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## Review

# Biological background of pediatric medulloblastoma and ependymoma: A review from a translational research perspective

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## Abstract

Survival rates of pediatric brain tumor patients have significantly improved over the years due to developments in diagnostic techniques, neurosurgery, chemotherapy, radiotherapy, and supportive care. However, brain tumors are still an important cause of cancer-related deaths in children. Prognosis is still highly dependent on clinical

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characteristics, such as the age of the patient, tumor type, stage, and localization, but increased knowledge about the genetic and biological features of these tumors is being obtained and might be useful to further improve outcome for these patients. It has become clear that the deregulation of signaling pathways essential in brain development, for example, sonic hedgehog (SHH), Wnt, and Notch pathways, plays an important role in pathogenesis and biological behavior, especially for medulloblastomas. More recently, data have become available about the cells of origin of brain tumors and the possible existence of brain tumor stem cells. Newly developed array-based techniques for studying gene expression, protein expression, copy number aberrations, and epigenetic events have led to the identification of other potentially important biological abnormalities in pediatric medulloblastomas and ependymomas.

**Key Words:** biological characteristics • ependymoma • epigenetic events • gene expression • medulloblastoma • protein expression • signaling pathways

## ► Introduction

The causes of pediatric brain tumors are largely unknown. Environmental factors, such as smoking, diet, and other exposures, do not predispose the brain to develop tumors.<sup>1</sup> Only a very small proportion of brain tumors are caused by hereditary gene defects ([Table 1](#)), irradiation, or immune suppression. Additional knowledge about the biological characteristics of pediatric brain tumors may provide new information about pathogenesis, facilitate diagnosis, contribute to better risk-group stratification for therapy, or be used to develop new therapeutic targets. To identify these biological factors, many techniques have been developed over the years. In this article, we review newly identified aberrantly expressed genes and proteins, chromosomal changes, DNA copy number abnormalities, and other genetic changes that may be important in the pathogenesis and biological behavior of two frequent pediatric brain tumor subtypes, medulloblastomas and ependymomas.

**View this table:** [Table 1](#). Hereditary syndromes predisposing to the development of a brain tumor  
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## ► Medulloblastoma

### *Clinical Aspects*

Medulloblastoma is the most common embryonal CNS tumor of childhood

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and is likely composed of biologically different subsets of tumors arising from stem and/or progenitor cells of the cerebellum. The World Health Organization recognizes at least five different histological types of medulloblastoma, and there is increasing evidence that prognosis and possibly response to therapy depend on the tumor's cell of origin and the cellular pathways active in tumor development and growth.

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Medulloblastomas, which by definition arise in the posterior fossa, are conventionally stratified on the basis of clinical parameters, such as extent of tumor at the time of diagnosis and completeness of surgical resection, into average-risk and high-risk (poor-prognosis) disease.<sup>2</sup> For children older than 3 years with nondisseminated disease and for partially resected "high-risk" disease, standard therapy includes both treatment with radiotherapy and adjuvant chemotherapy.<sup>3</sup> Five-year disease-free survival rates of 80% or more are now being reported by multiple groups for patients with average-risk medulloblastoma, and a major focus of new treatment approaches is the development of innovative ways to reduce long-term toxicity of therapy.<sup>3</sup> Approaches that have been used and are under study include reduction of the total dose of craniospinal radiation therapy, reduction of the volume of local boost radiotherapy, and use of less neurotoxic chemotherapeutic agents.<sup>3</sup> Even in patients with high-risk disease, with current means of treatment, 5-year survival rates of 60% or more are now being reported.<sup>4</sup> Most therapeutic approaches for "high-risk" patients have continued to use relatively high doses of craniospinal radiation therapy and aggressive chemotherapeutic approaches.<sup>4</sup>

The treatment for infants with medulloblastoma remains highly problematic. The volumes and doses of radiotherapy required for disease control cause significant brain injury in patients of all ages and predominantly manifest as long-term neurocognitive sequelae, but they are especially damaging in the very young child.<sup>5</sup> For this reason, most therapeutic approaches have focused on either delaying or eliminating radiotherapy by the use of increasingly aggressive chemotherapeutic approaches that have incorporated potentially neurotoxic drugs, such as methotrexate, or high-dose chemotherapy supported by autologous peripheral stem cell rescue.<sup>6</sup> There is some suggestion that such approaches are more effective, but some of these apparent improvements in survival may also be related to separation of more aggressive tumors, such as atypical teratoid/rhabdoid tumors, from the cohort of patients treated or the inclusion of lower-risk patients, such as those with desmoplastic tumors, in treatment protocols.<sup>7</sup> A major hope for the future is that the incorporation of biological agents targeting specific signaling pathways will not only make treatment more effective, but also allow a reduction in neurotoxic therapy.

### **Genetic and Biological Aspects**

**Developmental Signaling Pathways.** Several hereditary syndromes predispose to the development of a brain tumor ([Table 1](#)), and the underlying gene defects are thought to provide information about the critical genes in the pathogenesis of brain tumors. The genes mutated in syndromes predisposing to medulloblastoma development are frequently involved in cellular signaling pathways ([Table 2](#)), which are important regulators of brain development, such as sonic hedgehog (SHH), Wnt, and Notch ([Fig. 1](#)).

**View this table:** **Table 2.** Differentially expressed genetic and proteomic markers identified in [\[in this window\]](#) medulloblastomas and ependymomas [\[in a new window\]](#)

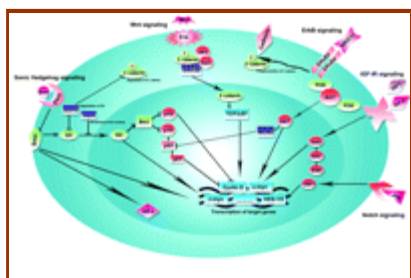


Fig. 1. Signaling pathways involved in the development of the brain and pathogenesis of medulloblastoma and ependymoma. Deregulation of these pathways is important in the pathogenesis of medulloblastoma and ependymoma. Interactions among these pathways are multiple and complex.

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**Sonic Hedgehog Signaling.** Gorlin's syndrome is an autosomal dominant disorder that is characterized by multiple developmental defects and a predisposition for basal cell carcinoma, rhabdomyosarcoma, and medulloblastoma.<sup>8</sup> The tumor suppressor gene *Patched 1 (PTCH1)* on chromosome 9q22.3, encoding a transmembrane surface receptor for hedgehog proteins, is mutated in this syndrome. The hedgehog–Patched signaling pathway controls normal development of the external granular layer of the cerebellum.<sup>9</sup> SHH, produced by Purkinje cells, binds to the PTCH1 receptor and induces proliferation of cerebellar granule cell precursors by relieving the inhibition of *Smo* and inducing activation of the Gli family of transcription factors.<sup>9</sup> Mutations in various components of the SHH pathway, such as *PTCH1* and *Smo*, occur in approximately 30% of sporadic medulloblastomas, predominantly desmoplastic medulloblastomas (Table 2). These tumors show up-regulation of important SHH target genes, such as *Gli1* and *BMI1*, indicating active SHH signaling. *BMI1* is overexpressed in medulloblastomas, which might result in the abnormal regulation of both the Rb and p53 pathways.<sup>10</sup> The importance of the SHH pathway in medulloblastoma is underlined by the observed growth inhibition after treatment with inhibitors of the SHH pathway.<sup>11</sup> Because only a small subset of *PTCH1* +/- mice develop medulloblastoma, other genetic events are thought to influence the susceptibility of developing medulloblastoma. For example, concomitant loss of *p53* or *Ink4C* has been shown to facilitate the development of medulloblastoma.<sup>12</sup>

**Wnt Signaling.** The Wnt signaling pathway may also be involved in regulating the embryonal development of the brain. One of the genes involved in this pathway, adenomatous polyposis coli (*APC*), is mutated in patients with Turcot's syndrome, who have a predisposition to develop colon cancers, glioblastomas, and

medulloblastomas (Table 2). APC forms a protein complex together with  $\beta$ -catenin, glycogen synthase kinase  $\beta$  (GSK3- $\beta$ ), and axin.<sup>13</sup> Activation of the Wnt pathway results in decreased  $\beta$ -catenin degradation followed by the interaction with TCF/LEF transcription factors and activation of Wnt targets, such as c-Myc, cyclin D1, and AXIN2.<sup>14</sup> Activating mutations in the Wnt pathway occur in a substantial number of medulloblastomas (Table 2).<sup>15,16</sup> Most mutations have been found in the  *$\beta$ -catenin* gene, but mutations in the *APC* and *AXIN2* genes and deletions of the *AXIN1* gene have also been described (Table 2). However, deletions of *AXIN1* were also identified in normal brain tissue, suggesting that at least some of the *AXIN1* deletions found in medulloblastoma represent polymorphisms or PCR artifacts.<sup>17</sup> Another marker associated with activation of the Wnt signaling pathway is increased expression of survivin, an apoptosis inhibitor (Table 2). Survivin expression is related to an unfavorable outcome, independent of clinical staging or tumor histology.<sup>18,19</sup> SOX gene family members can also regulate the Wnt signaling pathway.<sup>20</sup> Interestingly, *SOX4* and *SOX11* are overexpressed in predominantly classic medulloblastoma.<sup>21–23</sup>

The SHH and Wnt signaling pathways interact with each other, but also with other signaling pathways, including Notch, ErbB, and insulin-like growth factor (IGF) (Fig. 1). For example, cyclin D1, an important mediator of the proliferation of cerebellar granule cell precursors, is an important downstream target of SHH, Wnt, and Notch signaling. Moreover, medulloblastomas of *PTCH1* +/- mice show increased expression of genes involved in activation of both SHH and Wnt signaling.<sup>24</sup>

**Notch Signaling.** In the cerebellum, Notch2 is predominantly expressed in proliferating cerebellar granule cell precursors, whereas Notch1 is found in differentiated internal granule layer neurons.<sup>25</sup> Notch2 is overexpressed in a subset of medulloblastomas, whereas Notch1 expression is scarce. Activation of the Notch signaling pathway results in the transcriptional activation of helix-loop-helix transcription factors HES1 and HES5.<sup>26</sup> HES1 expression is associated with decreased survival rates of medulloblastoma patients (Table 2). It has been recently hypothesized that HES1 forms transcriptional repressor complexes with FOXG1 to negatively regulate the differentiation of neural progenitor cells.<sup>27</sup> Interestingly, the function of the *FOXG1* gene is deregulated in most medulloblastomas (Table 2). Treatment of medulloblastoma xenografts with inhibitors of the Notch signaling pathway results in decreased proliferation and increased apoptosis.<sup>28</sup>

**ErbB Signaling.** ErbB belongs to the receptor tyrosine kinase family I, which consists of four receptor tyrosine kinases (ErbB1–ErbB4) and a variety of ligands, including several neuregulins that are important in regulating the development of neuronal tissue.<sup>29</sup> ErbB4, especially the CYT1 isoform, is overexpressed in tumors with low Gli1 levels, which suggests that ErbB signaling is regulated by SHH signaling.<sup>30</sup> CYT1 is the only isoform of ErbB4 that is able to activate antiapoptotic phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB)/AKT signaling,<sup>31</sup> which is important in medulloblastoma development. Overexpression of the CYT1 ErbB4 isoform correlates with the anaplastic medulloblastoma subtype and ErbB2 expression levels. Because the ErbB2 gene is located on chromosome 17q11.2–q12, a region that is frequently gained in medulloblastomas, ErbB2 is regarded as a potential medulloblastoma oncogene. ErbB2 expression, especially in combination with high ErbB4 expression, has poor prognostic impact in medulloblastoma and is associated with the presence of metastases and a high mitotic index.<sup>29,32</sup> Overexpression of ErbB2 increases the migration of

nedulloblastoma cells in vitro, and prometastatic genes involved in, for example, cell adhesion and invasion are up-regulated by ErbB2.<sup>33</sup> Approximately one-third of the medulloblastomas coexpressing ErbB2 and ErbB4 also express the ErbB ligand NRG1- $\beta$ , suggesting an autocrine loop resulting in disease progression. Interestingly, one of the targets of NRG1- $\beta$  is *c-myc*.<sup>34</sup>

***c-myc* Signaling.** *c-Myc* belongs to the myc transcription factor family, which is important in cell cycle regulation, proliferation, and differentiation and is involved in many human malignancies.<sup>35</sup> *c-Myc* overexpression in medulloblastoma is associated with the large-cell/anaplastic subtype and poor survival (Table 2). *c-myc* activation can be caused by activation of the SHH and Wnt pathways,<sup>36</sup> translocations, activating mutations, viral insertion, and genomic amplification. In mouse models, *c-Myc* alone is not sufficient to induce medulloblastomas, but it is suggested that *c-Myc* cooperates with SHH in the pathogenesis of medulloblastoma.<sup>37</sup> The *c-Myc* binding protein JPO2 can potentiate *c-Myc* transforming activity and is associated with metastatic medulloblastoma (Table 2). We observed up-regulation of mRNA levels of BCAT1, a *c-myc* target, in metastatic medulloblastoma and also detected the BCAT1 protein in the cerebrospinal fluid of medulloblastoma patients.<sup>22</sup> Another member of the myc family, *n-myc*, is amplified in approximately 5% of medulloblastomas and is an important and direct target of the SHH signaling pathway promoting cell cycle progression in the developing cerebellum (Table 2). In concordance, *n-myc* up-regulation is observed in medulloblastoma associated with activated SHH signaling.<sup>38,39</sup> *n-myc* amplification correlates with unfavorable survival, but this correlation is less clear than for *c-myc*.<sup>40</sup> Prevention of *n-Myc* degradation by PI3K<sup>41</sup> may provide an explanation for the enhancing effect of IGF/PI3K signaling pathway on the SHH-related development of medulloblastoma.<sup>39</sup>

***IGF/PI3K* Signaling.** The IGF system also plays an important role in neuronal development and is involved in the development of brain tumors.<sup>42</sup> Most medulloblastomas overexpress the IGF-1 receptor (IGF-1R) protein, and more than half of medulloblastomas express the activated phosphorylated form of IGF-1R (Table 2). Moreover, activated forms of downstream signaling molecules of IGF-1R, such as insulin receptor substrate-1 (IRS-1), PI3K, AKT/PKB, Erk-1, and Erk-2, are detected in most medulloblastomas. Inhibition of IGF-1R signaling reduces medulloblastoma tumor growth.<sup>43</sup> This inhibition is augmented by constitutive GSK3- $\beta$  phosphorylation,<sup>44</sup> suggesting that the combined inhibition of the IGF-1R and dephosphorylation of GSK3- $\beta$  might be an effective treatment for medulloblastoma. The IGF-1R ligands IGF-1 and IGF-2 are important mitogens in cerebellar granule precursors and medulloblastoma.<sup>45,46</sup> Patti et al.<sup>46</sup> showed the presence of an autocrine loop causing IGF-1R activation and leading to proliferation in a medulloblastoma cell line. IGF-2 is a downstream target of SHH signaling,<sup>47</sup> and in concordance, IGF-2 overexpression is predominantly observed in desmoplastic medulloblastomas. The IGF-binding proteins (IGFBPs) modulate IGF action and are differentially expressed in brain tumors. We have observed increased IGFBP-2 and IGFBP-3 mRNA expression levels in medulloblastoma, which is accompanied by increased IGFBP-3 levels and IGFBP-3 proteolysis in the cerebrospinal fluid of brain tumor patients.<sup>48</sup> The IGF-1R signaling pathway may result in activation of AKT and PI3K, and also *ras*/MAPK (mitogen-activated protein kinase) signaling. Downstream targets of the *ras*/MAPK pathway and platelet-derived growth factor receptor B (PDGFRB) are up-regulated in metastatic medulloblastoma (Table 2).

## ► Cells of Origin

*lateral Cerebellar Hemispheres.* Activation of different signaling pathways in different medulloblastoma subtypes suggests that medulloblastomas have different origins. Potential cells of origin are the stem and/or progenitor cells in the external granular layer that have persisted after the first years of life and the pluripotent stem cells of the ventricular subependymal matrix, which are capable of differentiating into neuronal or glial cells. Several findings support this hypothesis of double origin. Desmoplastic medulloblastomas are usually found in the cerebellar hemispheres and are thought to arise from neural precursor cells in the external granule layer.<sup>49</sup> In concordance, they are characterized by activated SHH signaling and IGF-2 overexpression which affects the proliferation of cerebellar granule precursors. CXCR4, ATOH1, and the p75 neurotrophin receptor (p75<sup>NTR</sup>) are markers of the stem and/or progenitor cells in the external granular layer and are predominantly found in desmoplastic medulloblastomas (Table 2). CXCR4 is important for migration and cell cycle control of granular precursors and is a target of SHH. Aberrant activation of the CXCR4 receptor might contribute to an increased malignant potential, but mutations in CXCR4 are only rarely observed in medulloblastoma. ATOH1 is a basic helix-loop-helix transcription factor that influences the development of granular cerebellar precursors via the Notch pathway.<sup>50</sup> p75<sup>NTR</sup> belongs to the family of neurotrophins and neurotrophin receptors, which are important in the normal development of the cerebellum.<sup>51</sup> Expression of p75<sup>NTR</sup> is suggested to be a marker of tumor progression (Table 2). Another neurotrophin receptor, TrkC, is one of the first biological markers in medulloblastoma and is a strong predictor of favorable outcome (Table 2) probably because binding of the TrkC ligand to the receptor induces apoptosis.<sup>51</sup>

*Cerebellar Vermis.* In contrast to desmoplastic medulloblastomas arising in the lateral cerebellar hemispheres medulloblastoma subtypes arising in the cerebellar vermis are suggested to originate from cells in the ventricular matrix and Purkinje neurons. Calbindin and NeuroG1 expression are specific for stem and/or progenitor cells in the cerebellar ventricular zone. Calbindin is expressed in most classic medulloblastomas, and its expression may be a marker for recurrence in medulloblastoma (Table 2). NeuroG1 (NeuroD3) belongs to the NeuroD family of basic helix-loop-helix transcription factors, regulating the transcription of genes involved in neuronal differentiation.<sup>52</sup> NeuroG1 expression is correlated with the overexpression of myc and is indicative of a poor prognosis in medulloblastoma (Table 2).

OTX2 (head development gene) overexpression, observed in more than two-thirds of medulloblastomas, is also characteristic for the classic medulloblastomas arising in the cerebellar vermis (Table 2). However, because cells of the fetal external granular cerebellar layer are also shown to express OTX2, a subset of classic medulloblastomas negative for calbindin may also arise from the external granular layer.<sup>53</sup> OTX2 expression is correlated to the presence of proliferating, poorly differentiated cells with anaplastic features, but no correlation with outcome has been observed. Amplification of OTX2 occurs in up to one-third of primary medulloblastomas, but mutations have not been identified. OTX2 knockdown, either by small interfering RNAs

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biological background of pediatric medulloblastoma and ependymoma: A review from a translational rese... Page 8 of 30  
by treatment with all-*trans*-retinoic acid, induced apoptosis *in vitro*, which suggests that OTX2 might be an interesting therapeutic target.<sup>54</sup>

**Cytogenetics.** Much knowledge about cytogenetic abnormalities of brain tumors has been obtained by conventional cytogenetic, loss of heterozygosity (LOH), and molecular genetic analyses, for example, comparative genomic hybridization (CGH). Karyotyping reveals that balanced translocations are relatively infrequent in medulloblastomas (Table 3) compared with chromosomal gains and losses. No recurrent translocations have thus far been identified in medulloblastoma. Fig. 2 summarizes the chromosomal gains and losses in medulloblastomas identified by CGH. Conventional CGH can detect regions of copy number change, and the recent development of array-based CGH has resulted in higher-resolution analyses allowing more precise definition of which regions are involved. In addition, correlation of these data with gene expression levels may identify genes that are potentially important driver genes in these copy abnormalities.

**View this table:** Table 3. Balanced chromosomal translocations identified in medulloblastomas and ependymomas.  
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Fig. 2. Copy number aberrations and amplifications in medulloblastomas ( $n = 455$ )<sup>56,65,67,68,70,136,163,165,202,224-236</sup> and ependymomas ( $n = 354$ )<sup>97,99,100,113,237-245</sup> by CGH. Some studies provided only a summary of data<sup>62-64,88,98</sup> or did not distinguish between medulloblastomas and primitive neuroectodermal tumors,<sup>246</sup> and we excluded those results here. The numbers at the tops of the graphs indicated chromosome number.

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**Chromosome 17.** The most commonly reported cytogenetic change in medulloblastoma is loss of 17p in up to approximately 50% of medulloblastomas, often associated with a gain of 17q leading to the formation of an isochromosome 17q [i(17q)].<sup>55</sup> Because i(17q) can be found as a single structural abnormality, it may be a

primary event in medulloblastoma development. In some studies, loss of 17p was associated with a poor prognosis, while others failed to find this association.<sup>56,57</sup> The incidence of i(17q) is low in desmoplastic medulloblastoma compared with classic and large-cell anaplastic medulloblastoma. Despite the identification of several common chromosomal breakpoint regions at 17p11.2, 17p11.2–17q11.2, and 17q21.31 and various commonly deleted regions on 17p, for example, 17p13.1 and 17p13.3,<sup>58,59</sup> the affected tumor suppressor gene involved in the pathogenesis of medulloblastoma has not been identified thus far.

*p53*, one of the most important tumor suppressor genes, was initially suggested to be of importance in medulloblastoma, because it is localized on chromosome 17p13. However, despite the facts that (1) patients with germline *p53* mutations have a predisposition to develop medulloblastomas (Table 1), (2) loss of *p53* facilitates medulloblastoma development in mouse models,<sup>12</sup> and (3) up to 40% of medulloblastomas show *p53* protein expression indicating a dysfunctional *p53* protein, we and others have shown that the incidence of *p53* mutations in sporadic medulloblastoma is low (Table 2). Overexpression of the *p53* binding protein MDM2, known to cause inactivation of *p53*, is also very rare in medulloblastomas (Table 2). *p53* inhibition by PAX5 (early development gene) is suggested to play a role in medulloblastomas as the expression of PAX5 is deregulated in approximately 70% of cases (Table 2).

Besides *p53*, several other candidate tumor suppressor genes on 17p have been suggested. Interestingly, 17p carries several genes suggested to be involved in the regulation of SHH signaling. *HIC1*, located on 17p13.3, is aberrantly methylated in medulloblastoma, and the subsequent transcriptional silencing is associated with poor outcome (Table 2). Recently, loss of *HIC1* together with loss of *PTCH1* was found to result in a higher incidence of medulloblastomas.<sup>60</sup> This is probably related to the cooperation of *HIC1* and *PTCH1* in the silencing of *ATOH1* expression, which is required for medulloblastoma growth. *REN<sup>KCTD11</sup>*, a putative tumor suppressor gene located on chromosome 17p13.2, is deleted in 39% of medulloblastomas (Table 2). *REN<sup>KCTD11</sup>* inhibits medulloblastoma cell proliferation by antagonizing the activation of SHH target genes. Deletion of this gene might thus result in enhanced SHH signaling and increased proliferation of granule cell precursors. The myc inhibitor *Mnt*, mapped to 17p13.3, is also deleted or underexpressed in medulloblastoma. Because c-myc and n-myc are both targets of SHH signaling, loss of the *Mnt* gene on 17p might again link this chromosomal abnormality to SHH signaling.

Gain of 17q can also occur in the absence of a 17p deletion, suggesting that duplication of genes on 17q influence medulloblastoma development. An amplicon on 17q23.2 contains the *APPBP2* and *PPM1D* genes.<sup>59</sup> *PPM1D* overexpression can, for example, inhibit *p53* tumor suppressor activity.<sup>61</sup> Because the regions of loss of 17p and gain of 17q are large, the gene dosage effect of genes on 17p and 17q, rather than one tumor suppressor gene, may be tumorigenic in medulloblastoma.<sup>59</sup>

**Chromosome 7.** A cytogenetic abnormality that is often seen in combination with a gain of 17q is gain of chromosome 7. As for chromosome 17, the gene of interest is not yet identified. Hui et al.<sup>62</sup> found an amplification core at 7q34–q35 containing several oncogenes. A novel amplicon at 7q21.2 contained only the *CDK6* gene. Cyclin-dependent kinase 6 (CDK6) can phosphorylate retinoblastoma 1 (RB1), which is an

important regulator of proliferation and differentiation. CDK6 is overexpressed and indicates poor prognosis in medulloblastomas (Table 2).

**Other Copy Number Abnormalities.** Other recurrent abnormalities in medulloblastomas are losses on 6q, 8p, 10q, 11, 16q, 20, X, and Y and gains on 1q, 2p, 4q, 6q, 9p, 13q, 14q, and 18 (Fig. 2). Several regions with consistent copy number gain have been identified on 1q, for example, 1q21.3–23.1,<sup>62</sup> 1q32.1,<sup>62,63</sup> and 1q32.3–qter.<sup>63,64</sup> *HLX1* is suggested to be involved in the gain on 1q, because its expression was markedly increased in medulloblastomas.<sup>65</sup> Concerning losses on 6q, a small region of deletion is identified at 6q23.1.<sup>65</sup> The commonly deleted region on 8p is localized between 8p21.3 and 8p23.2, adjacent to the tumor suppressor gene *DLC1*.<sup>64,66</sup> The minimal region of overlap of losses on chromosome 16q is at the distal end of 16q, at 16q22.2–qter.<sup>67</sup> Regarding losses of chromosome 10, several minimal regions of overlap are observed, one involving the 10q23 region containing the *PTEN* gene, another involving a hemizygous deletion at 10q25.1, and a third involving the 10q26.3 region.<sup>67–69</sup> The *SUFU* gene, described as being mutated in a small subset of medulloblastomas, maps to 10q24.3 and is therefore suggested to have a role as tumor suppressor gene (Table 2). Loss of 11p is identified in 10%–20% of medulloblastomas (Fig. 2). However, LOH analyses show allelic loss of 11p in >50% of tumors.<sup>69</sup> Minimal overlapping regions of loss on chromosome 11 are 11pter–11p11.2 and 11q13.2–11qter. The region of gain on 14q is mapped to 14q12 and contains the *FOXG1* gene, which is aberrantly expressed in most medulloblastomas (described above; see "Notch signaling"). Loss of chromosome 20 frequently involves the whole chromosome. However, recently the commonly deleted region on chromosome 20 is identified at 20q13.2–q13.3,<sup>62,64</sup> but no target genes have been identified yet.

**Amplifications.** Gene amplifications are relatively rare in medulloblastomas. The identified amplification sites are displayed in Fig. 2. Several potential oncogenes are involved in these amplifications. *MYCL1* is an important candidate gene in the amplification region on chromosome 1p34.<sup>64</sup> The *c-myc* and *n-myc* genes on chromosomes 8q24 and 2p24, respectively, are amplified in a small proportion of tumors, mainly large-cell anaplastic medulloblastoma (Table 2). However, gain of 8q, including the three ribosomal genes *EEF1D*, *RPL30*, and *RPS20*, is also predictive of poor outcome independent of *myc* (Table 2). The amplicon on 5p15 involves the *hTERT* gene, known to be amplified and overexpressed in medulloblastoma (Table 2). *hTERT* is able to compensate for progressive telomere shortening, leading to immortalization. Amplification of *hTERT* is associated with tumor progression in medulloblastoma. Further analysis of the 9p amplification suggested the importance of the 9p23–p24 region, including the *JMJD2C* gene. The 11q22.3 region maps the cyclin D1 locus, which is amplified in a variety of tumors. A possible candidate gene for the 13q34 amplification is *IRS-1*,<sup>70</sup> which is amplified and overexpressed in a small subset of glioblastomas.

**Epigenetics.** Recently, epigenetic changes have also been shown to be important in tumorigenesis. Both histone modifications (acetylation, methylation, and phosphorylation) and hypermethylation of CpG motifs in promoter regions may induce transcriptional silencing of tumor suppressor genes.<sup>71</sup> Several putative tumor suppressor genes are aberrantly methylated in subgroups of medulloblastoma (Table 2). RASSF1A (RAS association domain gene) regulates cyclin D1 expression, which is important in controlling the cell cycle. In

In contrast to other malignancies, hypermethylation of *RASSF1A* in medulloblastoma is not accompanied by allelic loss of 3p21.3 or mutation, indicating that biallelic loss is the primary mechanism of inactivation of *RASSF1A*.<sup>72</sup> *CASP8* is a cysteine protease involved in death-receptor-mediated apoptosis.<sup>73</sup> We and others have shown that promoter hypermethylation of *CASP8* leading to loss of *CASP8* mRNA expression induces resistance to apoptosis induced by tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) in embryonal tumors of childhood, such as medulloblastoma and neuroblastoma.<sup>74</sup> In primary tumors, aberrant promoter methylation of *CASP8* was seen most frequently in classic and anaplastic medulloblastoma and is an independent unfavorable prognostic factor. Transcriptional silencing of *SGNE1/7B2*, a gene located on 5q11–15, occurs predominantly in classic medulloblastoma. *SGNE1* is a calcium-dependent serine protease that inhibits tumor cell proliferation. *ZIC2* is a zinc-finger transcription factor essential for the developing CNS, and its expression is down-regulated in medulloblastomas.<sup>75</sup> *p18<sup>INK4C</sup>* is a CDK inhibitor, and loss of expression of this gene can induce medulloblastoma in mouse models in collaboration with loss of *PTCH1* or *p53*.<sup>76</sup> Three members of the S100 gene family are found to be aberrantly methylated in 10%–20% of medulloblastomas (Table 2). Hypermethylation and silencing of *S100A6* is associated with the large-cell anaplastic subtype of medulloblastoma. In contrast, *S100A4* is hypomethylated, which results in increased expression. The prometastatic gene *S100A4* is a direct target of ErbB2 signaling, associated with a poor prognosis in medulloblastoma. *MCJ*, a member of the DNAJ protein family that influences chemotherapy resistance, can be inactivated by biallelic hypermethylation, but hypermethylation of one allele also occurs in combination with genetic loss of the second allele (Table 2). *Dickkopf-1 (DKK1)* is epigenetically silenced in medulloblastoma by histone acetylation in the promoter region (Table 2). *DKK1*, a Wnt signaling antagonist, is an important suppressor of cell growth and inducer of apoptosis.

**Proteomics.** Despite enormous progress in applications and sensitivity, proteomic techniques are not frequently used to screen for aberrantly expressed proteins in brain tumors. The proteome of two representative medulloblastoma cell lines, DAOY and D283MED, has been studied by two-dimensional gel electrophoresis with subsequent matrix-assisted laser desorption/ionization identification.<sup>77</sup> Several proteins described previously in other malignancies, such as SIP or HSP27 and other new candidate tumor-related proteins, were identified. We studied protein expression profiles of primary medulloblastomas using two-dimensional difference gel electrophoresis followed by mass spectrometry and found *STMN1* to be overexpressed in medulloblastoma (Table 2).

## ► Ependymoma

### **Clinical Aspects**

Ependymomas, predominantly occurring in the posterior fossa in childhood, may also arise supratentorially and account for approximately 10% of all intracranial tumors in childhood and a higher proportion, up to 30% in some series, in children younger than 3 years.<sup>78</sup> A variety of different subtypes of ependymomas have been identified, and the

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anaplastic variant seems to carry a worse prognosis.<sup>78,79</sup> Surgery remains a major component of the management of ependymomas, and patients with posterior fossa ependymomas who have tumors amenable to gross total resections and are subsequently treated with radiotherapy have a 70% or greater likelihood of long-term disease control and possible cure.

Recent studies have focused on the utility of chemotherapy followed by second-look surgery prior to radiotherapy in those patients whose tumors are not totally, or near-totally, resected.<sup>80</sup> Increasing evidence suggests that ependymomas are chemosensitive, but in older children chemotherapy has been primarily reserved for those patients with subtotally resected tumors or with anaplastic lesions. Conformal radiation therapy techniques are primarily used in children with ependymomas, and radiotherapy has now been used in cooperative group studies in children as young as 1 year. In very young children, especially those younger than 1 year, treatment with chemotherapy is often used in attempts to delay and, in select cases, obviate the need for radiotherapy, but high-dose chemotherapeutic regimens supported by autologous peripheral stem cell rescue have not been effective.<sup>80</sup> The incidence of leptomeningeal dissemination at the time of diagnosis has varied significantly among series, but in general, less than 10% of children will have disseminated disease at the time of diagnosis, and craniospinal radiotherapy is reserved for those with documented disseminated disease. Increasing evidence suggests that supratentorial ependymomas differ biologically from those arising in the posterior fossa. Although standard treatment of partially resected supratentorial ependymomas is the same as for partially resected posterior fossa tumors, studies are evaluating the efficacy of surgery alone for totally resected supratentorial tumors.

### **Genetic and Biological Aspects**

**Developmental Signaling Pathways.** Unfortunately, biological characteristics of ependymomas are largely unknown. This is mainly because ependymoma is a heterogeneous disease and can be subdivided into a wide range of subgroups based on histology and localization, which results in relatively small series of patients.

**NF2.** As in medulloblastomas, genetic syndromes associated with a predisposition to develop ependymomas, such as neurofibromatosis type 2 (NF2) (Table 1), were initially thought to provide clues about the genetic abnormalities involved in the pathogenesis of ependymomas. The *NF2* gene is located on 22q12, and because allelic loss of chromosome 22 is frequently observed in ependymomas, *NF2* was suggested to be a tumor suppressor gene involved in the development of ependymomas. However, mutations of the *NF2* gene are rarely observed in sporadic ependymomas, except for the spinal ependymomas (Table 2). Inactivation of *NF2* by hypermethylation is also rare (Table 2). Interestingly, although *NF2* does not play an important role in sporadic nonspinal ependymomas, the expression of *SCHIP-1*, an *NF2*-interacting gene, is significantly down-regulated in pediatric ependymomas (Table 2).

**MEN1.** Other hereditary forms of ependymoma are uncommon. Ependymomas have been described in patients with MEN1 syndrome, which is characterized by the development of multiple endocrine tumors.<sup>81</sup> The *MEN1* gene is located on chromosome 11q13, a region that is involved in allelic losses and rearrangements in ependymomas.<sup>82</sup> However, mutations in the *MEN1* gene are described in only a small number of recurrent ependymomas (Table 2).

An important recent finding is that gene expression signatures of ependymomas from different locations of the CNS correlate with those of the corresponding region of the normal developing CNS.<sup>83</sup> The differentially expressed genes are predominantly involved in the regulation of neural precursor cell proliferation and differentiation. In addition, ependymomas contain rare populations of cancer stem cells resembling radial glial cells, which are sufficient to give rise to tumor development in mice.<sup>83</sup> Therefore, these radial glial cells in different parts of the CNS may be predisposed to acquire distinct genetic abnormalities that transform them into cancer stem cells of supratentorial, infratentorial, and spinal ependymomas. These data imply that signaling pathways involved in the development of the brain and neural stem cells, such as Notch, Wnt, SHH, and p53, are important in the pathogenesis of ependymomas (Fig. 1).

**EPHB-EPHRIN and Notch Signaling.** Active EPHB-EPHRIN (intercellular tyrosine kinase signalling) and Notch signaling is indeed observed in ependymomas, especially in those located in the supratentorial region (Table 1). Both signaling pathways are important for the maintenance of neural stem cells in the cerebral subventricular zone.<sup>84,85</sup> The overexpression of the Notch target ErbB2 in most ependymomas and its correlation with proliferation and poor outcome also point to the importance of Notch signaling in ependymomas.

**Wnt Signaling.** Ependymomas have been described in patients with APC mutations associated with Turcot's syndrome.<sup>86</sup> However, in contrast to medulloblastomas, mutations in APC and  $\beta$ -catenin are not found in sporadic ependymomas (Table 2). Despite the absence of these mutations, gene expression profiling identifies aberrantly expressed genes involved in the Wnt signaling pathway, suggesting alternative mechanisms for disruption of this pathway.<sup>87</sup>

**SHH Signaling.** Involvement of SHH signaling in ependymomas is suggested by the overexpression of GLI2, a Gli-Kruppel family member (Gli), and serine threonine kinase 36 (STK36) and underexpression of ROR1B.<sup>88</sup> In addition, overexpression of the SHH target IGF-2 is frequently observed in these tumors (Table 2). Besides the overexpression of IGF-2, we have found overexpression of IGFBP-2, -3, and -5 in ependymomas, also suggesting the involvement of the IGF system in the pathogenesis of ependymomas.<sup>48</sup>

**p53 Signaling.** Only one patient with a germline p53 mutation has been reported with an ependymoma.<sup>89</sup> Despite the fact that p53 immunostaining is suggested to be associated with an unfavorable prognosis,<sup>90</sup> p53 mutations are extremely rare in sporadic ependymomas (Table 2). Other methods of p53 inactivation have been observed in subgroups of ependymomas but are also relatively uncommon. Some report a high incidence of *mdm2* expression and amplification in ependymomas, whereas others conclude that *mdm2* plays a role in only a very small number of patients (Table 2). *p73*, a gene that shares structural and functional homologies with p53 and is able to induce *mdm2*, is overexpressed in grade II ependymoma (Table 2). Inhibition of p53 expression by PAX5 is not of importance in ependymomas. The negative regulation of p53 by p14<sup>ARF</sup> is recently suggested to be of importance in subgroups of ependymomas. p14<sup>ARF</sup> is located on chromosome 9p21 together with two other tumor suppressor genes, p15<sup>INK4B</sup> and p16<sup>INK4A</sup>, which are all cell cycle regulators.<sup>91</sup> Expression of these genes is decreased by homozygous deletion, promoter

hypermethylation, or point mutations in several malignancies. In ependymomas, decreased levels of p14<sup>ARF</sup> protein correlate with increased tumor grade and p53 protein accumulation.<sup>92</sup> Deletion of the *16<sup>INK4A</sup>/p14<sup>ARF</sup>* locus has recently been associated with supratentorial ependymomas (Table 2). The observed frequency of inactivation by hypermethylation of the three tumor suppressor genes in ependymomas is variable (Table 2) and is observed more frequently in adults than in children.

**Gene Expression and Clinical Characteristics.** Although recent gene expression profiling studies from our and other laboratories have correlated sets of genes to patient characteristics, tumor location, and tumor grade, the significance of these genes in the pathogenesis of ependymomas still needs to be determined. Genes that are overexpressed in ependymomas compared with normal control tissue include *GLU*, *RAF1*, *SOX9*, *calyphosine*, *annexin A1*, and *YAP1*. We have shown that *SOX9* expression was associated with a favorable outcome in pediatric ependymomas (Table 2). Several genes are characteristic for tumor location. Intracranial ependymomas are characterized by the overexpression of *EMX2*, *MSI2*, *ABCG1*, *FLT1*, *TOP2A*, *CRIM1*, *AMK2D*, *TFPI2*, *EBI2*, *ACTR3*, *NRCAM*, *PAX3*, *NET1*, and *MSX1*, in which the first three were specifically up-regulated in supratentorial ependymomas and the last three in infratentorial ependymomas. *ADAM9*, *TFAM*, *EDN1*, and *GAS2L1* were down-regulated in intracranial ependymomas. HOX genes might play a role in the maintenance of the cancer stem-cell phenotype in spinal ependymomas, because HOX family members, such as *HOXB5* and *HOXA9*, are predominantly overexpressed in spinal ependymomas.<sup>83</sup>

Underexpression of proapoptotic nuclear factor- $\kappa$ B2 (NF- $\kappa$ B2) and pleckstrin and the overexpression of a PTEN homologue are associated with tumor recurrence.<sup>93</sup> Several genes, such as *NRCAM*, *COL4A2*, *CDK4*, and *survivin*, are overexpressed in ependymomas with high proliferation indices.<sup>94,95</sup> Tumor proliferation, reflected by Ki-67 positivity, is an important factor in the discrimination between low- and high-grade ependymoma and is a more reliable unfavorable prognostic factor than is histological grading.<sup>96</sup>

**Cytogenetics.** As is described for medulloblastomas, advanced cytogenetic techniques now allow more precise determination of chromosomal breakpoint regions and the identification of the genes involved. Table 2 and Fig. 2 provide the identified balanced translocations and a summary of observed copy number aberrations in ependymomas, respectively.

**Recurrent Copy Number Abnormalities.** Frequently observed copy number abnormalities in ependymomas are losses of 6, 9p, 10, 11, 13, 17, and 22 and gains of 1q, 5, 7, 9, and 12. Gain of 1q, for example, occurs more frequently in children than in adults, correlating with an intracranial tumor localization and grade III ependymomas.<sup>97,98</sup> More specified regions on chromosomes 1q, 1q21.1–32.1, and 1q25 are associated with unfavorable outcome.<sup>98,99</sup> As in medulloblastoma, the 5p15.3 region, containing the *hTERT* gene, is frequently gained in ependymomas, and high *hTERT* expression is associated with proliferation and unfavorable outcome (Table 2). Loss of 6q is associated with intracranial, predominantly infratentorial, tumors.<sup>100</sup> Gain of chromosome 7 is predominantly found in spinal cord tumors,<sup>97,100</sup> and gain or high-level amplification of epidermal growth factor receptor (EGFR) at 7p11.2 also predicts prognosis in intracranial tumors.<sup>98</sup> Another region of gain on 7p21 contains the candidate proto-oncogenes *TWIST1* and *HDAC9*,<sup>88</sup>

and a small region on 7q34 contains the *ARHGEF5* gene.<sup>98</sup> Gain of chromosome 12q and loss of chromosome 13 are predominantly observed in intracranial ependymomas.<sup>97,98</sup> *HOXC4* and *CDK4* on 12q13 are mentioned as genes important in the 12q gain.<sup>98,100</sup> Loss of 17p13.3 is associated with intracranial anaplastic ependymomas.<sup>88</sup> *HIC1* on 17p13.3 is suggested as the potentially involved oncogene. In addition to chromosomal loss, *HIC1* hypermethylation and consequent transcriptional repression are observed in a substantial percentage of ependymomas (Table 2), suggesting an important role in ependymoma development.

**Chromosome 22.** Monosomy 22 is found more frequently in adults than in children, which results from the higher incidence of spinal tumors in adults than in children. The existence of ependymomas with loss of 22q lacking *NF2* mutations suggests that other tumor suppressor genes are located on this chromosome. Multiple regions have been suggested, such as 22pter–22q11.2<sup>101,102</sup> distal to the *hSNF5/INI1* locus or 22q13.3, including the *SULT4A1* gene (Table 2). Mutations in *hSNF5/INI1* are rare or absent in ependymomas.<sup>103</sup> Gene expression profiling of ependymomas has revealed several underexpressed genes on 22q12.3–q13.3, for example, *FBX*, *c22orf2*, *CBX7*, and *SBF1*.<sup>87</sup> Interestingly, *CBX7* is involved in gene silencing of, for example, the *p16<sup>INK4A</sup>/p14<sup>ARF</sup>* locus (Table 2).

**Epigenetics.** Epigenetic studies have also identified genes potentially important in ependymoma pathogenesis (Table 2). Independent of clinical and histological subtype, *RASSF1A* is transcriptionally silenced by methylation in most ependymomas, suggesting a function as a tumor suppressor gene. The fact that methylation is almost 100% at every CpG site suggests that *RASSF1A* inactivation is an early event in tumorigenesis. *CASP8*, *TFRSF10C*, and *TFRSF10D* are genes involved in the TRAIL apoptosis pathway, and methylation of *CASP8* is suggested to be characteristic of low-grade myxopapillary ependymomas. *MGMT* is involved in DNA repair, and silencing of the gene is associated with increased sensitivity to alkylating agents in gliomas.<sup>104</sup>

## ► Conclusion and Future Directions

Much progress has been made in the identification of biological factors involved in the pathogenesis of pediatric medulloblastomas and ependymomas in the past years, but much has yet to be discovered. Deregulation of signaling pathways involved in brain development seems to play a more important role in the pathogenesis of these tumors than do abnormalities in well-known tumor oncogenes and tumor suppressors, such as *p53* or *EGFR*. Large collaborative studies are needed to provide insights into the importance of the genes discovered so far, in order to evaluate their possible use for improved risk stratification of patients and their use as therapeutic targets. In addition, data from newly developed techniques such as microRNA profiling and the use of single nucleotide polymorphisms or exon arrays may provide new insights into the regulation of posttranscriptional gene expression and alternative splicing.

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