with germline BRAF mutations and a glioma have not yet been reported.

**Pilocytic astrocytoma (PA)**

Approximately 85% of the cerebellar pilocytic astrocytomas are PAs, arising most commonly in the cerebellum, but also in the diencephalon, optic pathways (optic nerve, chiasm, tracts, and radiation), and brainstem [1,13]. PAs presenting in the context of NF-1 arise most often in the optic pathways (66%) [14].

About 60–70% of sporadic PAs, especially those in the midline and cerebellum [15], but not in the cerebral hemispheres, harbour genomic rearrangement of BRAF. The most common fusion partner is KIAA1549–BRAF fusion–duplication and the V600E mutation, are most common [7,10,16]. The KIAA1549–BRAF fusion occurs in conjunction with a tandem duplication of the BRAF locus at 7q34, resulting in fusion products lacking the auto-inhibitory domain of BRAF. Other fusion partners such as MKRN1, CLCN6, GNA11, FXR1, MACF1, FAM131B, and RNF130 have also been described [5,6,17]. The BRAF V600E mutation also occurs in about 9% of PAs, most commonly in diencephalic examples [18].

Other than BRAF alterations, alterations in FGFR1, KRAS, PTEN, NTRK3, and NTRK2 have also been reported in sporadic PAs, but at much lower frequencies (<5%), and they are usually in non-cerebellar PAs [5,6]. The second most common mutations in PAs are point mutations in FGFR1’s kinase domain, which activate the MAPK pathway. FGFR1-mutated PAs characteristically occur outside the cerebellum and in midline structures including the brainstem and third ventricle [19]. Internal tandem duplication of the tyrosine kinase domain of FGFR1 (FGFR1-ITD, FGFR1 TKD duplicated) is found rarely in PAs [5,6]. NF1 mutations are also rare in sporadic PAs [20]. The genetic alterations present in sporadic and NF1-associated PAs converge on the RAS/RAF/MEK/MAPK, PI3K/AKT, and mTOR signalling pathways to promote cell cycle progression and growth [21].

**Pilomyxoid astrocytoma (PMA)**

PMA, a variant of PA, is recognized by its distinctive monophasic growth pattern and angiocentric arrangement in a myxoid matrix [22]. PMAs occur predominantly in infants and young children and involve the hypothalamic/chiasmatic region. The unfavourable location of the majority of PMAs often precludes complete surgical excision and these tumours have a relatively poor outcome compared with PAs [23].

The distinction between PMA and PA is not always clear-cut. The two tumours exist on a histopathological
spectrum, and PMAs often mature into PAs over time [24–28]. Many PMAs harbour a KIAA1549-BRAF fusion, further supporting their close relationship to PAs [24].

Paediatric low-grade diffuse gliomas
Diffuse gliomas constitute less than 10% of paediatric LGGs [1]. Their infiltrative nature generally prevents a total surgical resection. Morphologically, they have an astrocytic, oligodendrogial, or mixed oligoastrocytic cytology and may be difficult to distinguish from PAs, especially in small biopsies. Most are diffuse astrocytomas (DAs), which occur primarily in the cerebral hemispheres and thalamus.

The majority of paediatric DAs have alterations in MYB, MYBL1, FGFR1, or BRAF [5,12,29]. MYB and MYBL1 alterations, which include episomal amplification and fusion with partner genes, such as PCDHGA1 and QKI, occur in approximately 25% of paediatric DAs [5,30]. The fusions result in loss of MYB’s C-terminal negative regulatory domains. Partial duplication of MYBL1 generates a truncated protein, also without its regulatory domain [29]. Alterations in FGFR1, which are rare in paediatric DAs, include intragenic duplication of the tyrosine kinase domain (TKD) and fusion with TACC1 [5]. The intragenic TKD duplication induces FGFR1 autophosphorylation and activation of both MAPK and PI3K pathways. Approximately 25% of paediatric DAs harbour a BRAF V600E mutation [12,18]. Rare examples of paediatric low-grade DA have been shown to harbour an H3.3 K27M mutation, and this is not necessarily associated with a poor outcome [5], although H3 K27M-mutant diffuse midline glioma is generally regarded as high-grade disease [2].

Paediatric low-grade diffuse oligodendrogliomas lie on a morphological spectrum with dysembryoblastic neuroepithelial tumour (DNET) and share genetic alterations with this glioneuronal tumour, particularly FGFR1 mutations and TKD duplications [12]. As for DAs, diffuse oligodendrogliomas with IDH mutation and 1p/19q co-deletion (synchronous deletion of both chromosomes 1p and chromosome 19q) are rare in the paediatric population, but can occur in older children and adolescents [5,12].

An important genetic distinction is emerging among diffuse low-grade gliomas at the older end of the paediatric age range, specifically between ‘paediatric-type’ disease without IDH mutation and ‘adult-type disease’ with IDH mutation. This distinction is associated with an important clinical difference. ‘Paediatric-type’ disease generally has an indolent clinical course; these diffuse WHO grade II tumours rarely progress to grade III or grade IV tumours. In contrast, ‘adult-type’ disease progresses in approximately 75% of cases [31].

Desmoplastic infantile astrocytoma (DIA) and ganglioglioma (DGG)
DIAs and DGGs (WHO grade I) represent about 0.5% of paediatric CNS tumours [1]. They are histopathologically similar, a neoplastic neuronal element being the only distinction. Virtually all of these tumours occur in patients under the age of 2 years [32]. They are generally large cystic tumours arising in the parietal or frontal lobe. The molecular profiles of DGGs and DIAs are essentially the same. Gain of 7q31 involving MET is found in more than 40% of DIAs/DGGs. Focal recurrent copy number losses are found at 5q13.3, 21q22.11 and 10q21.3. Large chromosomal alterations are rare. About 10% of DIAs/DGGs harbour a BRAF V600E mutation [33].

Diffuse leptomeningeal glioneuronal tumour (DLGNT)
DLGNT is a new entity in the 2016 CNS WHO classification [2]. It commonly presents as diffuse leptomeningeal disease around the spinal cord in children or adolescents [34]. A parenchymal component is seen in about 80% of cases. The tumours contain oligodendrocyte-like cells with low levels of mitotic activity. About 25% of the tumours will show anaplastic progression. A ganglion cell component is found in approximately 15% of DLGNTs. KIAA1549-BRAF fusions and chromosome 1p deletion are seen in most tumours, with combined 1q deletion in about 20% [34,35]. Although this entity bears similarity to oligodendroglioma or some glioneuronal tumours, IDH and BRAF V600E mutations have never been demonstrated.

Pleomorphic xanthoastrocytoma (PXA)
PXA is a relatively rare (0.5–1%) tumour, typically affecting children and young adults [36]. Most PXAs are supratentorial (96%) with a predilection for the temporal lobe (46%). PXAs commonly arise in the superficial cerebral cortex and often extend into the leptomeninges [37]. Seizures are the presenting symptoms in 70% of patients.

A BRAF V600E mutation occurs in about 65% of PXAs [18,33,38], especially those arising from the temporal lobe (90%). BRAF fusion–duplication is not detected in PXAs. Homozygous deletion of 9p21.3, which contains CDKN2A/B, is seen in 60% of PXAs [39]. About 5% of PXAs harbour TP53 mutations [40].

PXAs may undergo malignant transformation, and anaplastic PXA has been added to the 2016 CNS WHO classification as a distinct (grade III) entity [2]. An anaplastic grading requires five or more mitoses per 10 high-power fields. Necrosis may be present, but the significance of necrosis in the absence of elevated mitotic activity is uncertain [41]. Anaplastic PXAs show a similar frequency of BRAF V600E mutation to grade II PXAs [18]. There is no correlation between TP53 mutation and the presence of anaplastic features [42].

Astroblastoma
Astroblastoma is a rare tumour that develops in children and young adults as a well-circumscribed, peripheral hemispheric mass [43,44]. The tumour is characterized by ‘astroblastomatous pseudorosettes’, prominent
perivascular hyalinization, and ‘pushing borders’ at the interface with adjacent brain. Astroblastoma is an entity in the 2016 WHO classification, without a designated grading [2]. About 70% of astroblastomas may harbour an \textit{MN1} alteration, including fusions with \textit{BEND2} or \textit{CXXC5} [45]. Gains of chromosomes 20q and 19 are observed in some tumours [43].

Subependymal giant cell astrocytoma (SEGA)

SEGA is the most common CNS neoplasm in patients with tuberous sclerosis complex (TSC) and mutation of \textit{TSC1} or \textit{TSC2} [46]. SEGAs are typically located in the lateral ventricle, near the foramen of Monro along the subependymal region of the caudothalamic groove. Isolated SEGAs without other TSC-related lesions are likely due to somatic mosaicism or mutation of the TSC genes [47,48].

Glioneuronal tumours

Glioneuronal tumours encompass heterogeneous tumours with a mixed glial and neuronal morphology. Ganglioglioma and dysembryoplastic neuroepithelial tumour (DNET) are relatively common among these tumours [1].

Ganglioglioma (GG)

The histological hallmark of GGs is a combination of neoplastic ganglion cells and a glial component with features that can resemble the morphology of PA [49]. Anaplastic GGs are considered as low-grade neoplasms and only rarely progress from tumours of lower grade [61,62]. The 2-year survival for paediatric HGGs ranges from 30% for tumours in the cerebral hemispheres down to less than 10% for diffuse pontine gliomas [63]. Similar to adult HGGs, paediatric HGGs commonly arise in the cerebral hemispheres [1]. However, high-grade pontine gliomas occur nearly always in children and account for nearly half of the paediatric HGGs. Midline HGGs arising from the thalamus (13%), cerebellum (5%), and spinal

Dysembryoplastic neuroepithelial tumour (DNET)

DNETs are low-grade (WHO grade I) tumours commonly associated with medically intractable seizures [55]. They are mostly supratentorial with a predilection for the temporal lobe. Several histological forms of DNET have been described [56–58]. Simple, complex, and diffuse DNETs and mixed DNET/GG show no difference in age of onset, associated seizure type, or outcome [57]. Most DNETs harbour an alteration in \textit{FGFR1}, either a TKD duplication or a single nucleotide variation (SNV) [12,59]. \textit{BRAF V600E} mutation is also seen in a minority of DNETs, more frequently in classic DNETs and in extratemporal locations [12,60]. Similar to GG and PA, 20% of DNETs show gains of chromosome 5 or 7 [51].

Paediatric high-grade diffuse gliomas (HGGs)

Paediatric HGGs primarily encompass glioblastoma (GB) and its variants, which are WHO grade IV tumours, anaplastic astrocytoma (WHO grade III), and diffuse midline gliomas, including diffuse pontine glioma. Together, they comprise 15–20% of paediatric CNS tumours [1]. These tumours are characterized by brisk mitotic activity in grade III tumours and, additionally, microvascular proliferation and necrosis in grade IV tumours, similar to their adult counterparts. Although histologically similar, paediatric and adult HGGs can be distinguished by their clinical behaviours, locations, and genetic alterations (Table 2).

Paediatric HGGs nearly always arise as primary malignant neoplasms and only rarely progress from tumours of lower grade [61,62]. The 2-year survival for paediatric HGGs ranges from 30% for tumours in the cerebral hemispheres down to less than 10% for diffuse pontine gliomas [63]. Similar to adult HGGs, paediatric HGGs commonly arise in the cerebral hemispheres [1]. However, high-grade pontine gliomas occur nearly always in children and account for nearly half of the paediatric HGGs. Midline HGGs arising from the thalamus (13%), cerebellum (5%), and spinal

Table 2. Genetic alterations in paediatric high-grade gliomas

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<th>Entities</th>
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<tr>
<td>Anaplastic astrocytoma</td>
<td>\textit{TP53}</td>
<td>\textit{PDGFR} amplification/ rearrangement/ indels</td>
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<tr>
<td>Glioblastoma</td>
<td>\textit{TP53}</td>
<td>\textit{CDK2A} deletion</td>
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<tr>
<td>\textit{H3F3A(H3.3) G34R/N}</td>
<td>\textit{NTRK1-3} fusion genes</td>
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<td>\textit{IDH1}</td>
<td>\textit{MET} or \textit{EGFR} amplification</td>
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<td>\textit{NF1}</td>
<td>\textit{CDK4} or \textit{CDK6} amplification</td>
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<td>\textit{FGFR1}</td>
<td>\textit{MYCN} amplification</td>
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<td>\textit{PDGFR} amplification</td>
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<td>\textit{IDH1}</td>
<td>\textit{FGFR1}</td>
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<tr>
<td>\textit{DMBT1}</td>
<td>\textit{CDK2A/B} deletion</td>
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Epithelioid glioblastoma

\textit{BRAF V600E}

Diffuse midline glioma

\textit{H3F3A(H3.3) K27M}

\textit{HIST1H3A/B/C (H3.1)}

\textit{ACVR1 G338}

\textit{H3F3A(H3.3)}

\textit{G34R/V}

\textit{H3F3A}\n
\textit{H3.1}

\textit{H3.3}

\textit{3 deletion}

\textit{CDK4 amplification}

\textit{Loss of \textit{CDK2A/B} and \textit{DMBT1}}

\textit{9p21.3} deletion

\textit{(CDK2A/B)}

\textit{BRAF V600E}

\textit{IDH1} G338

\textit{ACVR1}

\textit{3 deletion}

\textit{CDK4 amplification}

\textit{Loss of \textit{CDK2A/B} and \textit{DMBT1}}

Bold script = present in at least 50% of tumours.

GG, ganglioglioma; PXA, pleomorphic xanthoastrocytoma.
HIST1H3B mutations occur in encoding the H3.3 isoform, and 20–25% of mutations in human cancer. Histone H3 K27M mutations are found in 80% of diffuse pontine gliomas [66]. They are also found in other medulloblastomas arising in the thalamus, cerebellum or spinal cord. These were the first histone mutations to be identified in human cancer.

About 75% of histone H3 mutations occur in H3F3A, encoding the H3.3 isoform, and 20–25% of mutations occur in HIST1H3B or rarely HIST1H3A/C, encoding H3.1 [65,67,68]. H3.3 and H3.1 mutations occur in a mutually exclusive manner. Activating somatic mutations in ACVR1, a type I receptor in the bone morphogenetic protein (BMP) signalling pathway, are identified in 25–30% of diffuse pontine gliomas. ACVR1 mutations almost always occur concurrently with a HIST1H3B K27M mutation in diffuse pontine gliomas that present at less than 5 years of age [69]. Hotspot G328 mutations are most common. While H3.1 K27M mutations are also found in thalamic HGGs, ACVR1 mutations have only been identified in diffuse pontine gliomas [65,67–69]. Approximately 30% of paediatric GBs harbour H3F3A mutations [70].

Histone H3.3, a replication-independent histone variant, is recruited to DNA via the ATRX–DAXX heterodimer [70]. Approximately half of the paediatric GBs harbour TP53 mutations. Tumours with combined H3F3A, ATRX, and TP53 mutations frequently demonstrate alternative lengthening of telomeres (ALT). PPM1D, which is frequently overexpressed in medulloblastoma, has been found to be mutated recurrently in midline HGGs [71]. The mutations are gain-of-function changes that result in attenuated activity of p53 and of CHK2, a DNA damage response protein.

Histone H3 K27 mutations are likely to be acting in a dominant fashion, as the mutant protein accounts for 5–15% of the total histone pool. The K27M mutation inhibits the polycomb repressive complex 2 (PRC2) [62], which leads to a global loss of lysine 27 methylation (H3K27me3) on wild-type histone H3 and derepression of PRC2 targets [72–75].

H3F3A G34R/V mutations are most commonly found in parietal, occipital, and temporal lobe HGGs from adolescents and young adults [66,70]. Mutations in ATRX and/or DAXX are identified in all tumours harbouring H3.3 G34 mutations. H3F3A G34-mutant HGGs, like the vast majority of paediatric HGGs, arise as primary malignancies, without evidence of a precursor lower-grade lesion [61]. Little is known about the function of the G34R/V mutations. H3F3A G34-mutant tumours show pronounced hypomethylation in subtelomeric regions [62]. The mutations reduce histone H3 lysine 36 trimethylation levels around histones carrying the mutation, but without the global dominant-negative effect of the K27M mutation [72]. Elevated MYCN levels have been observed in some tumours [76]. About 6–25% of paediatric hemispheric HGGs harbour a mutation in SETD2, an H3K36 methyltransferase, and show widespread H3K36me3 loss [65,77].

Frontal lobe HGGs in adolescents and young adults can harbour the IDH1 R132H mutation [62], the molecular hallmark of ‘adult-type’ HGGs that progress from a grade II tumour. IDH1-mutant tumours account for less than 10% of paediatric HGGs [62]. H3F3A and IDH1 R132H mutations are mutually exclusive [70]. IDH-mutant tumours characteristically show global DNA hypermethylation known as glioma-CpG island methylator phenotype (G-CIMP), likely caused by the generation of R-2-hydroxyglutarate [78,79], whereas IDH-mutant tumours show global hypomethylation signatures [62].

BRAF V600E mutations, NF1 mutations, and NTRK fusion genes are more commonly found in non-brainstem HGGs. About 10% of paediatric HGGs arising from the cerebral hemispheres harbour a BRAF V600E mutation [80]. BRAF V600E mutation has not been reported in diffuse pontine gliomas. BRAF fusion–duplications commonly found in PAs are not seen in HGGs. Approximately 50% of epithelioid GBs, a newly recognized variant in the 2016 CNS WHO classification [2], harbour a BRAF V600E mutation [81,82]. Epithelioid GBs have a predilection for children and younger adults, typically presenting as sharply demarcated superficial cerebral or diencephalic masses. Such cases may have an associated low-grade precursor, often but not invariably showing features of PXA [83]. Sporadic NF1 mutations are seen in 5–25% of paediatric HGGs, more commonly in HGGs arising from the cerebral hemispheres [65,67–70]. Activating fusions of the NTRK family of neurotrophin receptors (NTRK1–3) are seen in about 5% of all paediatric HGGs, with a high frequency (about 50%) observed in children younger than 3 years of age [5,6,65].

FGFR1 activating mutations are found predominantly in thalamic HGGs [68]. Mutations in TP53, PDGFRα, PIK3CA, and PIK3R1 are found in HGGs from all locations. TP53 mutations are found in more than half of paediatric HGGs, including diffuse pontine gliomas and other midline HGGs [65,67–70]. PDGFRα alterations, including amplification, rearrangement, indels, and mutations, are the most common RTK alterations and are found in about 30% of paediatric HGGs [65,84–88]. Mutations in the downstream PI3-kinase catalytic (PIK3CA) or regulatory (PIK3R1) subunits occur in 10–25% of paediatric HGGs. CDKN2A homozygous deletion is observed in about 25% of non-brainstem HGGs [86]. In diffuse pontine gliomas, focal amplifications of CDK4 or CDK6 are observed [85,88].

Interestingly, gene expression analyses have demonstrated close similarity between paediatric and adult HGGs. Three major groups of paediatric HGGs correlate with the Pronuclear, Proliferative, and Mesenchymal groups identified in adult HGGs [84,86,87]. Another classification divides both adult and paediatric GBs into six molecular groups: IDH, K27, G34, RTK I (PDGFRα), Mesenchymal, and RTK II (classic) [62]. The IDH group is characterized by tumours with IDH1...
or IDH2 mutations, mostly from young adults. K27 and G34 are the only groups associated with H3F3A mutations and include the youngest patients. Tumours in the K27 subgroup have a midline location (midbrain, brainstem, spinal cord), whereas G34 tumours most commonly arise in the cerebral white matter. The RTK I group, which shows a patient age range similar to that of the IDH group (median age 36 years old), is associated with PDGFRα amplification. The RTK II, or classic group, is enriched with tumours harbouring alterations typically present in adult primary GBs. The RTK II (classic) group shows significant overlap with Verhaak’s Classic group, and the RTK I (PDGFRα), IDH, and K27 groups show significant overlap with Verhaak’s Proneural group [89]. An additional group with a GB morphology but a high frequency of BRAF V600E mutation and a distinct methylation signature, which resembles that of PXA, has a more favourable outcome than GBs and is termed PXA-like [90]. The IDH, PXA-like, and G34 groups are associated with a longer overall survival than expected for GBs, whereas the K27, RTK, and Mesenchymal groups are associated with the shortest survival [62,90]. The presence of amplified oncogenes, such as EGFR, PDGFR, and MYCN, is associated with a poor outcome across groups.

Ependymomas

Ependymomas are the second most common malignant brain tumour in childhood [91], usually arising in the posterior fossa of young children in the first decade of life. Several recent studies demonstrated distinct molecular groups of ependymoma [92–97], each characterized by distinct clinical, anatomic, and genetic features. Tumours from the three principal CNS anatomic sites (supratentorial region, posterior fossa, spinal cord) can be distinguished by their gene expression profiles [98]. Two distinct molecular subtypes of posterior fossa ependymomas have been identified [93]. The more common ‘group A’ posterior fossa ependymomas, 48% of ependymomas from all sites [99], show minimal genomic alterations, occur predominantly in infants, and demonstrate activation of cancer-related signalling pathways, including those associated with VEGF, PDGFR, integrin, and MAPK. Group A tumours have elevated methylation across CpG islands, which is associated with epigenetic silencing of differentiation genes [96]. Group B posterior fossa ependymomas are less frequent than group A tumours and occur in adolescents and young adults. They generally display chromosome-wide ploidy changes. The mutation rates in both group A and group B are low, and no recurrent mutations have so far been found in either group A or group B posterior fossa ependymomas [96].

Approximately 70% of supratentorial ependymomas harbour C11orf95–RELA fusions within chromosome 11q, as a result of chromothripsis, a catastrophic chromosome shattering with erroneous DNA repair that results in the shuffling of DNA segments across the affected chromosome(s) [97,100]. C11orf95–RELA fusion transcripts are never found in posterior fossa tumours, once more highlighting the distinction between ependymomas at different CNS locations. C11orf95–RELA fusions lead to activation of the NF-κB signalling pathway [97,101]. RELA fusion-positive ependymoma is a newly recognized entity in the 2016 CNS WHO classification [2]. MAML1–YAP1 or less commonly FAM118B–YAP1 fusions are seen in RELA fusion-negative supratentorial ependymomas [97,102]. YAP1 fusion-positive tumours are more common in young children and show no evidence of chromothripsis. Subependymomas in all three CNS locations show predominantly balanced genomes and are much more common in adults [102].

The existence of nine molecular groups based on DNA methylation profiling – supratentorial RELA, supratentorial YAP1, supratentorial subependymoma, posterior fossa group A, posterior fossa group B, posterior fossa subependymoma, spinal cord classic ependymoma, spinal cord myxopapillary ependymoma, and spinal cord subependymoma – has been demonstrated [102]. The outcome of ependymoma in children, especially in infants, is poor; almost half die as a result of their disease. Supratentorial RELA fusion-positive and posterior fossa group A ependymomas together make up two-thirds of all cases and are associated with poor overall survival when compared with the other groups. However, these findings have yet to be confirmed in cohorts of patients treated on clinical trials.

Embryonal tumours

Embryonal tumours (Table 3), including medulloblastoma, atypical teratoid/rhabdoid tumour (AT/RT), and CNS primitive neuroectodermal tumours (CNS-PNETs), are the most prevalent paediatric malignant CNS tumours, together comprising 15–20% of all CNS tumours in children younger than 14 years of age [1]. These tumours are very rare in adults.

Medulloblastoma

Medulloblastoma is the most common childhood malignant CNS tumour [1]. By using a combination of therapies including surgical resection, risk-adjusted irradiation, and adjuvant chemotherapy, about 70% of paediatric medulloblastomas can be cured, although debilitating long-term sequelae are seen in some patients [103]. Medulloblastoma is a clinically and molecularly heterogeneous disease [104–106]. Three histologically defined variants are recognized alongside the classic tumour: desmoplastic/nodular (D/N), medulloblastoma with extensive nodularity (MBEN), and large cell/anaplastic (LC/A) [2]. Four molecular groups have been identified through transcriptome profiling: WNT (10%), SHH (30%), group 3 (15%),
Table 3. Genetic alterations in embryonal tumours

<table>
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<td>MB, WNT-activated</td>
<td>Activation of WNT pathway</td>
<td><strong>CTNNB1</strong>&lt;br&gt;<strong>DDX3X</strong>&lt;br&gt;Chromatin remodelling genes</td>
<td>Monosomy 6</td>
</tr>
<tr>
<td>MB, SHH-activated and TP53-wildtype</td>
<td>Activation of SHH pathway</td>
<td><strong>PTCH1</strong>&lt;br&gt;<strong>SMO</strong>&lt;br&gt;<strong>SUFU</strong>&lt;br&gt;TERT promoter</td>
<td>9q loss&lt;br&gt;10q loss</td>
</tr>
<tr>
<td>MB, SHH-activated and TP53-mutant</td>
<td>Activation of SHH pathway</td>
<td>(TP53)</td>
<td><strong>MYCN</strong> amplification&lt;br&gt;<strong>GLI2</strong> amplification&lt;br&gt;17p loss&lt;br&gt;Tetraploidy</td>
</tr>
<tr>
<td>MB, group 3</td>
<td>Elevated expression of MYC</td>
<td><strong>SMARCA4</strong>&lt;br&gt;Chromatin remodelling genes</td>
<td>Isochromosome 17q&lt;br&gt;Enhancer hijacking (<strong>GFI1/GFI1B</strong>)</td>
</tr>
<tr>
<td>MB, group 4</td>
<td></td>
<td><strong>SMARC81</strong>&lt;br&gt;<strong>SMARCA4</strong></td>
<td>22q deletion&lt;br&gt;Monosomy 22&lt;br&gt;(Chromosome 19q13.42 amplification, fusion)</td>
</tr>
<tr>
<td>AT/RT</td>
<td>Loss of INI1 or BRG1</td>
<td><strong>SMARC81</strong>&lt;br&gt;<strong>SMARCA4</strong></td>
<td><strong>MYCN</strong> amplification&lt;br&gt;Enhancer hijacking (<strong>GFI1/GFI1B</strong>)</td>
</tr>
<tr>
<td>ETMR</td>
<td>Chromosome 19q13.42 microRNA cluster amplification</td>
<td>FOXR2 overexpression</td>
<td>FOXR2 fusion products&lt;br&gt;Chromosome 1q gain&lt;br&gt;Loss of 16q&lt;br&gt;Chromosome 8 gain&lt;br&gt;CIC fusion or deletion</td>
</tr>
<tr>
<td>CNS NB-FOXR2</td>
<td></td>
<td><strong>CIC</strong> alteration</td>
<td><strong>MN1</strong> rearrangement&lt;br&gt;Loss of 16q&lt;br&gt;Chromosome 8 gain&lt;br&gt;<strong>BCOR</strong> alterations</td>
</tr>
<tr>
<td>CNS HGNET-MN1</td>
<td>Up-regulation of ETS transcription factor family</td>
<td></td>
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<tr>
<td>CNS HGNET-BCOR</td>
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Bold script = present in at least 50% of tumours.

AT/RT, atypical teratoid/rhabdoid tumour; ETMR, embryonal tumour with multilayered rosettes; CNS EFT-CIC, CNS Ewing sarcoma family tumour with CIC alteration; CNS HGNET-BCOR, CNS high-grade neuroepithelial tumour with BCOR alteration; CNS HGNET-MN1, CNS high-grade neuroepithelial tumour with MN1 alteration; CNS NB-FOXR2, CNS neuroblastoma with FOXR2 activation; MB, medulloblastoma.

and group 4 (45%) [105–107]. The 2016 WHO classification recognizes five genetically defined types of medulloblastoma: WNT-activated, SHH-activated and TP53-mutant, SHH-activated and TP53-wild type, and non-WNT/non-SHH incorporating group 3 and group 4 tumours [2].

The WNT group, the least common and the most homogeneous group, is characterized by activation of the WNT signalling pathway [105]. CTNNB1 mutations are identified in approximately 90% of tumours [108]. Nuclear accumulation of β-catenin is routinely used as a biomarker for WNT pathway activation, often in conjunction with the detection of monosomy 6, which is found in 80–85% of WNT medulloblastomas [107,109]. Mutations in DDX3X, an RNA helicase, are detected in 50% of the WNT tumours [108,110,111]. Mutations in chromatin remodelling genes, including SMARCA4 (25%), MLL2 (12.5%), CREBBP (6%), TRAPP (3%), and MED13 (3%), are also found in about half of the tumours. TP53 mutations are present in 15% of WNT tumours and are not associated with the poor prognosis associated with TP53-mutant SHH tumours [111,112]. Indeed, WNT-activated medulloblastomas are associated with an excellent outcome; patients without high-risk clinical factors, such as metastatic disease, nearly all survive following treatments with standard therapies [104,107]. In an attempt to reduce the long-term adverse CNS effects of irradiation, WNT medulloblastoma has become the focus of trials in which it is regarded as low-risk disease and suitable for reduced adjuvant therapy.

The SHH molecular group is the most heterogeneous, and all histological variants occur in this group. D/N tumours and MBENs are all classified as SHH-activated and account for just over half of SHH tumours [107,113], and LC/A tumours occur in this group almost as frequently as they do in group 3 [107]. Clinically, SHH medulloblastomas present most frequently in infants and adults; throughout most of childhood, they are relatively uncommon. Across three age-related categories: ‘infant’ (0–4 years), ‘children’ (4–17 years), and ‘adult’ (>17 years), SHH medulloblastomas show striking clinicopathological and genetic diversity [114]. MBENs fall into the infant category, while classic and LC/A tumours are most frequent in childhood. Adult tumours mostly have a D/N morphology.

Genetic alterations are unequally spread across the categories [114]. SUFU mutations tend to occur in the
infant category, while SMO mutations occur mostly in adults (30% of the tumours). MYCN and GLI2 amplification are detected mainly in the childhood group. PTCH1 alterations are common across the age groups (42% infant, 36% childhood, and 54% adult SHH tumours). The high prevalence of PTCH1 and SMO mutations in adult SHH medulloblastomas predicts responsiveness to SMO inhibitors, whereas the presence of downstream MYCN amplification or GLI2 amplification/mutations predicts lack of response. TERT promoter mutations (C228T and C250T) occur in 38% of SHH medulloblastomas and are present in 80% of adult SHH tumours [115,116]. Mutations in chromatin remodelling genes, including MLL2 (12%), BCOR (3%), and LBD1 (3%), occur in 21% of the tumours [110]. Mutations in DDX3X are seen in 11% of SHH tumours [108,110,111]. SHH tumours frequently showed loss of the whole of chromosome arm 9q [111].

Gorlin syndrome (GS; naevoid basal cell carcinoma syndrome) caused by de novo (60% of cases) or inherited germline PTCH1 mutations is an autosomal-dominant disorder characterized by developmental defects and various forms of cancer including medulloblastoma [117]. About 5% of patients develop D/N medulloblastoma during infancy [118]. The outcome for patients with GS and D/N medulloblastoma is mostly favourable following conventional therapy [119]. However, the presence of PTEN or GNA5 alterations may be associated with a relatively poor prognosis [120].

Highlighting the heterogeneity of SHH medulloblastoma is the contrast between the outcomes of two tumour types in different categories. MBENs in the infant category are associated with an excellent outcome, whereas SHH-activated LC/A tumours with MYCN amplification or a TP53 mutation are very aggressive, nearly always presenting with metastatic disease [104,105,107,113,114].

SHH-activated, TP53-mutant medulloblastoma is a genetically defined entity in the 2016 WHO classification [2]. TP53 mutations occur in 13% of SHH tumours, and many of these are germline mutations (Li–Fraumeni syndrome) [112,114]. SHH medulloblastomas with germline TP53 mutations frequently harbour amplifications in MYCN (42%) and/or GLI2 (30%) [109]. Childhood SHH tumours with TP53 mutations have an appalling outcome, especially in the presence of MYCN or GLI2 amplification [105]. SHH tumours with TP53 mutations commonly have tetraploidy [111]. Most SHH medulloblastomas with a TP53 mutation have an LC/A morphology and are high-risk tumours [2].

Non-WNT/non-SHH group 3 and group 4 medulloblastomas can be separated on gene expression or DNA methylation profiling, but overlap to some extent [109]. Both groups show a male preponderance. Isochromosome 17q occurs in both groups, though it is more common in group 4 tumours (80%) than in group 3 (26%) [109]. Both groups demonstrate recurrent structural alterations, including deletions, duplications, inversions, and complex rearrangements. Structural alterations that aberrantly induce the proto-oncogenes GFI1 or GFI1B through highly active enhancer elements (enhancer hijacking) [121] occur in 41% of group 3 and 10% of group 4 tumours [122]. GFI1 and GFI1B are activated in a mutually exclusive manner. Mutations in the chromatin remodelling KDM gene family (KDM1A, KDM3A, KDM4C, KDM5A, KDM5B, KDM6A, and KDM7A) and gain of EZH2 occur only in group 3 and group 4 medulloblastomas [110].

Patients with group 3 medulloblastoma have the worst outcome of the four molecular groups [105,123]. These tumours are more common in boys, often show an LC/A morphology, and nearly 50% are metastatic at the time of diagnosis [105]. They are characterized by MYC overexpression and in 17% of cases they harbour MYC amplification [123]. Group 3 tumours with metastasis, isochromosome 17q, or MYC amplification carry a dismal prognosis, but group 3 tumours with classic histology are standard-risk tumours [2].

Copy number changes that target genes in the TGF-β signalling pathway occur in 20% of group 3 tumours [109,124], and PVT1 alterations are present in 12% of the tumours [109]. Mutations in chromatin remodelling genes including SMARCA4 (11%), KDM family gene members (8%), MLL2 (4%), GPS2 (3%), MLL3 (1%), CREBBP (1%), and CHD7 (1%) are detected in 28.5% of group 3 tumours [108,110,111].

Group 4 is the most common molecular group with a strong gender bias (three times more male than female patients) [105]. Nearly all tumours show classic histology. About 10% harbour SNCAP tandem duplications, with OTX2 amplification in 5.5% and CDK6 amplification in 5% of tumours [109]. Mutations in chromatin remodelling genes, including KDM6A (13%), other KDM family members (4%), MLL3 (3%), CHD7 (3%), and ZMYM3 (3%), are seen across approximately 30% of cases [108,110,111]. Copy number changes that target genes in the NF-κB signalling pathway occur in group 4 tumours [109]. MYCN amplification seen in 5% of group 4 tumours is associated with a poor outcome [105].

Atypical teratoid/rhabdoid tumour (AT/RT) AT/RTs are highly malignant tumours typically occurring before 5 years of age, with a male predominance (male to female ratio: 1.3–1.5:1) and an estimated prevalence of 1–2% among paediatric CNS tumours [112–130]. A significant proportion of AT/RTs arise in children younger than 2 years. They are the most common malignant CNS tumour of children below 1 year of age. AT/RTs arise in supratentorial or posterior fossa locations with an approximately equal frequency, but rarely arise in the spinal cord. Infratentorial tumours located in the cerebellar hemispheres, cerebellopontine angle, or brainstem are more frequent in the first 2 years of life.

AT/RTs are characterized by loss of INI1/SMARCB1/BAF47 expression due to either germline (25–35%) or to somatic SMARCB1 mutations and/or deletions on chromosome 22q [131–133]. INI1 is a core
member of the adenosine triphosphate (ATP)-dependent SWI/SNF chromatin-remodelling complex. AT/RTs have an extremely low mutation rate, with INI1 alterations the sole recurrent event [134]. Loss of another SWI/SNF chromatin-remodelling complex member, BRG1/SMARCA4, due to SMARCA4 mutation is seen in rare AT/RTs [135]. Loss of nuclear INI1 or BRG1 immunoreactivity is routinely used for the diagnosis of these tumours. If an embryonal tumour has histological features and a polymorphism phenotype to suggest a diagnosis of AT/RT, but expresses both INI1 and BRG1, then a descriptive diagnosis of CNS embryonal tumour with rhabdoid features is available in the 2016 WHO classification [2]. The diagnosis of AT/RT itself requires immunohistochemical confirmation of the characteristic molecular deficit.

One recent study has identified three distinct molecular groups of AT/RT (TYR, SHH, and MYC), which are associated with differences in demographics, tumour location, and types of INI1 or epigenetic alteration [136]. AT/RT-TYR tumours are mostly (77%) infratentorial with large TYR (tyrosinase) and/or DCT. Monosomy 22 is seen in nearly 80% of the tumours. Tyrosinase is highly expressed in almost every case in this subgroup, but not in the other two subgroups, and may therefore serve as a specific marker. More than 80% of AT/RT-TYR tumours occur in patients younger than 1 year of age. The AT/RT-SHH group encompasses both supratentorial (55%) and infratentorial (45%) tumours and harbours focal INI1 or BRG1 alterations and overexpression of SHH pathway genes, including MYCN and GLI2. NOTCH signalling is also active in this group. Genome-wide hypermethylation is seen in both ATRT-TYR and ATRT-SHH subgroups. AT/RT-MYC tumours occur in patients older than 6 years of age and are mostly supratentorial (61%) with local INI1 deletions and overexpression of MYC and the HOX gene cluster.

C19MC-altered embryonal tumour with multilayered rosettes (ETMR)

ETMR occurs in young children and is associated with a poor prognosis; nearly all patients die within 1–2 years of diagnosis [137,138]. ETMR encompasses three histopathological patterns, including embryonal tumour with abundant neuropil and true rosettes (ETANTR), ependymoblastoma, and medulloepithelioma [90]. Genome-wide DNA methylation and copy number analyses have demonstrated biological overlap between these three histological entities [139].

ETMR is characterized by amplification of a locus at chromosome 19q13.42 that contains a microRNA cluster (C19MC) [140]. A fusion product containing C19MC and a nearby gene TTYH1 has also been identified in ETMR, which likely amplifies the expression of C19MC using the promoter of TTYH1 [141]. Up-regulation of DNMT3B DNA methyltransferase in ETMR may explain its distinctive epigenetic pattern [139]. Interphase fluorescence in situ hybridization (iFISH) for C19MC is now routinely used for the diagnosis of this group of aggressive embryonal tumours, a group now defined by its common cytogenetic alteration and designated “embryonal tumour with multilayered rosettes, C19MC-altered” in the new WHO classification. In the absence of C19MC amplification, a tumour with the typical histological features of an ETMR and ependymoblastoma (5%) should be diagnosed as embryonal tumour with multilayered rosettes, NOS. However, up to one quarter of embryonal tumours with the typical features of a medulloepithelioma lack C19MC amplification [138], so medulloepithelioma remains as a diagnostic entity in the WHO classification.

Newly identified CNS embryonal tumour entities

Using integrated genomic analyses, principally genome-wide DNA methylation profiling, a recent study has identified four new groups of high-grade CNS tumours [45]. The four new entities are CNS neuroblastoma with FOXR2 activation (CNS NB-FOXR2), CNS Ewing sarcoma family tumour with CIC alteration (CNS EFT-CIC), CNS high-grade neuroepithelial tumour with MNI1 alteration (CNS HGNET-MNI1), and CNS high-grade neuroepithelial tumour with BCOR alteration (CNS HGNET-BCOR). The CNS NB-FOXR2 group encompasses tumours characterized in most cases by an embryonal cytology, including the morphologies classified as CNS neuroblastoma and CNS ganglioneuroblastoma. Tumours in this group express OLIG2 and synaptophysin. Gain of chromosome arm 1q is associated with the CNS NB-FOXR2 entity (98%), with 50% showing loss of 16q and 30% gain of chromosome 8. Genomic fusion events lead to increased FOXR2 expression in these tumours. The CNS EFT-CIC group also contains a high frequency of tumours with an embryonal cytology, but there is more morphological variability among these tumours. Fusion events or deletion involving CIC are associated with up-regulation of the ETS transcription factor family, including ETV1, ETV4, ETV5, FLI1, and ETS1 in these tumours. The CNS HGNET-MNI1 group includes a high proportion of tumours with the morphology ascribed to astroblastomas. These tumours particularly affect female patients and present at an older age and have a better outcome than many CNS embryonal tumours. Genomic rearrangement fuses MNI1 with partner genes that include CXXC5 and BEND2. About 30% of the tumours show loss of chromosome 16q, and 16% show gain of chromosome 8. The CNS HGNET-BCOR group shows a variety of CNS tumour histologies and only in rare instances exhibits an embryonal morphology. Most tumours display balanced copy number profiles and BCOR alterations, including in-frame deletion/internal tandem duplications and frameshift mutations, and 79% of tumours demonstrate nuclear β-catenin immunoreactivity. The full clinicopathological profiles of these four tumour groups have yet to be fully elucidated.
Choroid plexus tumours

Choroid plexus tumours, including choroid plexus papilloma (CPP, WHO grade I), atypical choroid plexus papilloma (aCPP, WHO grade II), and choroid plexus carcinoma (CPC, WHO grade III), are rare intraventricular neoplasms predominantly occurring in children under 2 years of age [126]. No significant differences are observed when the molecular alterations of CPPs and aCPPs are compared [142]; hyperdiploidy is common in both.

Genomic, transcriptomic, and DNA methylation profiling has demonstrated clear segregation of CPCs from CPPs and aCPPs [142]. Germline alterations of TP53 (Li–Fraumeni syndrome) predispose to CPC [143,144]. Somatic TP53 mutations are observed in 60% of CPCs, and increased copies of mutated TP53 are associated with a worse outcome [142]. Deletion of PTEN has also been implicated in CPC [145–147]. CPCs are characterized by complex chromosomal alterations associated with patient age and prognosis [147]. Gains on chromosomes 1, 12, and 20; losses of chromosomes 5, 17, and 19p; and uniparental isodisomy (UPD) are common [142,146]. Chromosome 17 is most frequently affected by UPD. About 90% of CPCs exhibiting UPD of chromosome 17 harbour TP53 mutations. Chromosomal losses of 9, 19p, and 22q (hypodiploid CPC) are significantly more frequent in children younger than 3 years old, whereas gains of chromosomes 7, 8q, 14q, 19, and 21q (hyperdiploid CPCs) prevail in older patients [142,147]. TP53 mutations are more common in hypodiploid CPCs (90%) than in hyperdiploid CPCs (50%) [142]. Loss of 12q is associated with a shorter survival [147]. TAF12, NFYC, and RAD54L have been identified as potential oncopgenes in CPC [148].

Germ cell tumours

Worldwide, intracranial germ cell tumours account for 3–4% of paediatric brain tumours [149]; in Japan, however, their incidence is significantly higher, at over 15%. Pure germinomas are most common, and generally have a good prognosis.

KIT mutations are the most common alterations in intracranial germ cell tumours and are more often observed in pure germinomas (25% of cases) than in mixed tumours [150,151]. KRAS and NRAS mutations are also identified. KIT, KRAS, and NRAS mutations are mutually exclusive and together account for about 45% of cases. Recurrent focal amplifications affecting MTOR, CBL, and AKT1 are also found, indicating deregulation of the KIT/RAF and AKT/mTOR pathways in over 50% of intracranial germ cell tumours. Germline variants in JMJD1C are enriched in Japanese patients and may provide a potential explanation for the greater incidence of intracranial germ cell tumours in this ethnic group. JMJD1C is an H3K9 demethylase essential for maintenance of male germ cells [152].

Craniopharyngiomas

Craniopharyngiomas account for 3–5% of paediatric brain tumours and two histological subtypes are recognized: adamantinomatous and papillary [2]. The adamantinomatous variant predominates in children, but can arise throughout adulthood. Almost all adamantinomatous craniopharyngiomas harbour an activating mutation in CTNNB1 [153]. Papillary craniopharyngiomas are typically an adult disease and are characterized by BRAF V600E mutation [154].

Summary

The 2016 WHO classification of CNS tumours represents a pivotal moment when molecular alterations have been integrated alongside histopathological features for the first time. Molecular genetic studies have revealed signature molecular alterations: histone H3 mutations for some paediatric high-grade gliomas, RELA fusions for supratentorial ependymomas, loss of INI1/BRG1 expression for AT/RTs, C19MC copy number alteration for ETMRs, and clinically important molecular groups of medulloblastoma. These will be supplemented by others by the time of the next edition and fundamentally alter the perspective of the diagnostic process – linking histopathological and molecular testing for the optimum evaluation of paediatric CNS tumours.

References


