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Embryonal tumors in the WHO CNS5 classification: A Review

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Abstract

Embryonal tumors are a heterogenous group of neoplasms mostly defined by recurrent genetic driver events. They have been, previously, broadly classified as either medulloblastoma or supratentorial primitive neuroectodermal tumors (PNETs). However, the application of DNA methylation/gene expression profiling in large series of neoplasms histologically defined as PNET, revealed tumors, which showed genetic events associated with glial tumors. These findings led to the definitive removal of the term “PNET” in the 2016 World Health Organization (WHO) classification of CNS tumors. Moreover, further studies on a large scale of methylation profiling have allowed the identification of new molecular-defined entities and have largely influenced the 5th edition of the WHO classification of CNS tumors (WHO CNS5) for both medulloblastomas and other CNS embryonal tumors. The importance of molecular characteristics in CNS embryonal tumors is well represented by the identification of different molecular groups and subgroups in medulloblastoma. So, in the CNS5, the emerged group 3 and group 4 belong to the classification, and the four molecular and morphologic types are now combined into a unique section. Among other embryonal tumors, two new recognized entities are introduced in CNS5: CNS neuroblastoma, *FOXR2*-activated, and CNS tumor with *BCOR* internal tandem duplication (ITD). Embryonal tumor with multilayered rosettes (ETMR), already present in the previous classification now has a revised nomenclature as a result of the new *DICER1* alteration, additional to the formerly known C19MC. Regarding atypical teratoid/rhabdoid tumor (AT/RT), three molecular subgroups are recognized in CNS5. The combination of histopathological and molecular features reflects the complexity of all these tumors and gives critical information in terms of prognosis and therapy. This encourages the use of a layered diagnostic report with the integrated diagnosis at the top, succeeded by layers including the histological, molecular, and other essential details.

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Full Text

Introduction

Embryonal tumors were previously classified into two broad groups: medulloblastoma and PNET. The relevance of genome-wide studies over the years led to a reclassification of these entities.[1],[2] The application on a large scale of DNA methylation/gene expression profiling led to the identification of new molecular defined entities[3] [Table 1]. Here, we describe the newest molecularly defined types/subtypes of medulloblastoma and other embryonal tumors that will be included in the CNS5.{Table 1}

Medulloblastoma

In WHO CNS5, medulloblastomas are classified according to a combination of molecular and histopathological features. The current molecular classification, which reflects the clinico-biological heterogeneity of these neoplasms, is the result of extensive transcriptome and DNA profiling analysis.[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24] The new classification maintains the original established four principal molecular groups as in 2016 WHO,[7],[25],[26],[27],[28],[29],[30],[31],[32] i.e., wingless-activated (WNT)-activated, sonic hedgehog (SHH)-activated, and non-WNT/non- SHH. SHH tumors are divided, as in WHO 2016, on the basis of TP53 status (TP53- mutant and TP53-wildtype tumors) having very different clinico-pathological and biological characteristics.[26],[33] However, DNA methylation profiling has led to the identification of 12 subgroups. There are four subgroups of SHH medulloblastoma[34] and eight subgroups of non-WNT/non-SHH (group 3 and group 4) medulloblastoma [Table 2].[35] Such further stratification of the molecular subgroups has critical biological and clinical implications regarding prognosis and therapeutic options.[36],[37],[38],[39],[40],[41],[42],[43] This is demonstrated in the subgroup of medulloblastoma arising in very young children with poor prognosis; the standard treatment with chemotherapy is still too high for these young patients,[13],[38] and new trial evidence suggests promising targeted therapies.[44],[45]{Table 2}

Immunohistochemistry can still be used to discriminate between WNT, SHH, and non-WNT/non-SHH medulloblastomas.[46] The WNT-activated group is identified by the nuclear immunoreactivity for beta-catenin, which is expressed in most neoplastic cells; however, some cases can show weak and variable expression. The SHH-activated group is defined by the cytoplasmic immunostaining for GAB1 and YAP1 proteins. Both WNT and SHH medulloblastoma groups show cytoplasmic immunoreactivity for Filamin A. Non-WNT/non-SHH tumors show a cytoplasmic expression for beta-catenin and are immunonegative for GAB1 and YAP1 [Table 2], [Figure 1]. However, DNA methylation profiling is considered the standard method for determining medulloblastoma group or subgroup status.[27],[47]{Figure 1}

WHO CNS5 retains the four histological types listed in the 2016 WHO classification i.e., classic, desmoplastic/nodular, medulloblastoma with ex-tensive nodularity, and large cell/anaplastic[20],[36],[48],[49] [Figure 2], but compared to 2016 WHO, they have been combined into a single chapter named “medulloblastoma, histologically defined” in which the morphological variation as patterns of a single tumor type are described. However, it is acknowledged that there is a correlation between the histological patterns and the molecular subgroup i.e., 1) desmoplastic/nodular medulloblastomas and medulloblastomas with extensive nodularity belong to the SHH molecular group and most are in the SHH-1 and SHH-2 sub-groups; 2) WNT tumors have classic morphology, and 3) most large cell/anaplastic tumors are included in either to the SHH-3 subgroup or to the non-WNT/non-SHH (i.e. group 3/4) subgroup 2.[25],[50] The twelve molecular subgroups are not included in the CNS5.{Figure 2}

On the basis of such heterogeneity, medulloblastomas have to be classified in a layered and integrated format containing a combination of histopathological and molecular features.

However, in the absence and impossibility to perform molecular analyses, the diagnostic pathologist is always given the option to report such tumors using the not otherwise specified (NOS) and not elsewhere classified (NEC) options.[51]

Medulloblastomas can originate in several inherited cancer syndromes[52],[53] such as Gorlin (SUFU and PTCH1 mutations),[54],[55],[56],[57],[58],[59] Li-Fraumeni (TP53 mutations),[60] familial adenomatous polyposis (APC mutations),[61] Rubinstein–Taybi (CREBBP mutations),[62] and Nijmegen (NBN mutations).[63] A new one has been recently identified, which is listed in WHO CNS5, i.e., ELP1-medulloblastoma syndrome. Germ-line mutations of ELP1 gene can be present in 40% among pediatric patients with SHH medulloblastoma TP53 wild-type.[64]

Other CNS embryonal tumors

The other embryonal tumors listed in WHO CNS5 are AT/RT; Embryonal tumor with multlayered rosettes (ETMR); CNS neuroblastoma, FOXR2- activated, and CNS tumor with BCOR internal tandem duplication (ITD). Whereas AT/RT and ETMR were included in previous WHO classifications, CNS neuroblastoma, FOXR2-activated, and CNS tumor with BCOR ITD are new to CNS5. Moreover, cribriform neuroepithelial tumor (CRINET) has been introduced as a provisional entity within this category. As for other CNS tumors, the broad designation CNS embryonal tumor NEC or NOS is included for embryonal tumors that lack molecular features for a more specific diagnosis.

Atypical teratoid/rhabdoid tumor and cribriform neuroepithelial tumor

The definition of AT/RT in WHO CNS5 practically overlaps that of the previous edition: a highly malignant composed of poorly differentiated cells showing focal or diffuse rhabdoid features with polyphenotypic differentiation and genetically defined by biallelic inactivation of SMARCB1 (also known as hSNF5, INI1, or BAF47)[65],[66],[67],[68],[69],[70] or rarely (in <5% of cases) of SMARCA4 (BRG1).[68],[71] In the majority of the cases, the diagnosis of these tumors still relies on the histology and immunohistochemistry showing the typical differentiation along neuroepithelial, epithelial, and mesenchymal lines and, most important, loss of expression of SMARCB1 (INI1) [Figure 3] or SMARCA4 (BRG1) in the rare cases with such mutation.{Figure 3}

The most important change in CNS5 is the identification of three molecular sub-groups defined by DNA methylation and/or gene expression profiling. These three molecular subgroups are named AT/RT-TYR, AT/RT-SHH, and AT/RT-MYC. Each subgroup delineates different groups of patients in terms of age, site of origin, and SMARCB1/chromosome 22 alteration pattern [Table 3].[72],[73]{Table 3}

AT/RT-SHH tumors (~44%) exhibit an overexpression of proteins involved in the pathways of SHH and Notch signaling. The median age of patients is 20 months and in 67% of cases, they arise in the supratentorial compartment. Compound heterozygous SMARCB1 point mutations are frequently seen in this group.[74]

AT/RT-TYR tumors (~34%) are characterized by an upregulation of proteins involved in the melanosomal pathway (tyrosinase), the bone morphogenetic protein (BMP) pathway, and development-related transcription factors, including OTX2. These tumors occur in very young patients (median age: ~12 months) and are localized mainly in the infratentorial compartment. Loss of SMARCB1 gene is mostly generated by the mutation in one allele and a complete or partial loss of chromosome 22, removes the second allele[74]

AT/RT-MYC tumors (~22%) are characterized by the expression of the MYC oncogene and HOX cluster genes. This group, compared to AT/RT-SHH or AT/RT-TYR groups, affects older patients (median age: ~27 months).[74] They are more commonly supratentorial, rarely they can occur in the spinal cord. The rare AT/RTs occurring in adults are confined in the sellar region and also belong to this group.[75] Potential immunohistochemical surrogate markers for identification of AT/RT-SHH and AT/RT-TYR subgroups are antibodies against ASCL1 and tyrosinase, respectively.[72],[76] Moreover, a recent study has found a significant correlation between histological patterns and molecular subgroups.[77]

SMARCB1- deficient AT/RT can occur in the setting of the rhabdoid tumor predisposition syndrome 1 with a frequency between 26% and 41%, whereas the risk of rhabdoid tumor predisposition syndrome 2 in a patient with a SMARCA4-deficient tumor is substantially higher.

In WHO CNS5, cribriform neuroepithelial tumor is a provisional entity distinct from AT/RT and defined as “a nonrhabdoid neuroectodermal tumor characterized by cribriform strands and ribbons and showing loss of nuclear SMARCB1 expression.” This is a remarkably rare neoplasm occurring mostly in the periventricular areas (lateral, third, and fourth ventricles) in infants (mean age 20 months). Histologically, these are composed of strands and ribbons conferring a cribriform pattern of nonrhabdoid cells with strong positivity for EMA and loss of SMARCB1 expression. In terms of DNA methylation profiling, the tumor clusters within the AT/RT molecular subtype AT/RT-TYR. There are only a small number of reported cases which thus does not permit to delineate the biological behavior of this lesion. However, small retrospective series have shown significantly longer survival compared to standard AT/RT-TYR cases.

Embryonal tumor with multilayered rosettes

The term “embryonal tumor with multilayered rosettes (ETMR)” has been introduced as a unifying diagnosis for tumors with diverse histological designations such as ependymoblastoma, embryonal tumor with abundant neuropil and true rosettes (ETANTR), and medulloepithelioma all characterized by a molecular hallmark i.e., the amplification of the microRNA cluster on chromosome 19 (C19MC) present in ~90% of the ETMR cases.[78],[79] For this reason, in WHO 2016, the entity was designated as “Embryonal tumor with multilayered rosettes C19MC-altered.” The discovery that tumors lacking the C19MC amplification frequently harbor biallelic DICER1 mutations, of which the first hit is generally present in the germline of the patients, led to the removal of the term “C19MC-altered” in the nomenclature of this entity in WHO CNS5.

ETMRs more frequently occur in the cerebral hemispheres but they can also develop in the infratentorial compartment involving the cerebellum and brainstem.[80],[81],[82],[83] The histological feature of these tumors includes embryonal cells organized in a pseudostratified epithelium around a central area of neuropil containing a lumen to form multilayered mitotically active rosettes [Figure 4]a. The three main histological patterns comprise: embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma, and medulloepithelioma. These three histological patterns, based on DNA methylation profile and gene expression, cluster in the same group, reflecting a different morphological range of the same tumor entity. ETMR with embryonal tumor with abundant neuropil and true rosettes (ETANTR) histology shows a biphasic architecture including more compact areas with hyperchromatic nuclei and scant eosinophilic cytoplasm arranged in a sheet-like pattern along with wide neuropil-like areas with scattered neoplastic neurocytic and ganglion cells. In dense areas, multilayered rosettes are more frequently found. ETMRs with ependymoblastoma histology show large sheets of poorly differentiated rosettes and low neuropil content. ETMR with medulloepithelioma pattern has different patterns including papillary, tubular, or trabecular structures appearing like the primitive neural tube, constituted by neoplastic pseudostratified neuroepithelium with an external [Periodic acid–Schiff (PAS)-positive] limiting membrane. Different differentiation patterns like epithelial, myeloid, osteoid, myoid, or other mesenchymal differentiation, including even melanin pigmented cells can be identified.{Figure 4}

All three histological patterns show a strong and diffuse cytoplasmic immunoreactivity for LIN28A. Such expression can also be observed in some glial, neoplasms, atypical teratoid rhabdoid tumor (AT-RTs), germ cell tumors, and some non-CNS neoplasms.[84],[85] However, within the appropriate histological setting, LIN28A is a very useful marker for the diagnosis of ETMR [Figure 4]b confirmatory diagnosis which requires the molecular detection of C19MC amplification or DICER1 mutations.

C19MC microRNA cluster alteration at 19q13.42 has been found only in ETMRs and occurs in approximately 90% of cases[86],[87] [Figure 4]c. These are usually focal amplifications, but fusions can also occur, generally with TTYH1. C19MC alterations can be easily detected by array-based copy-number profiling [Figure 4]d or interphase fluorescence in situ hybridization (FISH). The absence of C19MC alteration in ETMR suggests the presence of DICER1 mutations. Such mutations are observed only in the 5% of C19MC negative ETMR and almost all of these cases are in the setting of a DICER1 genetic tumor syndrome. Rare ETMRs without a C19MC alteration or DICER1 mutation should be classified as ETMR NEC. Despite intensive multimodal treatment, the survival rates for ETMR remain very poor.

CNS neuroblastoma, FOXR2-activated

CNS neuroblastoma, FOXR2 activated (CNS NB-FOXR2), is a new entry in WHO CNS5. Its discovery originates from the re-evaluation by DNA methylation analysis of a previous CNS-PNET cohort in which many tumors could be included in specific entities. Additionally, four new entities were delineated based on specific DNA methylation profiles and genetic alterations.[1],[88] One of these new entities showed morphological similarity with CNS neuroblastoma and harbored chromosomal rearrangements leading to an increased expression of the forkhead box R2 (FOXR2) gene.

CNS NB-FOXR2 histologically displays embryonal architecture composed of densely packed undifferentiated embryonal cells with hyperchromatic nuclei and inconspicuous cytoplasm arranged in a sheet-like pattern. Vascular pseudorosettes and Homer-Wright rosettes may be encountered. Mitotic Figures and apoptotic bodies are abundant/frequent. Areas of necrosis are commonly present. Some cases show focal neurocytic differentiation and a collection of mature ganglion cells (“ganglioneuroblastoma”). Most of these tumors disclose a strong

immunopositivity for OLIG2, whereas GFAP and vimentin are not expressed. Areas with neurocytic/ganglionic differentiation show positivity for synaptophysin [Figure 5]a, [Figure 5]b, [Figure 5]c. Overexpression of TTF-1 is also present in most tumors.{Figure 5}

The detection of FOXR2 rearrangements necessitates next-generation sequencing method, however alterations affecting the FOXR2 locus on chromosome Xp11.21 may be visible by copy-number analysis [Figure 5]d. Nevertheless, the presence of a distinct cluster that includes CNS NB-FOXR2 by DNA methylation profiling, highly facilitates the diagnosis of these tumors. In contrast to ETMR, patients with CNS NB-FOXR2 present at an older age, have exclusively supratentorial tumors, and show higher response as well as superior survival rates.[89]

CNS tumor with BCOR internal tandem duplication (ITD)

The inclusion in WHO CNS5 of CNS tumors with BCOR ITD as embryonal tumors, maybe provisional, in view of the fact that these neoplasms are not definitively neuroectodermal. Exon 15 BCOR ITDs have been reported in several histologically similar sarcomas, and therefore there is no consensus as to whether these tumors should be considered neuroepithelial or mesenchymal neoplasms.

They occur mainly in young patients with an age ranging from 0 to 22 years and are usually located in the cerebral or cerebellar hemispheres. They are generally composed of uniform oval or spindleshaped cells, with round or oval nuclei showing a delicate chromatin pattern. Glioma-like fibrillary areas can be present as well as others with compact fascicular patterns frequently associated with a branching capillary network. The formation of ependymomalike perivascular pseudorosettes is quite characteristic, and myxoid or microcystic areas are often encountered. Palisading necrosis is commonly observed. Mitoses are frequent. For such protean histology, the differential diagnosis includes high-grade gliomas, ependymomas, and embryonal tumors. By immunohistochemistry, the constant expression of vimentin and CD56 associated with negativity or scarce expression of OLIG2, GFAP, or S100 support the diagnosis [Figure 6].[88] Widespread strong nuclear expression of BCOR is a sensitive marker, but it is not specific because it may also occur in other tumors, such as astroblastomas[90] or solitary fibrous tumors.[91]{Figure 6}

The definitive diagnosis relies on the molecular detection of a heterozygous ITD in exon 15 of the BCOR gene. As for other embryonal tumors, DNA methylation and gene expression profiles are reliable methods to identify CNS tumors with BCOR ITD from other CNS tumors.[1] Although the clinical data are limited due to the rarity, the overall survival of the patients harboring these tumors is poor.[90]

CNS embryonal tumor NOS

With this term, WHO CNS5 defines a CNS tumor with embryonal histology and immunophenotype in which no alteration that would classify it as one of the molecularly defined CNS embryonal tumors can be detected or cases that, for any reason, are not susceptible to analysis.

Conclusions

All the classification systems have to be considered a work in progress, whichprovide both great opportunities in terms of research and therapeutic challenges. CNS5 exemplifies the concept that today the pathological diagnosis of CNS embryonal tumors is the result of a complex integration of histology, immunohistochemistry, and molecular features, and such diagnosis represents the basis for clinical decision making.

For nonmedulloblastoma tumors, a useful approach could be to start using three simple antibodies (synaptophysin, vimentin, and Olig2). They can give initial information and subsequent suggestions for the next more appropriate testing. So, for example, in the context of a morphologic embryonal neoplasm, the expression of Olig2 and synaptophysin should lead to the suspicion of of a CNS NB-FOXR2. In this case, the next step should be the molecular documentation of the FOXR2 rearrangement. Tumors presenting with undifferentiated small neoplastic cells and multilayered rosettes showing immunopositivity for synaptophysin, Olig2 and vimentin are suggestive of ETMR. In this case, the immunohistochemical analysis for LIN28 should be performed; in the case of positive expression, the molecular test (sequencing or FISH test) is mandatory to confirm the presence of C19MC alteration. In the case of positivity for vimentinor, a combination of vimentin and Olig2 in the context of a poorly differentiated neoplasm, immunostaining for BCOR can be useful, even though this antibody is not specific and can be expressed by other nonembryonal tumors. Furthermore, in this case, molecular analysis for the detection of BCOR ITD is required. In the case of a neoplasm with rhabdoid morphology and a polyphenotypic differentiation, the expression of vimentin alone or in combination with synaptophysin and Olig2 can suggest a diagnosis of AT/RT. In this last case, the loss of INI1 or BRG1 protein supports the diagnosis of AT/RT [Figure 7].{Figure 7}

For medulloblastoma, WHO CNS5 highlights the clinical and biological heterogeneity of this neoplasm. The integration of molecular information is an essential component of the classification although it raises some controversies and challenges. On one hand, the discovery of numerous molecular subgroups opens the possibility to the development of more specific target therapies, however, clinical trials on a small group of patients would not provide significant results. Also treating uniformly tumors harboring different molecular alterations would lead to the loss of critical therapeutic implications. So far, treatment for non medulloblastoma embryonal tumors remains the removal surgery followed by further additional treatments when required like craniospinal radiation as well as chemotherapy and eventually most effective molecular-targeted therapies.[92] However, the increasing number of molecularly defined tumors included in a specific entity represents the basis to develop precise treatments for these children.

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Conflicts of interest

There are no conflicts of interest.

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Figure 1: Anaplastic medulloblastoma, SHH subtype, p53 mutated. (a) H and E. Neoplastic cells show some pleomorphic enlarged bizarre nuclei (20 × magnification). (b) Filamin-A immunostain showing a diffuse cytoplasmic positivity (20 × magnification) (c) Diffuse nuclear expression of p53 (20 ×). (By courtesy of Dr. Cynthia Hawkins, SickKids Hospital, Toronto, Canada)

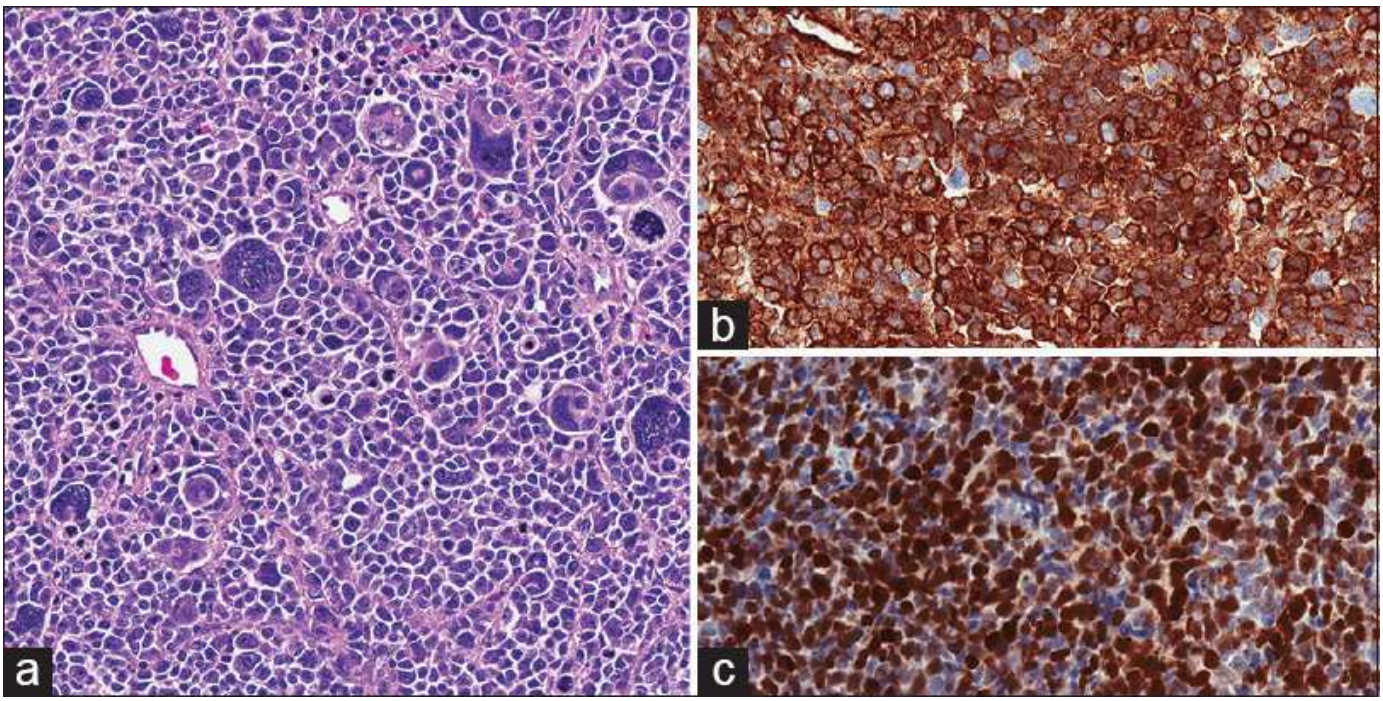

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Figure 2: Different histological types of medulloblastoma (H&E). (a) Classic type (20 ×). (b) Desmoplastic/nodular medulloblastoma (20X). (c) Medulloblastoma with extensive nodularity (10X). (d) Largecell/anaplastic medulloblastoma (40 ×)

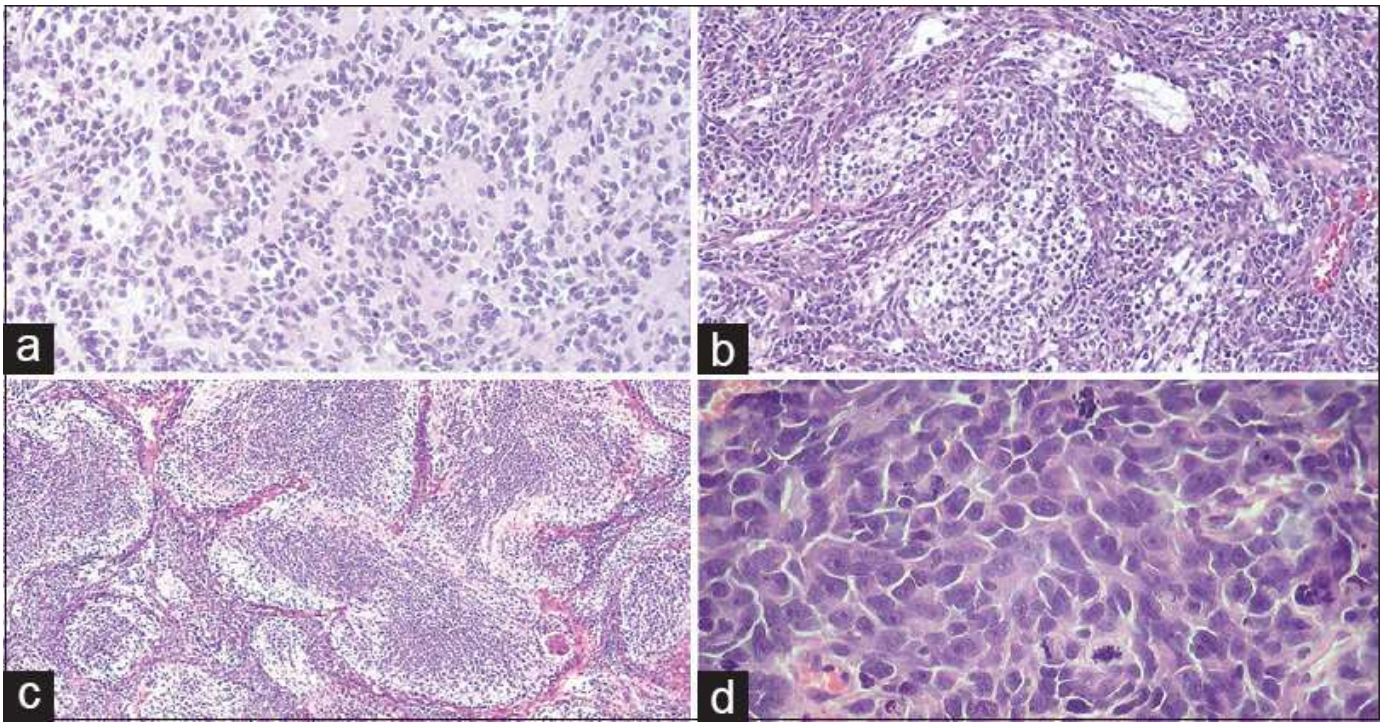

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Figure 3: ATRT. (a) H and E. Neoplasticrhabdoidcells display a perivascular arrangement (20 ×). (b) The tumorhas medium-sized, round cells with distinct borders, eccentric nuclei, and prominent nucleoli (H and E) (40 ×). (c) INI1 immunostainshowing positive endothelial and reactivecells. Tumorcells are negative for INI1 protein (20X)

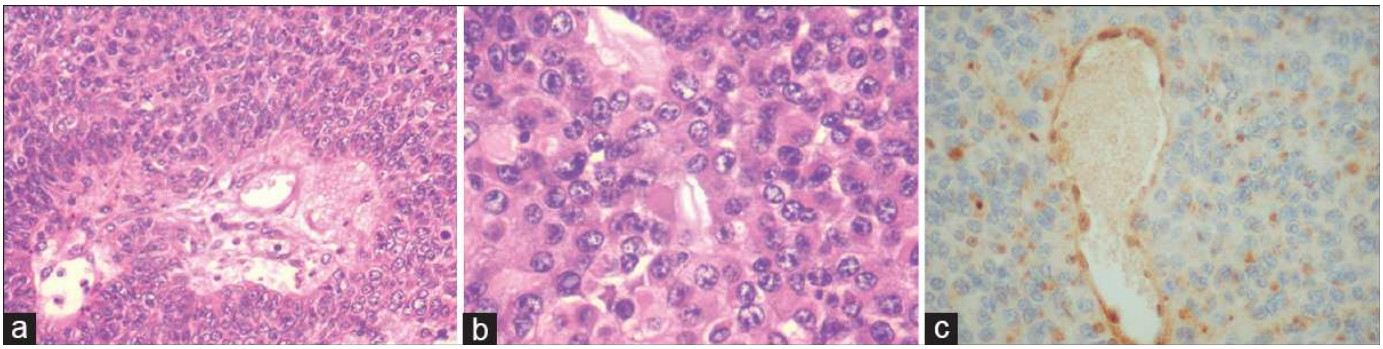

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Figure 4: ETMR. (a) H and E. Neoplastic cells with hyperchromatic nuclei. Multilayeredrosettes (arrows) are identified. (20 ×). (b) Immunohistochemistry for LIN28 showing strong cytoplasmic stain (20 ×). (c) FISH shows amplification at 19q13.42 (green signals). (d) Copy number variation analysis with *C19MC* amplification (arrow)

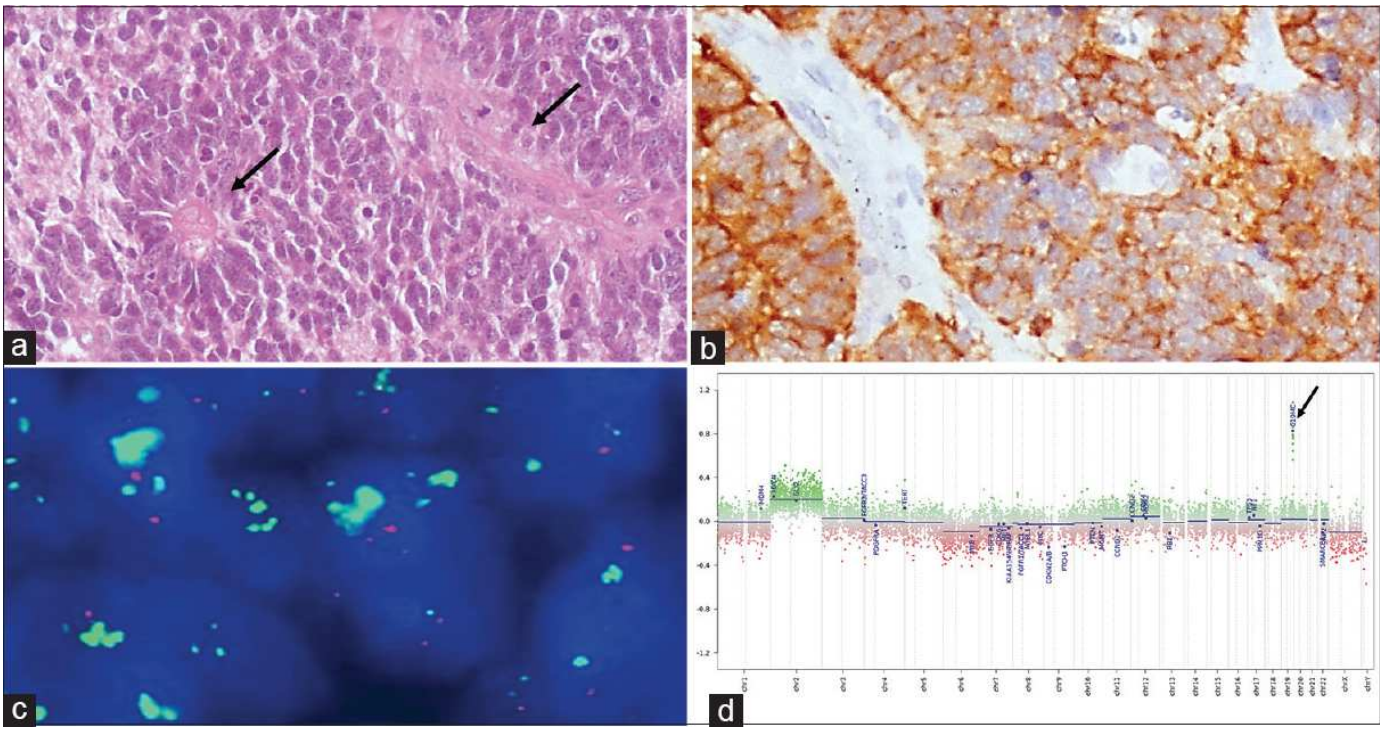

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Figure 5: CNS neuroblastoma, FOXR2-activated. (a) H and E. Neoplasticcells with small, round nuclei surrounded by a clear halo (40 ×). (b) Synaptophysin immunoexpression (10 ×). (c) Olig2 immunoexpression (10 ×). (d) Copy number variation. Gain of chromosome 1q (arrow) and focal or total loss of 16q (star)

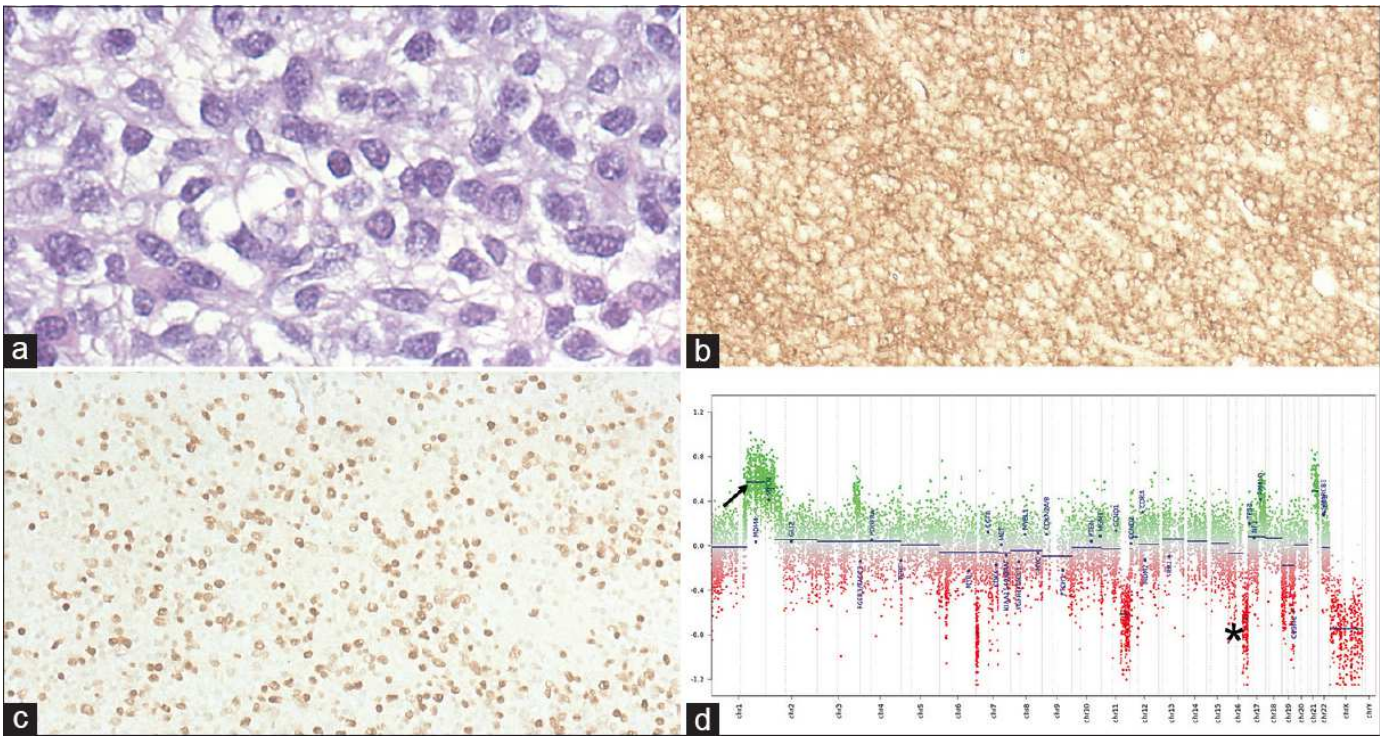

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Figure 6: CNS tumor with BCOR internal tandem duplication (ITD). (a) H and E. Tumor cells show an oligo-like aspect with monotonous round to oval nuclei, fine chromatin, and indistinct nucleoli. Evident some microcystic formation (40 ×). (b) Nuclear BCOR immunostaining (10 ×). (c) Diffuse immunopositivity for vimentin (10 ×)

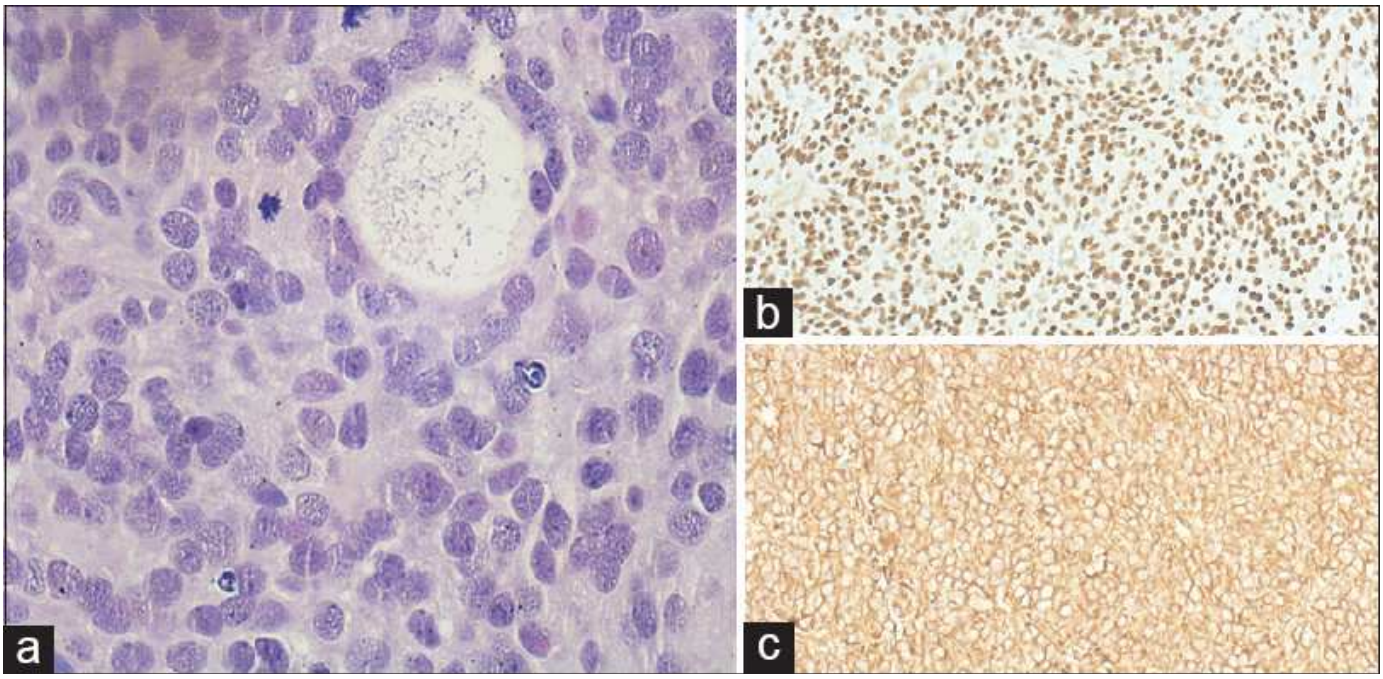

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Figure 7: Diagnostic algorithm for approaching diagnosis of non-medulloblastoma embryonal tumors, including the integration of immunohistochemical and molecular analysis

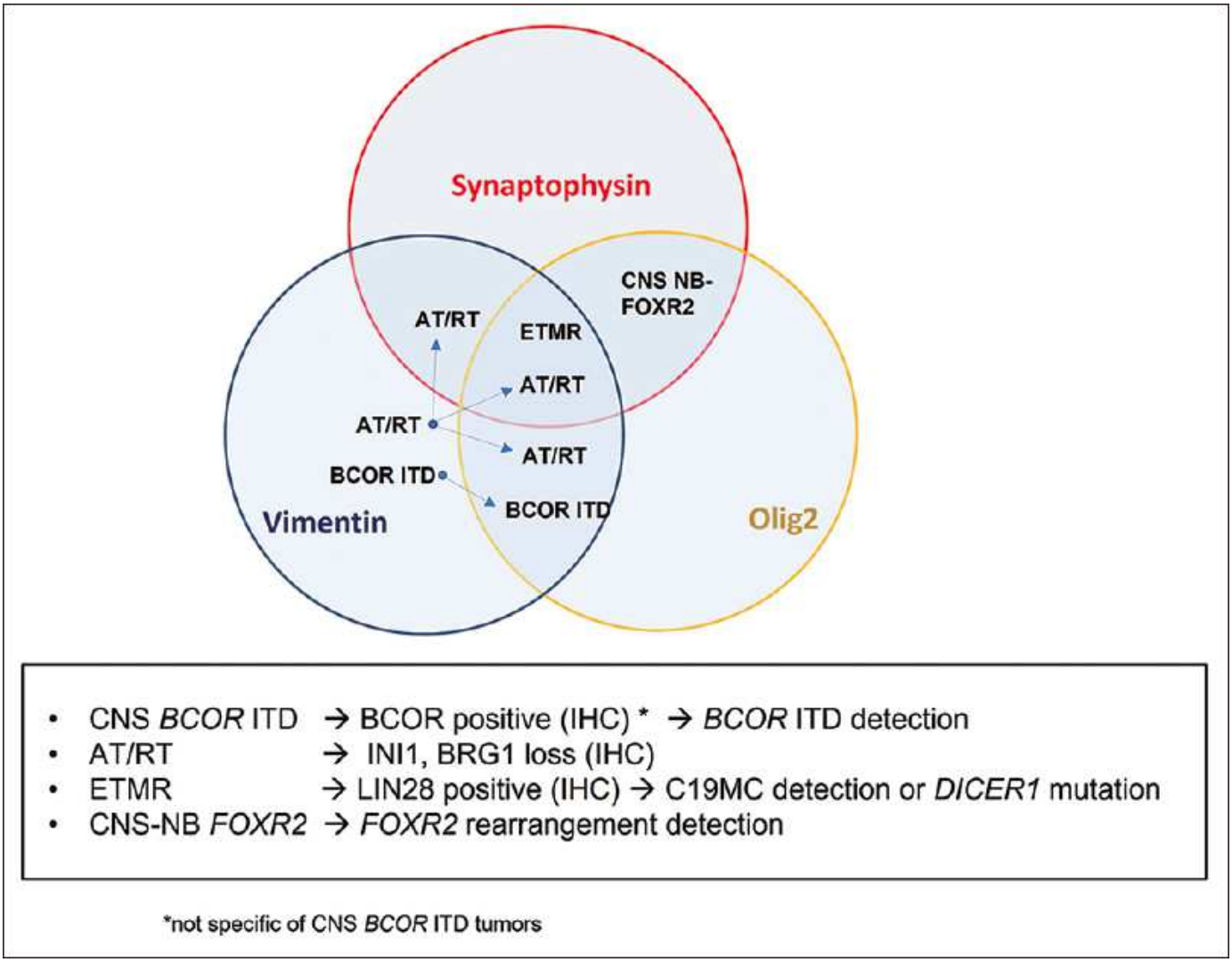

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Table 1: Embryonal Tumors: Comparison between 2016 and fifth WHO classification

WHO Classification 2016	*WHO Classification 2021 (CNS5)*
Medulloblastomas, genetically defined	*Medulloblastomas*
Medulloblastoma, WNT-activated	Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated, and TP53-wildtype	Medulloblastoma, SHH-activated, and TP53-wildtype
Medulloblastoma, SHH-activated, and TP53-mutant	Medulloblastoma, SHH-activated, and TP53-mutant
Medulloblastoma, non-WNT/non-SHH	Medulloblastoma, non-WNT/non-SHH
Medulloblastomas, histologically defined	Medulloblastomas, histologically defined
Medulloblastoma, classic	*Other CNS embryonal tumors*
Desmoplastic/nodular medulloblastoma	Atypical teratoid/rhabdoid tumor
Medulloblastoma with extensive nodularity	Cribriform neuroepithelial tumor
Large cell/anaplastic medulloblastoma	Embryonal tumor with multilayered rosettes
Embryonal tumor with multilayered	CNS neuroblastoma, FOXR2-activated
rosettes C19MC-altered	CNS tumor with BCOR internal tandem duplication (ITD)
Other CNS embryonal tumors	CNS embryonal tumor NOS
Medulloepithelioma	
CNS neuroblastoma	
Atypical teratoid/rhabdoid tumor	
CNS embryonal tumor with rhabdoid features	

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Table 2: Clinico-pathological and genetic characteristics of medulloblastoma groups

Molecular groups	*WNT*	*SHH*		*G3*	*G4*
		TP53 wild type	*TP53 mutated*		
Age	Childood	Infancy/Adulthood	Childood	Childood	All age groups
Location	Central, frequently contiguous to brainstem		Hemispheric (rarely midline)	Midline (filling 4th ventricle)	Midline (filling 4th ventricle)
Histology	Mostly classic, rarely large cell anaplastic	Desmoplastic/Large cell/anaplastic	Nodular	Classic, Large cell anaplastic	Classic, Large cell anaplastic
Immunohisto chemestry	Nuclear beta-catenin Filamin A positive YAP1 positive GAB1 negative	P53 negative	Cytoplasmic beta catenin Filamin A positive YAP1 positive GAB1 positive p53 positive	Cytoplasmic beta catenin Filamin A negative YAP1 negative GAB1 negative	
Subgroups	α, β		α, β, γ, δ	II, III, IV (Group 3) I, V, VII (Group 3/4)	VI, VIII (Group 4)
Genetics	CTNNB1, DDX3X, SMARCA4 and TP53 mutations	PTCH1, SMO, SUFU, TP53 mutation	TERT promoter mutations	MYC, OTX2, SMARCA4, NOTCH, TGF-β mutations	MYCN, KDM6A, CDKNA, mutation, SNCAIP duplications
Chromosomal abnormalities	Monosomy of chromosome 6	9q deletion, 10q loss	MYCN amplification, GLI2 amplification, 17p loss	MYC amplification, isodicentric 17q, 1q gain, 5q and 10q loss	MYC amplification, isodicentric 17q, 8, 10 and 11 loss, 4, 7 17, and 18 gain
Outcome of subgroups (5 years survival)	97% (α), 100% (β)	69.8% (α), 67.3% (β), 88% (γ), 88.5% (δ)		50% (II) 43% (III) 80% (IV) 77% (I) 59% (V) 85% (VII)	81% (VI) 81% (VIII)
Metastasis (%)	12%	20%(α), 33%(β), 9% (γ), 9% (δ)		57% (II) 56% (III) 58% (IV) 35% (I) 62% (V) 45% (VII)	45% (VI) 50% (VIII)

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Table 3: Clinico-pathological and genetic characteristics of AT/RT molecular subgroups

Molecular subgroups	*AT/RT-SHH*	*AT/RT-TYR*	*AT/RT-MYC*
Incidence	44%	34%	22%
Age	2-5 years (median age: 20 months)	0-1 years (median age: 12 months)	>3 years (median age: 27 months)
Location	More frequently supratentorial	More frequently infratentorial	More frequently supratentorial (rarely spinal)
Copy Number Alteration of Chromosome 22	None	Complete loss (monosomy)/partial loss	None
SMARCB1 alterations	Point mjutations/Focal deletions	Point mutations/Focal deletions	Extensive deletions
Involved pathway	SHH and NOTCH pathway	BMP and melanosomal pathway	Overexpression of MYC gene and HOX cluster genes