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### Accumulation of genomic aberrations during clinical progression of medulloblastoma.

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#### Abstract

Medulloblastomas comprise the most frequent malignant brain tumor in childhood and one of the biggest challenges in pediatric oncology. The current concept suggests that these tumors may undergo stepwise progression as it has been shown for other brain tumors. However, conclusive evidence of molecular progression over time has not been demonstrated yet for medulloblastoma. In the present study, 28 pairs of medulloblastoma at primary diagnosis and at the time of recurrence, either occurring as local tumor regrowth or tumor dissemination, were histopathologically and molecularly analyzed. Cytogenetic analysis included interphase fluorescence in situ hybridization for five genomic loci (MYC, MYCN, 17p, 17q, 6q) that have previously been identified as prognostic markers in primary tumors. Of 16 tumors showing early recurrence (<4 years after first diagnosis), only one showed increased histological anaplasia in the secondary lesion (6%), and two acquired genomic lesions indicative for a more malignant phenotype (13%). In contrast to this, of 12 tumors with a time to recurrence of 4 years or more, nine tumors (75%) showed a more malignant phenotype either reflected by increased anaplasia alone or by both increased anaplasia and acquirement of genomic aberrations known to be associated with inferior patient outcome. These results suggest that early recurrence in medulloblastoma mainly occurs in tumors with a highly malignant genotype and phenotype per se, whereas late recurrence is often dependent on tumor evolution toward a more malignant biology. Therefore, biopsy of recurrent tumors should be performed to assess the biologic properties of the relapsed tumor, especially when targeted therapy approaches are considered.

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