The Similarities and Differences between Intracranial and Spinal Ependymomas: A Review from a Genetic Research Perspective

Chang-Hyun Lee, M.D., Jung Hun Ohn, M.D., Chi Heon Kim, M.D., Ph.D., Chun Kee Chung, M.D., Ph.D.,* and Jung Hun Ohn, M.D.,**

Ependymomas occur in both the brain and spine. The prognosis of these tumors sometimes differs for different locations. The genetic landscape of ependymoma is very heterogeneous despite the similarity of histopathologic findings. In this review, we describe the genetic differences between spinal ependymomas and their intracranial counterparts to better understand their prognosis. From the literature review, many studies have reported that spinal cord ependymoma might be associated with NF2 mutation, NEFL overexpression, Merlin loss, and 9q gain. In myxopapillary ependymoma, NEFL and HOXB13 overexpression were reported to be associated. Prior studies have identified HIC-1 methylation, 4.1B deletion, and 4.1R loss as common features in intracranial ependymoma. Supratentorial ependymoma is usually characterized by NOTCH-1 mutation and p75 expression. TNC mutation, no hypermethylation of RASSF1A, and GFAP/NeuN expression may be diagnostic clues of posterior fossa ependymoma. Although MEN1, TP53, and PTEN mutations are rarely reported in ependymoma, they may be related to a poor prognosis, such as recurrence or metastasis. Spinal ependymoma has been found to be quite different from intracranial ependymoma in genetic studies, and the favorable prognosis in spinal ependymoma may be the result of the genetic differences. A more detailed understanding of these various genetic aberrations may enable the identification of more specific prognostic markers as well as the development of customized targeted therapies.

Key Words: Ependymoma · Genetics · NF2 · Spinal · Intracranial.

INTRODUCTION

Ependymomas are glial tumors that are thought to arise from primitive ependymal or subependymal cells in the vicinity of the ventricles and remnants of the central spinal canal4,5,6. Microscopically, ependymomas are moderately cellular gliomas corresponding to WHO grade 2 neoplasms and are well demarcated with a sharp tumor-parenchyma interface. In aspect of intracranial ependymomas, so far the cure for this disease has eluded us and despite its histological benignancy, the majority of patients will die from their disease. Although intracranial ependymoma is associated with an aggressive clinical course and poor prognosis, spinal ependymoma is linked with an indolent clinical course and good prognosis. The more difficult thing to estimate clinical course of ependymal tumors is that they are heterogeneous with regard to morphology, localization, and age at first clinical manifestation. In children, 90% of ependymomas develop in the intracranial region and are associated with frequent recurrences. In adults, 60% of ependymomas develop in the spinal cord, and recurrence is rare. The differences between intracranial and spinal ependymomas make the extrapolation of data from one to the other difficult. Moreover, recent findings suggest that the histologic diagnosis of ependymomas may be insufficient for assigning an appropriate risk stratifica-
Although intracranial and spinal ependymomas are histopathologically similar, their molecular biology is very heterogeneous, and they possess different DNA copy number alterations, messenger-RNA expression profiles, and genetic and epigenetic alterations as well as diverse transcriptional programs\(^\text{[13,17,20,40,41]}\). The genetic landscape of ependymoma is also heterogeneous; these tumors show mostly complex aberration patterns with frequent deletions or gains of chromosomes, and the main losses occur on chromosomes 1p, 4q, 6q, 9, 10, 13q, 16, 17, 19q, 20q, and 22q\(^\text{[13,17,35,47,48,51]}\). Some genetic researches revealed substantially different frequencies of genetic aberrations for different tumor locations\(^\text{[7,15,23,44]}\). Therefore, these results support the hypothesis that the histological entity “ependymoma” in fact comprises a group of related diseases that likely require different approaches and treatments\(^\text{[17,28,40]}\). Furthermore, conventional therapies may fail to control tumor growth and progression due to the inherent heterogeneity of ependymoma, as demonstrated by analyses of their genetic and molecular anomalies\(^\text{[18,49]}\). In this review, we describe the genetic differences between spinal ependymomas and their intracranial counterparts to better understand their prognosis. Research to improve our knowledge of the genetic differences between spinal and intracranial ependymomas will be essential to guide therapeutic strategies and estimate their prognoses.

**Statistical analysis**

For the statistical analyses, we used the R : A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria) and the R-package “exact2×2”, which is a Fishers exact test tool. If the statistical significance of a difference in genes, proteins, and chromosomal mutations was not described in each paper, we calculated the p-value using Fisher's exact 2 by 2 frequency probability to compare spinal ependymoma with its intracranial counterpart. For all tests, a level of p<0.05 was considered statistically significant.

**MOLECULAR GENETIC ABERRATIONS**

Spinal cord ependymomas frequently exhibit mutations in NF2, NEFL overexpression, Merlin loss, and 9q gain, while intracranial ependymomas do not\(^\text{[5,7,12,20,40]}\). In addition, spinal cord ependymomas involve HES1, MYC, and GFAP overexpression\(^\text{[15,13]}\). In myxopapillary ependymomas (MPEs), NEFL overexpression is frequently observed\(^\text{[6]}\). Intracranial ependymomas commonly display HIC-1 methylation, 4.1B deletion, and 4.1R loss\(^\text{[5,14]}\). Supratentorial ependymoma display mutations in NOTCH-1, NeuN and p75 overexpression, and low expression of GFAP protein\(^\text{[12,13]}\). Mutation in TNC, lack of hypermethylation in RASSF1A, and GFAP/NeuN expression may provide clues for the diagnosis of posterior fossa ependymoma\(^\text{[12,14]}\). Although MEN1 and TP53 mutations have been rarely reported in ependymoma, they might be related to its recurrence or metastasis\(^\text{[12,21]}\). In turn, NEFL overexpression indicates a good prognosis and longer progression-free survival\(^\text{[27]}\). A graphical illustration of the key genes, proteins, and chromosomal aberrations related to the ependymoma subgroups according to tumor location is given in Fig. 1.

**NF2 and Merlin**

A variety of numerical and structural chromosomal abnormalities have been found to be associated with ependymomas; inactivation of NF2 gene, as well as sporadic mutations in NF2, on chromosome 22q12 have been well documented in ependymoma\(^\text{[22,24,36,38]}\). The importance of the NF2 gene to ependymoma pathogenesis is further emphasized by the observation that NF2 gene mutations and the loss of Merlin, the protein encoded by the NF2 gene, are found in 30–71% of sporadic (non-syndromal) ependymomas\(^\text{[5,38]}\). Among 4 studies included in this review, 2 studies showed that mutation of NF2 gene is observed only in spinal ependymoma and not in intracranial ependymoma, as shown in Table 1\(^\text{[27]}\). Another study reported that NF2 loss was strongly associated with spinal ependymoma at the protein level, Merlin, whereas at the DNA level, this was only a trend\(^\text{[30]}\). Some studies reported that NF2 mutations were found in a high percentage of spinal ependymoma cases (WHO grade II) especially and in few cases of MPE (WHO grade I), subependymoma (WHO grade I), and anaplastic ependymoma (WHO grade III) as well as all intracranial ependymomas\(^\text{[7,27]}\).

**HIC1**

Hypermethylated in cancer 1 (HIC1) gene is located on chromosome 17p13.3. Although only one study dealt with HIC1 gene in ependymoma, it clearly demonstrated that low or absent expression of the HIC1 gene is frequently found in human ependymomas and that hypermethylation was significantly more common in intracranial ependymomas than spinal tumors, as shown in Table 1 (intracranial : 94% vs. spinal : 65%; p=0.019)\(^\text{[26]}\). A chromosomal study reported that loss of chromosome arm 17p DNA sequences was common in sporadic pediatric intracranial ep-
endomesmas and many different human tumors, including gliomas and medulloblastomas.

**4.1B, DAL-1, and 4.1R**

Both 4.1B and DAL-1 genes are located on chromosome 18p11 and are involved in different mechanisms that modulate cell growth, motility, adhesion, and cytoskeleton organization. Inactivation of 4.1B and DAL-1 gene expression may lead to tumorigenesis and/or promote tumor progression. One study reported that 4.1B deletions were commonly observed in intracranial ependymomas compared with its spinal counterpart in Table 1 (intracranial: 49% vs. spinal: 25%; p=0.038), and protein 4.1B loss was seen in 3 of 4 intracranial tumors and 1 of 5 spinal cord tumors in Table 2. Losses of DAL-1 gene and DAL-1 protein were more frequently observed in intracranial ependymomas than in the spinal cord form, although this difference did not reach statistical significance. Among another proteins in the 4.1 family in Table 2, loss of protein 4.1R expression was statistically associated with intracranial location (intracranial: 88% vs. spinal: 47%; p=0.003) and young age (pediatric: 93% vs.

Table 1. Genes closely correlated with ependymoma

| Locus | Gene      | Author            | Spinal | Intracranial | p     | Comments     |
|-------|-----------|-------------------|--------|--------------|-------|--------------|
| 22q12 | NF2 mutation | Ebert et al.      | 6/17 (35%) | 0/39 (0%) | 0.0063 | E II, 6/8 (75%) |
|       |           | Bettegowda et al. | 9/19 (47%) | 0/40 (0%) | 0.0002 |               |
|       |           | Lamszus et al.    | 5/31 (16%) | 0/14 (0%) | 0.30  | E II, 3/23 (13%); E III, 2/4 (50%) |
|       |           | Singh et al.      | 5/14 (36%) | 1/11 (9%) | 0.18  | E II, 4/10 (40%); MPE, 1/4 (25%) |
| 17p13 | HIC-1 methylation | Wuha et al.     | 13/20 (65%) | 30/32 (94%) | 0.019 |               |
| 18p11 | 4.1B deletion | Rajaram et al.    | 8/32 (25%) | 24/49 (49%) | 0.038 |               |
| 8p21 | NEFL overexpression | Barton et al. | 10/21 (48%) | 1/12 (8%) | 0.05  | MPE, 8/13 (62%) |
| 9q33 | TNC overexpression | Gupta et al. | 3/19 (16%) | 13/31 (42%) | 0.05  | ST, 5/15 (33%); PF, 8/16 (50%) |
| 11q13 | MEN1 mutation | Lamszus et al. | 0/7 (0%) | 1/12 (8%) | 0.31  |               |
| 17q21 | HOXB13 overexpression | Barton et al. | 10/21 (48%) | 2/9 (22%) | 0.25  | MPE, 9/13 (69%) |
| 8q11–12 | c-mos expression | Athanasiou et al. | 1/5 (20%) | 15/29 (52%) | 0.34  |               |
| 18p11 | DAL-1 deletion | Singh et al. | 2/14 (14%) | 4/11 (36%) | 0.35  |               |
| 9q34 | NOTCH1 expression | Gupta et al. | 5/19 (26%) | 13/31 (42%) | 0.37  | ST, 11/15 (73%); PF, 3/16 (19%) |
| 9q22 | SHC1/SIPR3 (EDG3) expression | Magrassi et al. | 10/19 (53%) | 11/16 (69%) | 0.49  |               |
| 9p21 | CDKN2A (P16) deletion | Rajaram et al. | 12/47 (26%) | 15/45 (33%) | 0.49  |               |
| 3p21 | RASSF1 (RASSF1A) methylation | Hamilton et al. | 18/20 (90%) | 12/15 (80%) | 0.63  |               |
| 13q14 | RB deletion | Rajaram et al. | 12/47 (26%) | 10/45 (22%) | 0.81  |               |
| 4q12 | PDGFRα overexpression | Barton et al. | 16/19 (84%) | 11/13 (85%) | 1.0  | MPE, 11/13 (85%) |
| 17q12 | ERBB2 expression | Gilberston et al. | 1/1 (100%) | 64/78 (82%) | 1.0  | Pediatric patients |
| 10q23 | PTEN mutation | Bettegowda et al. | 0/8 (0%) | 1/8 (13%) | 1.0  |               |
|       |           | Ebert et al.      | 0/23 (0%) | 0/39 (0%) | 1.0  |               |

*p-value calculated by 2×2 table. E I: ependymoma (WHO Grade II), E III: anaplastic ependymoma (WHO grade III), MPE: myxopapillary ependymoma, ST: supratentorial ependymoma, PF: posterior fossa ependymoma.

Table 2. Proteins closely correlated with ependymoma

| Protein       | Gene       | Author            | Spinal | Intracranial | p     | Comments     |
|---------------|------------|-------------------|--------|--------------|-------|--------------|
| Merlin loss   | NF2        | Singh et al.      | 5/15 (33%) | 0/12 (0%) | 0.047 |               |
|               |           | Rajaram et al.    | 2/5 (40%) | 0/4 (0%) | 0.44  |               |
| 4.1R loss     | EPB41 (4.1R) | Rajaram et al. | 47% | 0% | 0.003 |               |
| DAL-1 loss    | EPB41L3    | Singh et al.      | 2/15 (13%) | 5/12 (42%) | 0.185 |               |
| 4.1B loss     | EPB41L3    | Rajaram et al.    | 1/5 (20%) | 3/4 (75%) | 0.21  |               |
| HES1 overexpression | HES1     | Gupta et al.      | 10/19 (53%) | 10/31 (32%) | 0.25  |               |
| MYC overexpression | MYC      | Gupta et al.      | 12/19 (63%) | 14/31 (45%) | 0.25  |               |
| HEY2 overexpression | HEY2     | Gupta et al.      | 11/19 (58%) | 20/31 (65%) | 0.77  |               |
| GFAP expression | GFAP     | Hagel et al.      | 4/4 (100%) | 15/21 (71%) | 0.54  |               |
| MDM2 overexpression | MDM2   | Suzuki and Iwaki | 4/5 (80%) | 17/21 (81%) | 1.00  |               |
| NeuN expression | RBFOX2  | Hagel et al.      | 1/4 (25%) | 5/21 (24%) | 1.00  |               |
| p75 expression | NGFR      | Hagel et al.      | 0/4 (0%) | 3/21 (14%) | 1.00  |               |

*p-value calculated by 2×2 table. Protein expression of immunohistochemistry was defined as moderate or strong staining.
adult: 48%; p<0.001), although presence of 4.1R deletion did not differ substantially between subsets according to tumor location and age. sunitinib has been FDA approved, including imatinib mesylate, sorafenib, and temsirolimus targeting of this receptor tyrosine kinase may be an appropriate therapeutic option for supratentorial ependymomas in future.

**NEFL, HOXB13, and PDGFRA**

MPE is regarded to be distinct molecularly from intracranial ependymoma as well as other spinal ependymomas. MPE is characterized by high expression levels of some genes, including NEFL, HOXB13, and PDGFRA. A previous study reported that NEFL immunoreactivity in the spinal ependymoma was substantially high compared to that in intracranial ependymoma in Table 1 (spinal: 48% vs. intracranial: 8%; p=0.03). NEFL immunoreactivity was positive in 8 of 13 (62%) MPE cases, which is very high compared with subependymoma and ependymomas in both spinal and intracranial region. Another study reported that high expression of NEFL could predict a longer progression-free survival in supratentorial ependymomas.

Both HOXB13 and PDGFRA genes were investigated in one paper and there was not a significant difference in immunoreactivity by tumor location. This study also found that PDGFRA demonstrated high sensitivity but poor specificity for ependymoma, since most intracranial ependymoma cases were positive for HOXB13. In this study, the immunoprecipitation of Shc3 and EDG3 proteins was reported for ependymomas with amplification of SHC3 and EDG3 genes, which suggests that the 2 proteins co-operate and are important for ependymomas. However, the differences in gene mutations and protein overexpression were not substantial between spinal and intracranial ependymomas.

**SHC3 and S1PR3**

SHC3 and S1PR3 genes are located on chromosome 9q22.1-2. Dysregulation of SHC3 expression is involved in the survival of anaplastic astrocytomas and glioblastomas. The S1PR3 gene is also known as EDG3 and likely contributes to the regulation of angiogenesis and vascular endothelial cell function. The co-immunoprecipitation of Shc3 and EDG3 proteins was reported in ependymomas with amplification of SHC3 and EDG3 genes, which suggests that the 2 proteins co-operate and are important for ependymomas. However, the differences in gene mutations and protein overexpression were not substantial between spinal and intracranial ependymomas.

**MEN1**

The MEN1 gene is located on chromosome 11q13, a region that is involved in allelic losses and rearrangements in ependymomas. Ependymomas have been described in patients with MEN1 syndrome, which is characterized by the development of multiple endocrine tumors. However, mutations in the MEN1 gene have been described in only a small fraction of recurrent ependymomas. In one study, only 1 intracranial ependymoma patient had an MEN1 mutation among the 12 intracranial and 27 spinal ependymoma patients. The patient with the MEN1 mutation exhibited lesion recurrence twice and metastasis.

**RB and CDKN2A (P16^INK4A)**

Retinoblastoma susceptibility (RB) gene on chromosome 13q14 and cyclin-dependent kinase inhibitor 2A (CDKN2A) gene, also known as P16^INK4A, on chromosome 9p21 are key tumorsuppressor genes in a cell cycle regulatory pathway that is commonly inactivated in a wide range of cancers. The disruption of either RB or CDKN2A gene leads to deregulated cell proliferation and supports tumor progression. Several studies reported that there were no significant genetic associations of 9p and 13q with ependymoma grade, recurrence, or death, suggesting that 9p and 13q deletions do not have obvious associations with tumor grade, age, location, or overall prognosis in Table 1. Therefore, they might not play a prominent role in the malignant progression of ependymomas.

**c-mos**

c-mos, the proto-oncogene located on chromosome 8q11-12 in humans, encodes mos, a 39-kD protein that is a component of the mitogen-activated protein kinase transduction pathway. In one study, almost half of the ependymal tumors were immunopositive for mos, and overexpression of mos identified a biologically aggressive subgroup of ependymal tumors. However, only 5 spinal ependymoma cases were enrolled among the 34 tumor cases, and the expression incidence of c-mos gene did not differ substantially between subsets according to tumor location.
differ significantly by location in Table 1 (intracranial: 52% vs. spinal: 20%; \( p=0.34 \)).

**RASSF1 (RASSF1A)**

Ras association domain family protein 1, isoform A (RASSF1) gene is located on chromosome 3p21.3 and has been shown to be involved in a variety of malignancies, including brain tumors such as gliomas and medulloblastomas\(^{14}\). Recent evidence has also suggested that the extensive hypermethylation of tumor suppressor genes, including CDKN2A, CDKN2B, HIC1, RASSF1A, CASP8, MGMT, and TP73, is an important mechanism in the pathogenesis of ependymoma\(^{33}\). Rajaram et al.\(^{13}\) reported that extensive hypermethylation across the RASSF1 CpG island was detected frequently in 18 of 20 (90%) spinal ependymomas and 12 of 15 (80%) intracranial ependymomas. The incidence of RASSF1 hypermethylation was not different between spinal and intracranial ependymomas. Other researchers reported that both supratentorial and spinal ependymomas frequently displayed RASSF1 gene hypermethylation, whereas posterior fossa tumors did not\(^{30}\). Thus, the absence of RASSF1A hypermethylation may be a diagnostic indicator of posterior fossa ependymoma.

**ERBB2**

ERBB2 gene is a member of the RTK I family and is located on chromosome 17q12. This gene encodes a member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases. The ErbB2 receptor was reported to be frequently over-expressed in childhood intracranial ependymoma\(^{10}\), with the expression of ErbB2 identified in 82% of tumors. However, only one spinal ependymoma case was enrolled among the 121 tumor cases, and the expression difference by tumor location was not significant.

Another study demonstrated that Merlin negatively regulated spinal neural progenitor cell survival and glial differentiation in an ErbB2-dependent manner and that NF2-associated spinal ependymomas exhibited increased ErbB2 activation, indicating that ErbB2 may be a potential therapeutic target for NF2-associated spinal ependymomas\(^{10}\). The importance of ERBB2 in NF2-associated tumors is also highlighted by recent research showing that lapatinib inhibits vestibular schwannoma growth\(^{11}\).

**MDM2**

Oncogene MDM2, localized on chromosome 12q14-15, encodes a nuclear-localized E3 ubiquitin ligase. The encoded protein, MDM2, can promote tumor formation by targeting tumor suppressor proteins, such as p53, for proteasomal degradation. Thus, the protein is believed to act as a cellular regulator of the p53 protein\(^{39}\). One previous study showed that MDM2 was overexpressed at similar levels in intracranial and spinal ependymomas in Table 2 (intracranial: 81% vs. spinal: 80%; \( p=1.00 \))\(^{36}\).

**TP53**

The TP53 tumor suppressor gene on chromosome 17p13.1 is frequently mutated in human cancers, and it is important in the pathogenesis of other central nervous system tumors\(^{8}\). One study found that TP53 was mutated in only 1 of 31 ependymoma patients\(^{8}\), and another study reported that TP53 was mutated in only 1 of 16 patients\(^{8}\). Therefore, TP53 does not seem to be important in the pathogenesis of ependymomas, unlike other brain tumor types in which p53 mutations play a role in the progression of tumors\(^{8}\).

**GFAP, NeuN, and p75**

Prior study suggested that immunohistochemical (IHC) expression of p75, NeuN and GFAP differed in ependymomas depending on tumor topography supporting the view of divergent cells of origin\(^{30}\). They showed that glial markers such as NeuN and GFAP were preferentially expressed in infratentorial lesions, whereas neuronal markers such as p75 were found in supratentorial tumors, which reached statistically significant difference between supratentorial and infratentorial ependymomas for p75, GFAP, and NeuN\(^{39}\). However, the difference between spinal and intracranial tumors did not show a statistical significance for p75, GFAP, and NeuN.

**CYTOGENETIC ABERRATIONS**

**Chromosome 9q gain and loss of heterozygosity (LOH) 9**

Gene amplification is an important mechanism to enhance gene expression in many tumors. Large gains and losses of the long arm of chromosome 9 have been repeatedly described in studies using cytogenetic and molecular analyses of ependymomas, and 9q gain was mapped to 9q12-32 and 9q22-31 intervals\(^{12,23,30}\). A study that included 50 patients reported that chromosome 9q33-34 gain was more frequently observed in spinal ependymoma than in intracranial counterpart in Table 3 (intracranial: 29% vs. spinal: 79%; \( p=0.001 \), which showed a statistically significant difference\(^{22}\). Another study involving 35 patients reported that chromosome 9q22-22.2 gain was commonly detected in both spinal and intracranial ependymomas in Table 3 (intracranial: 69% vs. spinal: 53%; \( p=0.49 \))\(^{20}\).

Two studies investigated 9q deletion in ependymoma\(^{16,36}\), and neither found a substantial difference between spinal and intracranial ependymomas. In a study that included 48 patients with ependymoma, 9q deletions, particularly of DCR1, were found significantly more often in supratentorial tumors than in tumors with an infratentorial location in pediatric patients (\( p=0.007 \))\(^{36}\).
Intracranial Gliomas

Monoranu et al. 6/19 (32%) and ependymoma

Chromosomal aberrations closely correlated with ependymoma

| Chromosome | Author                     | Spinal | Intracranial | p   |
|------------|----------------------------|--------|--------------|-----|
| 9q gain    | Gupta et al. 15/19 (79%)   | 9/31 (29%) | 0.01*       |
|            | Magrassi et al. 10/19 (53%)| 11/16 (69%) | 0.49*       |
| LOH 22     | Ebert et al. 7/19 (37%)    | 6/39 (15%) | 0.2         |
|            | Huang et al. 6/14 (43%)    | 6/19 (32%) | 0.72*       |
|            | Bettegowda et al. 7/8 (88%)| 5/8 (63%) | 0.57*       |
|            | Lamszus et al. 16/31 (52%)| 4/14 (29%) | 0.20*       |
|            | Kraus et al. 7/15 (47%)    | 4/20 (20%) | 0.29*       |
| LOH 9      | Schneider et al. 10/18 (56%)| 20/30 (67%) | 0.54*       |
|            | Huang et al. 3/13 (23%)    | 6/20 (30%) | 1.00*       |
| 6q deletion| Monoranu et al. 14/18 (78%)| 20/31 (65%) | 0.52*       |
|            | Huang et al. 5/13 (38%)    | 6/20 (20%) | 0.71*       |
|            | Olsen et al. 1/3 (33%)     | 6/14 (43%) | 1.00*       |
| LOH 11q    | Lamszus et al. 3/31 (10%)  | 4/14 (29%) | 0.18*       |
| LOH 10q    | Ebert et al. 2/22 (9%)     | 3/34 (9%)  | 1.00*       |

*p-value calculated by 2×2 table. LOH: loss of heterozygosity

LOH 22q

The most frequent genetic change in sporadic ependymomas is monosomy 22, suggesting the presence of an ependymoma tumor suppressor gene on chromosome 22. The majority of relevant studies reported that LOH of 22q was more frequent in spinal ependymoma than in intracranial ependymoma, although this difference did not reach statistical significance. Although NF2 gene mutations are observed distinctively in spinal ependymoma, no clear association between LOH 22 and NF2 mutations has been found. Hence, these data may either suggest the presence of another tumor suppressor gene on chromosome 22 or result from a chromosomal instability causing the random deletion of genomic material.

 Chromosome 6q deletion

Losses and rearrangements of genetic material on chromosome 6q are frequently detected in human malignancies, including central nervous system tumors such as gliomas. Three studies reported a correlation between chromosome 6q deletion and ependymoma, and the incidences of 6q deletion between spinal and intracranial ependymomas were similar.

LOH of 10q and 11q

In studies of LOH of chromosomes 10 and 11, no correlation between the tumor location and the LOH was observed. One study found that LOH of 10q was observed regardless of tumor location, showing a trend related to tumor grade (WHO grade III: 24%; WHO grade II: 4%; WHO grade I: 0%). Another study reported that LOH of 1q was associated with neither tumor location nor tumor grade and that there was a highly significant inverse association between LOH 1q and LOH 22q, which suggests that loss of genetic information on either 1q or 22q could represent independent and alternative mechanisms involved in ependymoma pathogenesis.

CONCLUSION

Spinal ependymoma has been found to be quite different from intracranial ependymoma in genetic studies, and the favorable prognosis in spinal ependymoma may be due to these genetic differences. Ependymoma in the spinal cord may be related with NF2 mutations, NEFL overexpression, and 9q gain. Its intracranial counterpart may be related with HIC-1 methylation, 4.1B deletion, and 4.1R loss. A more detailed understanding of these various genetic aberrations may enable the identification of more specific prognostic markers as well as the development of customized targeted therapies.

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References

1. Ahmad ZK, Brown CM, Cueva RA, Ryan AE, Doherty JK: ErbB expression, activation, and inhibition with lapatinib and trypthostin (AG825) in human vestibular schwannomas. Otol Neurotol 32: 841-847, 2011
2. AndreuIuolo F, Puget S, Peyre M, Dantas-Barbosa C, Boddaert N, Philippe C, et al.: Neuronal differentiation distinguishes supratentorial and infratentorial childhood ependymomas. Neuro Oncol 12: 1126-1134, 2010
3. Athanasiou A, Perusovic B, Quilty RD, Gorgoulis VG, Kittas C, Love S: Expression of mos in ependymal gliomas. Am J Clin Pathol 120: 699-705, 2003
4. Barton VN, Donson AM, Kleinschmidt-DeMasters BK, Birks DK, Handler MH, Foreman NK: Unique molecular characteristics of pediatric myxopapillary ependymoma. Brain Pathol 20: 560-570, 2010
5. Bettegowda C, Agrawal N, Jiao Y, Wang Y, Wood LD, Rodriguez FJ, et al.: Exonic sequencing of four rare central nervous system tumor types. Oncotarget 4: 572-583, 2013
6. de Bont JM, Packer RJ, Michiels EM, den Boer ML, Pieters R: Biological background of pediatric medulloblastoma and ependymoma: a review from a translational research perspective. Neuro Oncol 10: 1040-1060, 2008
7. Ebert C, von Haken M, Meyer-Puttlitz B, Wiestler OD, Reifenberger G, Pietsch T, et al.: Molecular genetic analysis of ependymal tumors. NF2 mutations and chromosome 22q loss occur preferentially in intramedullary spinal ependymomas. Am J Pathol 155: 627-632, 1999
8. Fink KL, Risinger EJ, Schold SC Jr, Nisen PD: Infradrenal cell 53 gene mutations in ependymomas. J Neurooncol 27: 111-115, 1996
9. Garcia C, Gutmann DH: NF2/Merlin controls spinal cord neural progenitor function in a Rac1/ErbB2-dependent manner. PLoS One 9: e97320, 2014
10. Gilbertson RJ, Bentley L, Hernan R, Hultila TT, Frank AJ, Haapasalo H, et al.: ERBB receptor signaling promotes ependymoma cell proliferation and represents a potential novel therapeutic target for this disease. Clin Cancer Res 8: 3054-3064, 2002
11. Gonzalez-Gomez P, Bello MJ, Alonso ME, Arjona D, Lomas J, de Campos JM, et al.: CpG island methylation status and mutation analysis of the RB1 gene essential promoter region and protein-binding pocket domain in nervous system tumours. Br J Cancer 88: 109-114, 2003
12. Gupta RK, Sharma MC, Suri V, Kakkar A, Singh M, Sarkar C: Study of chromosome 9q gain, Notch pathway regulators and Tenascin-C in ependymomas. J Neurooncol 116: 267-274, 2014
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13. Hagel C, Tresal A, Fehlert I, Harder J, von Hartmanns F, Kern M, et al. Supra- and infratentorial pediatric ependymomas differ significantly in NeuN, p75 and GFAP expression. J Neuropathol Exp Neurol 2013; 72: 191-197.

14. Hamilton DW, Lusher ME, Lindsey JC, Ellison DW, Clifford SC. Etiologic genetic inactivation of the RASSF1A tumor suppressor gene in ependymoma. Cancer Lett 2005; 227: 75-81.

15. Huang B, Storostik P, Küh I, Tonn JC, Roggendorf W. Loss of heterozygosity on chromosome 22 in human ependymomas. Acta Neuropathol 2003; 105: 415-420.

16. Huang B, Storostik P, Schraut H, Krauss J, Sörensen N, Roggendorf W. Human ependymomas reveal frequent deletions on chromosomes 6 and 9. Acta Neuropathol 2006; 106: 357-362.

17. Johnson RA, Wright KD, Poppleton H, Mohankumar KM, Finkelestein D, Pounds SB, et al. Cross-species genomic match of driver mutations and cell compartments to model ependymoma. Nature 2010; 466: 632-636.

18. Kilday JP, Rahman R, Dyer S, Ridley I, Lowe J, Coyle R, et al. Pediatric ependymoma: biological perspectives. Mol Cancer Res 2009; 7: 765-786.

19. Korkushon A, Witt H, Helsicher T, Benner A, Remke M, Ryzhova M, et al. Molecular staging of intracranial ependymomas in children and adults. J Clin Oncol 2010; 28: 3182-3190.

20. Kraus I, de Miguel W, Sörensen N, Herold C, Schiöcher C, Tonn JC, et al. A tumor suppressor gene at 22q11 is involved in the pathogenesis of ependymal tumors and distinct from bSNF5/INI1. Acta Neuropathol 2011; 120: 69-74.

21. Lamszus K, Lachenmayer L, Heinemann U, Klöve I, Finck H, Hiddes K, et al. Molecular genetic alterations on chromosomes 11 and 22 in ependymomas. Int J Cancer 2001; 91: 803-808.

22. Magrassi L, Conti L, Lanterna A, Zuccato C, Marchioni M, Cassini P, et al. Shc affects human high-grade astrocytomas survival. Oncogene 2005; 24: 5198-5206.

23. Magrassi L, Marziano N, Inzani F, Cassini P, Chiaramida I, Skrap M, et al. EDG3 and SHC3 on chromosome 9q22 are co-amplified in human ependymomas. J Neurooncol 2010; 103: 5223-5233.

24. Modena P, Luandi F, Facchinetti F, Veltman J, Reid JF, Minardi S, et al. EDG3 and SHC3 on chromosome 9q22 are co-amplified in human ependymomas. Cancer Lett 2010; 290: 36-42.

25. Moderna P, Luandi F, Facchinetti F, Veltman J, Reid JF, Minardi S, et al. Identification of tumor-specific molecular signatures in intracranial ependymoma and association with clinical characteristics. J Clin Oncol 2014; 24: 5233-5243.

26. Monoranu CM, Huang B, Zangen IL, Rutkowsi S, Gerber NU, et al. Correlation between 6q25.3 deletion status and survival in ependymoma and association with clinical characteristics. J Clin Oncol 2014; 32: 3182-3190.

27. Obien TK, Goronova L, Meling TR, Micci F, Scheie D, Due-Tønnessen NU, et al. Correlation between 6q25.3 deletion status and survival in ependymoma and association with clinical characteristics. J Clin Oncol 2014; 32: 4815-4830.

28. Park JS, Lim JH, Song K, Cho H, Chun KS, Kim JH, et al. Supratentorial and spinal pediatric ependymomas display a hypermethylated phenotype which includes the loss of tumor suppressor genes involved in the control of cell growth and death. Acta Neuropathol 2012; 123: 711-725.

29. Rubio MP, Correa KM, Ramesh V, MacCollin MM, Jacoby LB, von Deimling A, et al. Analysis of the neurofibromatosis 2 gene in human ependymomas and astrocytomas. Cancer Res 1994; 54: 45-47.

30. Scheil S, Brüderlein S, Eicker M, Herms J, Hernl-Jörg, Mende-C, Stein HH, et al. Low frequency of chromosomal imbalances in anaplastic ependymomas as detected by comparative genomic hybridization. Brain Pathol 2001; 11: 133-143.

31. Schneider D, Monoranu CM, Huang B, Rutkowsi S, Gerber NU, Krauss J, et al. Pediatric supratentorial ependymomas show more frequent deletions on chromosome 9 than infratentorial ependymomas: a microsatellite analysis. Cancer Genet Cytogenet 1999; 190: 96-99.

32. Sheer CJ, The DNR4/ARF network in tumour suppression. Rev Mol Cell Biol 2001; 2: 731-737.

33. Singh KP, Gutmann DH, Fuller CE, Newsham JF, Perry A: Differential involvement of protein 4.1 family members DAL-1 and NF2 in intracranial and intraspinal ependymomas. Mod Pathol 2002; 15: 526-531.

34. Suzuki SO, Iwaki T: Amplification and overexpression of mdm2 gene in ependymomas. Mod Pathol 2000; 13: 548-553.

35. Taylor MD, Poppleton H, Fuller C, Su X, Liu Y, Jensen P, et al. Radial glia cells are candidate stem cells of ependymoma. Cancer Cell 2005; 8: 323-335.

36. Teo C, Nakaji P, Symonds P, Tobias V, Cohn R, Smeer R: Ependymoma. Childs Nerv Syst 2003; 19: 270-285.

37. Vera-Bolanos E, Aldape K, Yuan Y, Wu J, Wani K, Necessito-Reyes MJ, et al. Clinical course and progression-free survival of adult intracranial and spinal ependymoma patients. Neuro Oncol 2017; 19: 440-447.

38. von Haken MS, White EC, Daneshvar-Shyesther L, Sih S, Choi E, Kalra R, et al. Molecular genetic analysis of chromosome arm 17p and chromosome arm 22q DNA sequences in sporadic pediatric ependymomas. Genes Chromosomes Cancer 1997; 20: 37-44.

39. Wala A, Koch A, Hartmann W, Mack H, Schramm J, Sörensen N, et al. Analysis of HIC-1 methylation and transcription in human ependymomas. Int J Cancer 2006; 118: 542-549.

40. Wang Z, Zhang J, Ye M, Zhu M, Zhang B, Roy M, et al. Tumor suppressor role of protein 4.1B/DAL-1. Cancer Cell 2001; 8: 323-335.

41. Wase S, Zhang J, Ye M, Zhu M, Zhang B, Roy M, et al. Tumor suppressor role of protein 4.1B/DAL-1. Cell Mol Life Sci 2004; 51: 4815-4830.

42. Wani K, Armstrong TS, Vera-Bolanos E, Rahghunathana A, Ellison D, Gilbertson R, et al.: A prognostic gene expression signature in infratentorial ependymoma. Acta Neuropathol 2012; 123: 727-738.

43. Ward S, Harding B, Wilkins P, Harkness W, Hayward R, Darling JL, et al. Gain of 1q and loss of 22 are the most common changes detected by comparative genomic hybridization in paediatric ependymoma. Genes Chromosomes Cancer 2003; 37: 59-66.

44. Witt H, Mack SC, Ryzhova M, Bender S, Sill M, Isserlin R, et al.: Identification of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. Cancer Cell 2003; 20: 143-157.

45. Yang I, Nagasawa DT, Kim W, Spasic M, Trang A, Lu DC, et al.: Chromosomal anomalies and prognostic markers for intracranial and spinal ependymomas. J Clin Neurosci 2012; 19: 779-785.

46. Zadnik PL, Gokaslan ZL, Burger PC, Bettegowda C: Spinal cord tumours: advances in genetics and their implications for treatment. Nat Rev Neu-
51. Zheng PP, Pang JC, Hui AB, Ng HK: Comparative genomic hybridization detects losses of chromosomes 22 and 16 as the most common recurrent genetic alterations in primary ependymomas. Cancer Genet Cytogenet 122: 18-25, 2000

52. Zhou XP, Li YJ, Hoang-Xuan K, Laurent-Puig P, Mokhtari K, Longy M, et al.: Mutational analysis of the PTEN gene in gliomas: molecular and pathological correlations. Int J Cancer 84: 150-154, 1999