

Chromosome 17 alterations identify good-risk and poor-risk tumors independently of clinical factors in medulloblastoma

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Current risk stratification schemas for medulloblastoma, based on combinations of clinical variables and histotype, fail to accurately identify particularly good- and poor-risk tumors. Attempts have been made to improve discriminatory power by combining clinical variables with cytogenetic data. We report here a pooled analysis of all previous reports of chromosomal copy number related to survival data in medulloblastoma. We collated data from previous reports that explicitly quoted survival data and chromosomal copy number in medulloblastoma. We analyzed the relative prognostic significance of currently used clinical risk stratifiers and the chromosomal aberrations previously reported to correlate with survival. In the pooled dataset metastatic disease, incomplete tumor resection and severe anaplasia were associated with poor outcome, while young age at presentation was not prognostically significant. Of the chromosomal variables studied, isolated 17p loss and gain of 1q correlated with poor survival. Gain of 17q without associated loss of 17p showed a trend to improved outcome. The most commonly reported alteration, isodicentric chromosome 17, was not prognostically significant. Sequential multivariate models identified isolated 17p loss, isolated 17q gain, and 1q gain as independent prognostic factors. In a historical dataset, we have identified isolated 17p loss as a marker of poor outcome and 17q

gain as a novel putative marker of good prognosis. Biological markers of poor-risk and good-risk tumors will be critical in stratifying treatment in future trials. Our findings should be prospectively validated independently in future clinical studies.

Keywords: Medulloblastoma, survival, risk stratification, cytogenetic, isochromosome, i(17q), monosomy 6, 1q gain, 17p loss, 17q gain.

Medulloblastomas are the most common malignant brain tumors of childhood. Refinements in clinical risk stratification, combined with more intensive treatment protocols, have resulted in survival estimates for patients with standard risk disease in excess of 80% at 5 years.^{1,2} However, current risk stratifications still rely largely on clinical factors—age, presence of metastatic disease, and extent of resection—combined with histological subtype and do not yet accurately discriminate either the children who will be cured with current treatment or those who will die of disease despite optimal treatment. Although expression profiling has been shown to be the best predictor of outcome,^{3,4} several less costly histopathological and biological risk factors have also shown utility,^{5–10} and stratification schemes relying on combinations of clinical factors, chromosomal copy number changes, and immunohistochemistry have been suggested.^{8,11–13}

The chromosomal changes reported to predict survival in medulloblastoma include loss of 17p,^{7,14,15} gain of 17q,^{8,15} presence of an isodicentric chromosome 17 (idic(17)(p11.2)),^{7,16} gain of 1q,¹⁷ and monosomy 6 in association with *WNT* pathway activation.^{18,19}

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However, medulloblastomas are rare tumors and most reports of biological variables with putative prognostic significance are based on small series. We sought to identify the prognostic impact of these chromosomal changes in a larger dataset. By combining our previously reported series of 41 medulloblastomas²⁰ with other series with explicit survival data related to chromosomal copy number abnormalities, we generated a combined dataset representing 227 patients. We report here our results from correlating alterations in chromosomes 1q, 6, and 17 with survival in the combined dataset.

Materials and Methods

Selection of Datasets

All studies that reported separate data for gain and loss of individual chromosome arms were included in the analysis. The datasets included are summarized in Table 1. Several additional studies (total $n = 95$ patients) reported data from fluorescence in situ hybridization (FISH), loss of heterozygosity analyses, or a combination but did not give separate information on gain and loss for each chromosome arm.^{21–25} They were not included in the analysis.

Data Collection

For each study, data on loss and gain were collected separately for each chromosome arm. To allow direct comparisons between the datasets, copy number changes along a whole chromosome arm were grouped together. Reporting of metastatic disease at presentation was variable. Some authors reported Chang stage, and others reported metastases to be present or absent. Where Chang staging was presented, all tumors staged at $>M0$ were classed as metastatic. It was not always possible to differentiate death from disease and death from other causes. To maximize the sample size, only overall survival data were analyzed. Event-free and progression-free survival data, although included in some reports, were not analyzed. Some series reported data on samples from initial presentation and from relapsed disease. To increase homogeneity within the dataset, samples from relapsed tumors were excluded from the analysis.

Statistical Analysis

All statistical computations were carried out in R.²⁶ Log-rank tests were used to evaluate differences in survival. Survival curves were estimated using the Kaplan–Meier method, and the resulting curves were used to estimate 5-year overall survival (OS). Cox's proportional hazards model was used to evaluate the contribution of individual risk variables to outcome. However, only 65/227 samples had a complete dataset for all variables examined. Therefore, to maximize the number of samples included in validating the model, we planned

a series of modified multivariate models ($n = 15$) that systematically examined all possible combinations of input variables with missing data in addition to chromosome 17 variables, for which data were complete. For each combination of input variables, cases with missing data were excluded and the model was applied to the modified dataset. A criterion-based variable selection procedure was used to select the variables included in the final model for each combination according to the R package *bootStepAIC*. Models were internally validated to assess the stability of individual variables by performing 1000 bootstrap iterations per model. This resulted in a series of bootstrapped models of progressively decreasing sample size with combinations of prognostic variables. The input and output variables for each model are reported.

Results

Six studies ($n = 186$ samples) reported chromosomal comparative genomic hybridization (CGH) or array CGH data,^{17,27–31} and a further study ($n = 41$) reported FISH data for chromosome 17.¹³ Treatment details were given for 130 patients (57%), of whom 81 (62%) had surgery and chemoradiotherapy, 39 (30%) had surgery and radiotherapy, and 5 (4%) had surgery alone. The median age at surgery was 8.5 years (range 0 to 43). Radiotherapy was given to 91% of children (<16 years) and 96% of adults for whom data were available. A greater proportion of children had additional chemotherapy (78% vs 24%). The full dataset is given in the Supplemental Data.

The Prognostic Significance of Established Clinical Risk Factors in the Dataset Reflected Previous Reports

In total, 52 patients (26%) had metastatic disease. There was a clear survival disadvantage for these patients. The predicted 5-year survival rates for those with and without metastases were $41 \pm 7\%$ and $70 \pm 4\%$ ($p < 0.001$; Fig. 1A). Gross tumor resection was achieved in 77/138 (56%) for whom data were reported and was associated with an improved outcome (5-y OS $75 \pm 5\%$ versus $50 \pm 7\%$, $p < 0.001$; Fig. 1B). The estimated 5-year OS for patients with nonmetastatic, completely resected tumors was $81 \pm 5\%$. Age at diagnosis was not a prognostic factor in this dataset. The five-year OS for those aged under 3 ($n = 28/227$, 21%) was $68 \pm 9\%$ versus $63 \pm 4\%$ for those over 3 ($p = 0.827$). The adult (≥ 16 years) 5-year OS was $65 \pm 4\%$ versus $57 \pm 9\%$ for children ($p = 0.292$).

Histological details were recorded for 184 patients (81%). The tumors were classified as classic ($n = 108$, 59%), desmoplastic/nodular ($n = 48$, 27%), showing focal moderate anaplasia ($n = 14$, 8%), moderate anaplasia ($n = 5$, 3%), or severe anaplasia ($n = 9$, 5%). Tumors with severe anaplasia had a worse outcome on univariate analysis (3-y OS $11 \pm 11\%$ vs $72 \pm 4\%$). Other histotypes had no prognostic impact (Fig. 1C). Correlation of particular copy number aberrations with histotypes was

Table 1. Summary of the studies included in the analysis. All studies that reported separate loss and gain data for each chromosome arm were included in the analysis. The number of patients, age range, and method of analysis reported by each study are shown, with the number (%) of cases affected by each of the clinical and biological variables analyzed. Individual studies are referenced in the text.

First Author	Year	N	Method	Age	Under 3	Mets	Incomplete Resection	Severe Anaplasia	1q gain	Mono 6	Isolated 17p loss	Idic(17)(p11.2)	Isolated 17q gain
Eberhart ³¹	2002	27	cCGH	9 (2–43)	6 (22)	9 (33)	–	7 (26)	5 (10)	0	0	5 (19)	7 (26)
Gilbertson ¹³	2001	41	FISH	8 (3–30)	0	11(27)	23 (56)	0	–	–	8 (20)	12 (29)	0
Lo ¹⁷	2007	48	aCGH	8 (1–26)	8 (17)	11 (23)	7 (70)*	3 (6)	9 (19)	2 (4)	0	11 (23)	6 (13)
McCabe ²⁷	2006	41	aCGH	9 (1–38)	5 (12)	5 (12)	–	0	11 (35)**	2 (7)**	0	17 (34%)	10 (24)
Michiels ²⁸	2002	14	cCGH	9 (3–17)	1 (7)	–	–	–	4 (29)	1 (7)	3 (21)	4 (29)	5 (36)
Nicholson ²⁹	1999	29	cCGH	7 (0–32)	4 (14)	7 (24)	20 (69)	0	4 (14)	0	3 (10)	8 (28)	5 (17)
Reardon ³⁰	1997	27	cCGH	8 (2–20)	4 (15)	8 (30)	10 (37)	–	4 (15)	3 (11)	1 (4)	7 (26)	6 (22)

Ages are given as median (range).
 Frequencies of other variables are given as n (%).
 *Resection data were given for 10/48 cases.
 ** Data for 1q and chromosome 6 were given for 31/41 cases.

limited by the small numbers in each group. However, cases with severe anaplasia had a high incidence of 1q gain (6/9 cases, 67%, chi-square $p = 0.007$), and nodular/desmoplastic tumors had a particularly low incidence of idic(17)(p11.2) (6/48 cases, 13%, $p = 0.013$).

Loss of 17p and Gain of 17q Had Opposite Prognostic Associations

In total, 81/227 cases (36%) had 17p loss, the majority ($n = 64$) in the context of an idic(17)(p11.2). Idic(17)(p11.2) formation had no prognostic value (5-y OS $58 \pm 7\%$ vs $65 \pm 4\%$, $p = 0.444$). Isolated loss of 17p without associated 17q gain was identified less frequently ($n = 15$) but was associated with a significantly worse outcome (5-y OS $18 \pm 14\%$ vs $66 \pm 4\%$, $p = 0.003$). Gain of 17q was seen in 103/227 cases (45%) and had no impact on survival (5-y OS $66 \pm 5\%$ vs $61 \pm 5\%$, $p = 0.461$). However, over half of the cases (64/104, 62%) had an idic(17)(p11.2). The remainder, without associated 17p loss, showed a trend toward improved survival (5-y OS $78 \pm 7\%$ vs $60 \pm 4\%$, $p = 0.128$). Thus, classification based on chromosome 17 data alone indicated a survival hierarchy (Fig. 2A), with estimated 5-year OS rates of $78\% \pm 7\%$ for isolated 17q gain, $69 \pm 5\%$ with normal chromosome 17, $58 \pm 7\%$ with idic(17)(p11.2), and $18 \pm 14\%$ with isolated 17p loss. Of note, the cases with 17q gain consisted approximately equally of trisomy 17 and isolated gain of 17q. Both subsets showed the same trend toward improved survival, although the smaller sample sizes in each group resulted in less significant differences in outcome when analyzed individually. Loss and gain of small regions within chromosome 17 were reported only rarely. There were no overlapping minimal regions of loss or gain.

When the chromosome 17 outcome data were stratified according to clinical criteria, the survival advantage was still apparent. For metastatic disease, two patterns were seen (Fig. 2B). In general, patients with nonmetastatic disease had better 5-year OS ($72 \pm 8\%$ to $75\% \pm 9\%$) than those with metastatic disease ($8 \pm 8\%$ to $49 \pm 11\%$), with the following two exceptions. Gain of 17q without associated 17p loss was associated with good survival and isolated loss of 17p with poor survival irrespective of metastatic disease.

Stratification by surgical resection revealed a similar pattern. Isolated 17q gain was associated with good survival—estimated 5-year OS $81 \pm 12\%$ and $78 \pm 14\%$ following complete and incomplete resection, respectively. In contrast, isolated 17p loss was associated with poor survival—estimated 5-year OS 0% and $17 \pm 14\%$ following complete and incomplete resection. Tumor resection had no demonstrable effect on survival for cases with an idic(17)(p11.2) (5-y OS $63 \pm 11\%$ and $56 \pm 12\%$). For cases with a normal chromosome 17, the completeness of resection had a greater impact (5-y OS $83 \pm 6\%$ and $51 \pm 12\%$, respectively).

An attempt was made to analyze the prognostic significance of chromosomal changes in adults and children

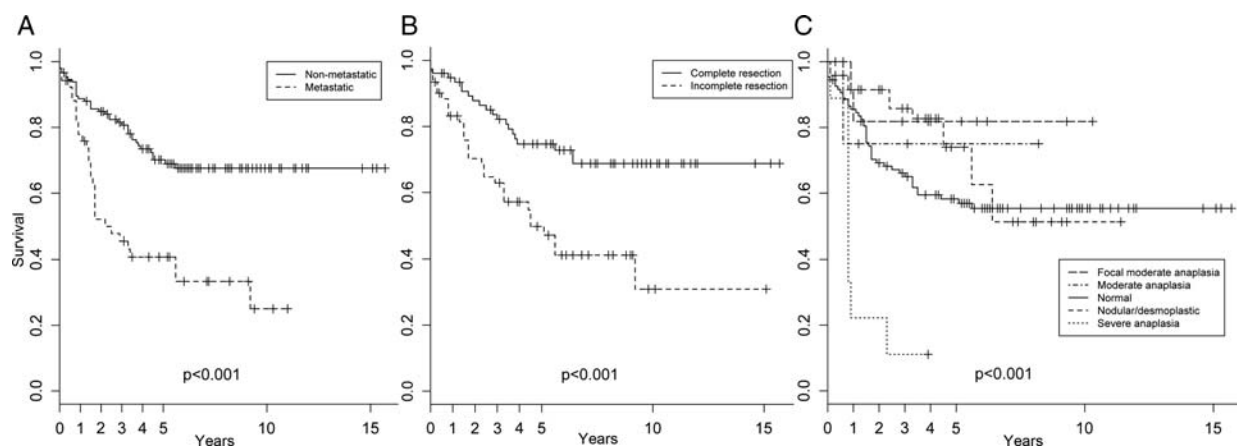


Fig. 1. Univariate analysis of established clinical risk factors in the combined dataset. The Kaplan–Meier method was used to estimate survival according to the presence of metastases at diagnosis (A), the extent of primary surgical resection (B), and histological subtype (C). Survival in the dataset was inferior for the groups with metastatic disease (5-yr OS $41 \pm 7\%$ vs $70 \pm 4\%$) and incomplete resection (5-yr OS $50 \pm 7\%$ vs $75 \pm 5\%$). Severe anaplasia correlated with poor survival (3-yr OS $11 \pm 11\%$ vs $72 \pm 4\%$).

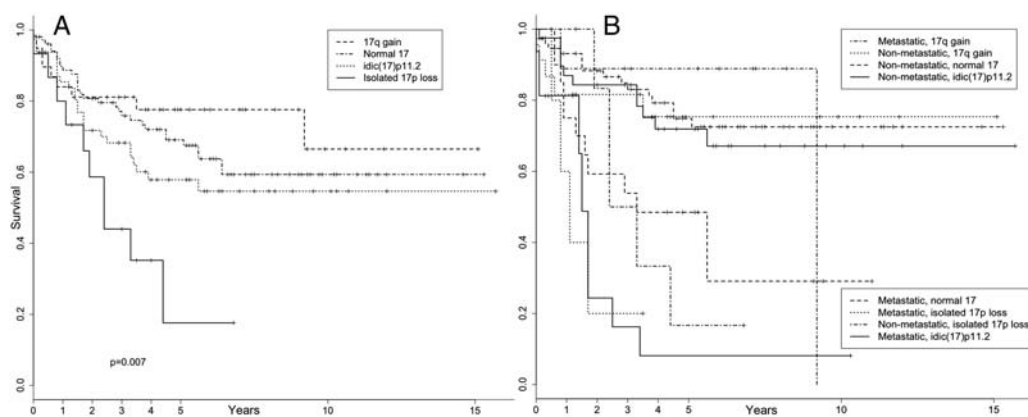


Fig. 2. The influence of chromosome 17 alterations on survival. (A) Chromosome 17 alterations were associated with significantly different outcomes. Estimated 5-year survival for isolated 17q gain, isodicentric chromosome 17, and isolated 17p loss were $78\% \pm 7\%$, $58 \pm 7\%$, and $18 \pm 14\%$, respectively. (B) The prognostic associations of 17p loss and 17q gain were still apparent following stratification according to clinical risk criteria. Metastatic patients with 17q gain had predicted 5-year OS similar to that of nonmetastatic patients. The longest surviving patient with 17q gain, with an incompletely resected primary tumor and metastatic disease, died at 9.2 years. The cause of death was not clear. In contrast, isolated 17p loss was associated with poor outcome, irrespective of the presence or absence of metastases.

separately. The subgroup analysis revealed identical trends in adults and children, although the reduction in numbers in each subgroup led to a fall in statistical significance. Stratification by chromosome 17 data alone demonstrated best survival in the subgroups with isolated 17q gain (adult $n = 3$, 5-y OS 100% ; child $n = 36$, 5-y OS $76 \pm 8\%$) and the worst for isolated 17p loss (adult $n = 5$, 5-y OS 0% ; child $n = 10$, 5-y OS $47 \pm 17\%$). This chromosome 17–based survival hierarchy was more striking for adults ($p = 0.004$) than children ($p = 0.162$). Further subgroup analysis stratified by metastatic disease status and completeness of resection was precluded by small or absent numbers in several subgroups, although where data were present the same trends were observed.

Copy number data for 1q and chromosome 6 were available from studies reporting chromosomal or array

CGH (total $n = 186$).^{17,28–31} On univariate analysis of the pooled dataset, gain of 1q (36/186, 19%) was associated with worse outcome (5-y OS $49 \pm 9\%$ vs $69 \pm 4\%$, $p = 0.021$; Fig. 3A). Only 2 adults had 1q gain, precluding meaningful subgroup analysis based on age. The association between 1q gain and poor outcome has been reported in only a single series, by Lo et al.¹⁷ When these data were removed from the dataset (remaining $n = 138$), outcome was equal between those with and without 1q gain (5-y OS $58 \pm 10\%$ and $66 \pm 5\%$, respectively, $p = 0.53$; Fig. 3B).

Monosomy 6 was a rare finding, seen in only 8/186 cases (4%, 7 children, 1 adult). Although the survival curve showed superior survival for cases with monosomy 6, there was no statistical difference in survival between the two groups (5-y OS $75 \pm 15\%$ and $64 \pm 4\%$, respectively, $p = 0.583$; Fig. 3C). Two of the

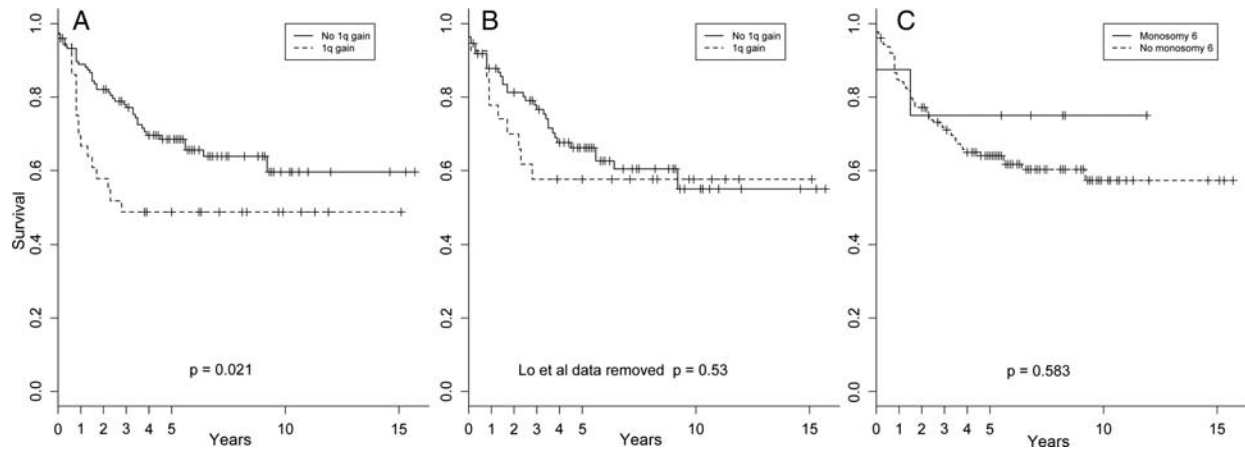


Fig. 3. The influence of other chromosomal alterations on survival. In the combined dataset, univariate analysis showed 1q gain to be associated with inferior survival (A). However, the data were skewed by a single report with a high mortality rate for cases with 1q gain. When those data were removed (B), there was no survival difference between the two groups. (C) Monosomy 6 was a rare finding. Although there was an appearance of improved outcome for these cases, the difference was not statistically significant.

8 patients with monosomy 6 died of disease, both within 2 years of diagnosis. Details of treatment, metastatic disease, and tumor resection were not available for all cases, including the patients who died.

We attempted to fit a Cox proportional hazards model to the data to determine whether the chromosomal alterations studied had additive predictive value over established clinical risk factors. However, although all studies reported complete chromosome 17 data, reporting of other variables was inconsistent between studies and only a minority of cases (65/227, 29%) had a complete dataset. The proportional hazards model based on these few cases contained only the clinical variables of metastatic disease, incomplete resection, and severe anaplasia.

To maximize the number of cases for which a multivariate model could be built, we created a series of modified datasets ($n = 15$) designed to systematically examine all possible combinations of variables in addition to chromosome 17, as described in the Methods section. We then fit multivariate models to the modified datasets using a bootstrapped criterion-based variable selection procedure (1000 bootstrap iterations per model). Details of the combinations of input variables and those included in the final models are shown in Table 2. Metastatic disease and incomplete resection remained prognostically significant in all models in which they were included ($n = 8$); histological subtype was prognostic in 6/8 models (75%); isolated 17p loss in 8/15 (53%); 17q gain without *idc(17)(p11.2)* in 4/15 (27%); 1q gain in 2/8 (25%) and *idc(17)(p11.2)* in 2/15 (13%). Monosomy 6 was not retained as a significant variable in any of the final models.

Discussion

The historical nature of this dataset is reflected in the relatively low rate of complete surgical resection and the relatively high number of patients who were not given combined chemoradiotherapy following surgery.

However, although treatment for medulloblastoma has changed significantly during the 13 years spanning the studies included in this analysis, for patients with completely resected, nonmetastatic tumors the 5-year survival of $81 \pm 5\%$ was comparable to that reported by recent large, prospective trials. Notwithstanding recent improvements in therapy, metastatic disease (Chang stage M2-3) continues to predict poor survival in prospective series.^{1,32,33} The influence of completeness of tumor resection on outcome is less clear, and large trials that report current best practice therapy have reported conflicting results.^{32,34}

Gain of 17q Has Not Previously Been Identified as a Predictor of Good Risk

Here we report associations between 17p loss and poor outcome and between 17q gain and improved outcome. Until recently the issue of chromosome 17 alterations in predicting outcome has been confused by several factors. Most studies have reported small numbers, with insufficient power to detect survival effects, and several authors have therefore reported chromosome 17 alterations to have no impact on survival.^{11,17,21–24,35} The variables correlated to survival have been 17p loss,^{14,22,23,35,36} *idc(17)(p11.2)* formation,^{21,24} 17q gain or a combination of these,^{8,11,15–17} and the analysis of multiple different chromosome 17 alterations using a variety of techniques has further confused the issue. The analysis we report here from a large, pooled historical dataset indicates that isolated 17p loss, *idc(17)(p11.2)* formation, and isolated 17q gain have markedly different prognostic value.

Isolated 17p loss has recently been reported to correlate with poor outcome by several independent groups in addition to this report.^{7,8,13} Our identification of a trend toward improved outcome with isolated 17q gain is novel. One previous study has correlated 17q alterations with survival.⁸ Explicit data were not reported. In that

Table 2. Multivariate models. To minimize the effects of missing data, a series of modified datasets were generated to systematically examine combinations of input variables while excluding missing data. Multivariate models were built from these data using a bootstrapped criterion-based variable selection procedure with the R program “bootStepAIC.” The combinations of variables examined in each model and the effect on sample size of excluding cases with missing values are shown. Each row corresponds to one model. Variables selected for inclusion in the final model for each combination are highlighted gray. The variables included in $\geq 25\%$ of final models were (in decreasing order of stability) metastatic disease and incomplete resection, severely anaplastic histology, isolated 17p loss, isolated 17q gain, and 1q gain.

Sample Size	Metastases	Incomplete Resection	Histology	idic(17)(p11.2)	17p loss*	17q gain*	1q gain	Monosomy 6	p-Value**
201	•			•	•	•			<0.001
186				•	•	•	•	•	0.019
184			•	•	•	•			<0.001
173	•		•	•	•	•			<0.001
161	•			•	•	•	•	•	<0.001
143			•	•	•	•	•	•	0.002
138		•		•	•	•			<0.001
133	•		•	•	•	•		•	<0.001
132	•	•		•	•	•			<0.001
111		•	•	•	•	•			<0.001
105	•	•	•	•	•	•			<0.001
97		•		•	•	•	•	•	0.038
92	•	•		•	•	•	•	•	0.025
70		•	•	•	•	•	•	•	0.006
65	•	•	•	•	•	•	•	•	0.004

*17q gain and 17p loss not in the context of an idic(17)(p11.2).

**Likelihood ratio test p-value.

study, 17p loss and idic(17)(p11.2) were both associated with poor OS. In direct contrast to our data, however, isolated 17q gain was also correlated with poor outcome. Reasons for the discrepancy between the studies are not immediately clear. The analysis we report and that of Pfister and colleagues share common drawbacks. They are both retrospective and report a variety of therapeutic protocols. In the Pfister study alone, at least 4 protocols were followed. Both studies used a combination of CGH (or array CGH) and FISH to analyze copy number. In the dataset we report here, all cases of 17q gain without 17p loss were identified using metaphase or array CGH, while in the Pfister study, 43/50 samples with 17q gain were identified using interphase FISH. In our hands, dual color interphase FISH has given unreliable results in the detection of single copy gain, due to difficulty in reliably distinguishing closely packed adjacent nuclei in paraffin-embedded tissue (unpublished data). Nonetheless the Pfister dataset was large and its 17q findings were replicated in a test set ($n = 80$) and a validation set ($n = 260$). Our dichotomous findings are interesting and should be further explored in future prospective studies. Why 17p loss should associate with poor survival and 17q gain with improved survival are not clear.

The Specific Relationship between Monosomy 6 and Outcome Is Not Yet Clear

Several independent groups have recently reported associations between monosomy 6, mutations of the catenin (cadherin-associated protein) beta 1 gene (*CTNNB1*),

nuclear immunopositivity for *CTNNB1*, and nonmetastatic disease.^{10,18,19,40} The precise relationships between these factors are yet to be established. To date there is insufficient evidence to support the biological equivalence of nuclear beta-catenin expression, *CTNNB1* mutations, and wingless-integrated (Wnt) pathway activation, and it is not clear why alterations in the sequence or expression of *CTNNB1* should relate to loss of one copy of chromosome 6. To our knowledge, 21 cases have so far been reported with monosomy 6 in association with either nuclear *CTNNB1* expression, *CTNNB1* mutations, or Wnt pathway activation. Other cases are reported either with monosomy 6 and no evidence of Wnt pathway activation ($n = 2$)¹⁹ or evidence of Wnt/*CTNNB1* activation without monosomy 6 ($n = 7$).^{10,19,40} However, while there is strong evidence of an association between nuclear *CTNNB1* expression and improved survival,^{9,10} the specific links between monosomy 6, Wnt pathway activation, and survival have yet to be identified. Our pooled data did not support a prognostic relationship. However, monosomy 6 is a very rare finding in medulloblastoma, precluding meaningful analysis outside of a very large series of tumors. Of interest, in keeping with previous literature, none of the patients with monosomy 6 in our pooled dataset had metastatic disease.

In conclusion, we have analyzed the prognostic value of chromosomal alterations in a large, combined dataset of medulloblastomas. We have shown that isolated 17p loss had clear negative prognostic value, while isolated 17q gain showed a trend to improved outcome independently of clinical criteria. We have shown that idic(17)(p11.2) did not clearly correlate with outcome.

Further, we report that published data are not yet sufficiently robust to show a convincing association between 1q gain and survival. The findings from this historical series should be investigated in future prospective studies. The identification of particularly poor-risk and good-risk tumors, even if the relative numbers are small, will be critical in stratifying treatment in future trials. A significantly greater challenge will be to identify the single-gene correlates of the large-scale chromosomal changes discussed here.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

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