

The 1p Deletion Is Not a Reliable Marker for the Prognosis of Patients with Neuroblastoma¹

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ABSTRACT

Human neuroblastoma cells often have deletions of the distal short arm of chromosome 1 (1p). Earlier studies using chromosome analysis had suggested that the 1p deletion is correlated with a poor survival chance for the patient. We have reevaluated this possibility by analyzing 51 neuroblastomas for loss of heterozygosity (LOH) at 1p. We detected LOH in 32% of the cases. LOH did not correlate with the age of the patients at diagnosis or with tumor stage but was correlated significantly with amplification of the *MYCN* proto-oncogene. Nine of 10 *MYCN*-amplified tumors had deletions in 1p ($P < 0.001$). Survival chances of patients with tumors carrying *MYCN* amplification together with the deletion at 1p were decreased significantly (eight of nine affected patients died) compared with a patient group without any of these aberrations ($P < 0.001$). However, the deletion of 1p alone without *MYCN* amplification was not associated with a poor outcome compared with patients who had neither deletion nor amplification (only two of eight affected patients died; $P = 0.803$). From these data we conclude that 1p deletions are not reliable markers to determine a patient's prognosis. They may, however, identify a subgroup of neuroblastomas in which *MYCN* is amplified readily, resulting in rapid tumor progression.

INTRODUCTION

Neuroblastoma is the most frequent type of solid tumor in children, with an annual incidence of 1 per 100,000 in Germany (1). Prognostic parameters for neuroblastoma patients are both tumor stage and age of the patient at the time of diagnosis. Localized tumors (stage I or II), stage IVs tumors, and tumors in children younger than 1 year of age at diagnosis are associated with a good survival prognosis, whereas advanced or metastatic tumors (stage III or IV) or tumors in children older than 1 year of age are correlated with a poor prognosis. Cytogenetic studies (2-4) have identified partial monosomy of 1p as the most consistent chromosomal aberration in neuroblastoma cells. On the basis of RFLP markers, the incidence of LOH³ at 1p varied in different studies between 22 and 89% (5-9). Most of the deletions overlap at 1p36, which indicates that loss of genetic information from this band may contribute to neuroblastoma. Some of these studies (10, 11) have suggested on the basis of cytogenetic analyses a prognostic value of 1p deletion with a correlation to shorter survival time, but the clinical significance has remained a matter of controversy. Part of this controversy has been due to the fact that 1p deletions have been evaluated together with another genetic alteration, *MYCN* amplification. The amplification of the gene *MYCN* has been shown to be correlated strongly with advanced clinical stages and low survival chances (12, 13). Neuroblastoma has been the first tumor in which

gene amplification as a molecular aberration turned out to be of clinical significance (for review, see Ref. 14).

In this study, we have analyzed 51 neuroblastomas for both deletions at 1p with RFLP and (CA)_n microsatellite markers and the status of *MYCN* to delineate the significance of 1p deletions. Statistical analysis revealed no significant correlation of 1p deletions alone with stage, age at diagnosis, or poor outcome, whereas *MYCN* amplification together with 1p deletions was associated with poor survival chances. These data show that only *MYCN* amplification, not 1p deletion, is an independent marker that can be used to assess the prognoses of patients with neuroblastoma.

MATERIALS AND METHODS

Tumor and Control DNA. Fifty-one neuroblastoma samples were obtained from different hospitals cooperating within the framework of the German Neuroblastoma Study Group. Tumors were staged at diagnosis according to the system of Evans *et al.* (15). Briefly, stage I and II tumors are localized; stage III tumors are regional; stage IV tumors are widely metastatic; and stage IVs tumors are found in infants younger than 1 year with a high rate of spontaneous regression. Reference DNA was isolated from peripheral blood lymphocytes or from EBV-transformed lymphoblastoid cell lines of the corresponding patient.

RFLP Analysis. Preparation, digestion, and Southern analysis were done as described (8). DNA probes to detect LOH on 1p were used: p1-79 (16), p1-31 (17), LMS1 (18), and YN22 (19, 20), which are located on the loci *D1Z2*, *D1S112*, *D1S7*, and *D1S57*, respectively. *MYCN* amplification was determined by using the 1.0-kb insert of the plasmid Nb-1 (21).

(CA)_n Microsatellite Analysis. PCR analysis was done as described (22). Four microsatellite loci, *D1S243*, *D1S199*, *D1S216*, and *D1S305* from 1p, and the locus *D1S249* from 1q were analyzed (22).

Statistical Analysis. The significance of the correlation between 1p deletion and clinical stage or patient's age at diagnosis, respectively, was examined by the Fisher's exact test (23, 24). The survival curves were estimated by the Kaplan-Meier method (25).

RESULTS

Detection of 1p Deletions by RFLP and (CA)_n Polymorphism. Fifty-one tumors and the cell line HD-MG-1, established from one of these tumors, were analyzed by PCR amplification of five polymorphic (CA)_n repeats. Twenty-one of these tumors were analyzed additionally with four RFLP markers. All 51 patients showed a heterozygous genotype in the reference DNA from peripheral blood lymphocytes at one or more loci on 1p. A total of 17 tumors (32%) had 1p deletions, which varied in size but seemed to include the distal end of 1p (data summarized in Table 1).

Correlation between 1p Deletions, Tumor Stage, and Patient's Age at Diagnosis. Three patients had tumors according to Evans' stage IVs; another three patients had stage I tumors. Six patients had stage II tumors; nine patients stage III tumors; and 30 patients stage IV tumors. Twelve of 30 stage IV, 2 of 9 stage III, 2 of 3 stage I, and 1 of 3 stage IVs tumors had deletions in 1p. In none of the six stage II tumors was a deletion detected.

For the statistical analysis, the prognostically favorable stages I, II, and IVs were combined and compared with the prognostically unfav-

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³ The abbreviation used is: LOH, loss of heterozygosity.

Table 1 Distribution of 1p LOH in neuroblastomas

Patient	Chromosomal local									
	<i>DIS243</i> 1p36	<i>DIS199</i> 1p33	<i>DIS216</i> 1p21	<i>DIS305</i> zentromer	<i>DIS249</i> 1q32-qter	<i>DIZ2</i> 1p36.3	<i>DIS112</i> 1p36.11	<i>DIS7</i> 1p35-p33	<i>DIS57</i> 1p35-p32	<i>MYCN</i>
90	+	n.i.	+	-	-	+	n.i.	n.i.	+	1
248	+	+	n.i.	-	-	n.d.	n.d.	n.d.	n.d.	1
267	+	n.i.	+	+	-	n.d.	n.d.	n.d.	n.d.	110
230	+	+	n.i.	-	-	n.d.	n.d.	n.d.	n.d.	60
88	n.i.	+	+	-	-	+	n.d.	+	n.d.	80
82	+	+	-	-	n.i.	+	n.d.	+	n.d.	1
241	+	+	-	n.i.	-	n.d.	n.d.	n.d.	n.d.	100
126	+	+	n.i.	-	n.i.	+	n.d.	+	n.d.	20
96	+	+	+	-	-	+	n.i.	+	+	100
239	+	+	-	-	n.i.	n.d.	n.d.	n.d.	n.d.	1
123	+	+	n.i.	-	n.i.	+	n.i.	+	n.i.	1
101	+	+	n.i.	-	n.i.	+	n.d.	+	n.d.	90
244	+	+	+	-	-	n.d.	n.d.	n.d.	n.d.	80
242	+	n.i.	+	n.i.	-	n.d.	n.d.	n.d.	n.d.	70
246	+	-	-	n.i.	-	n.d.	n.d.	n.d.	n.d.	1
250	n.i.	+	n.i.	-	-	n.d.	n.d.	n.d.	n.d.	1
76	n.i.	+	n.i.	-	-	n.d.	n.d.	n.d.	n.d.	1

^a +, deleted; -, not deleted; n.d., not determined; n.i., not informative.

Table 2 Clinical and genetic data of neuroblastoma patients

Patient	Sex	Stage	Age (mo)	Tissue	Survival (mo)	Status	<i>MYCN</i>	1p
90	M ^a	IVs	2	Primary tumor	48	+	1	+
51	M	IVs	7	Primary tumor	51	+	1	-
188	M	IVs	0	Primary tumor	28	+	1	-
248	F	I	12	Primary tumor	22	+	1	+
267	M	I	26	Primary tumor	15	+	110	+
261	M	I	1	Primary tumor	11	+	1	-
117	M	II	3	Primary tumor	41	+	1	-
214	M	II	8	Primary tumor	12	+	1	-
252	F	II	15	Primary tumor	?	-	1	-
255	M	II	23	Primary tumor	6	+	1	-
39	F	II	36	Primary tumor	61	+	1	-
265	M	II	53	Primary tumor	?	-	1	-
88	F	III	51	Metastatic tumor	19	-	80	+
230	F	III	59	Primary tumor	7	-	60	+
92	M	III	1	Primary tumor	43	+	1	-
79	F	III	6	Primary tumor	15	-	1	-
266	M	III	12	Primary tumor	21	+	1	-
42	M	III	19	Primary tumor	60	+	1	-
237	F	III	44	Metastatic tumor	17	+	1	-
81	F	III	67	Tumor-relapse	50	+	1	-
83	M	III	85	Primary tumor	28	-	15	+
250	M	IV	1	Bone marrow	19	+	1	+
82	M	IV	3	Primary tumor	12	-	1	+
242	F	IV	10	Primary tumor	11	-	70	+
241	F	IV	19	Bone marrow	8	-	100	+
96	M	IV	20	Primary tumor	7	-	100	+
126	F	IV	20	Primary tumor	8	-	20	+
239	F	IV	23	Primary tumor	15	+	1	+
246	M	IV	38	Primary tumor	19	-	1	+
123	M	IV	42	Primary tumor	43	+	1	+
101	M	IV	51	Primary tumor	4	-	90	+
244	M	IV	58	Primary tumor	9	-	80	+
76	F	IV	88	Primary tumor	48	+	1	+
186	F	IV	6	Primary tumor	27	+	1	+
221	F	IV	13	Primary tumor	23	+	1	-
45	F	IV	17	Primary tumor	14	-	1	-
47	M	IV	18	Primary tumor	41	+	1	-
103	F	IV	22	Primary tumor	16	-	1	-
46	F	IV	28	Primary tumor	17	-	1	-
260	M	IV	30	Primary tumor	14	-	1	-
125	M	IV	38	Primary tumor	40	+	1	-
256	M	IV	39	Primary tumor	4	+	1	-
236	F	IV	42	Primary tumor	25	+	1	-
34	F	IV	42	Primary tumor	70	+	1	-
218	M	IV	52	Primary tumor	25	+	1	-
118	M	IV	53	Primary tumor	16	-	1	-
264	F	IV	55	Bone marrow	8	+	1	-
247	M	IV	74	Primary tumor	19	+	1	-
168	M	IV	83	Primary tumor	37	+	1	-
100	F	IV	122	Primary tumor	?	-	1	-
119	M	IV	246	Primary tumor	21	+	1	-

^a M, male; F, female; survival, months after diagnosis; status: +, alive; -, dead; ?, unknown; *MYCN*: 1, single copy; >1, amplified; 1p: +, deleted; -, no deletion.

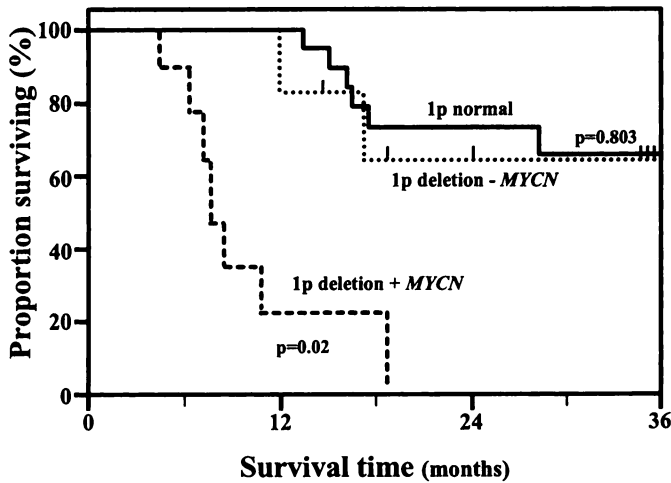


Fig. 1. Survival curves of patients with and without *MYCN* amplification and 1p deletions. $P = 0.02$ for patients with 1p deletions and *MYCN* amplification compared with patients with 1p deletions without *MYCN* amplification; $P = 0.803$ for patients with 1p deletions without *MYCN* amplification compared with patients without aberrations. The median follow up time for 1p-normal patients was 28 months; the median follow-up time for patients with 1p deletions without *MYCN* amplification was 25 months; individual follow-up times are indicated by vertical bars.

avorable stages III and IV. Applying Fisher's exact test, no significant correlation between 1p deletion and tumor stage was found ($P = 0.7278$).

Thirty-seven patients were older than 1 year at the time of tumor diagnosis. Twelve of these children had tumors with 1p deletions. In comparison, 5 of 14 children who were younger than 1 year at diagnosis had tumor with 1p deletions. Again, these data do not suggest a significant correlation between 1p deletions and age at diagnosis (clinical data are summarized in Table 2).

***MYCN* Amplification and 1p Deletion.** Ten of the 51 tumors had *MYCN* amplification (data not shown). Nine of these 10 tumors had 1p deletions. The deleted region included the 1p21-pter region in 8 of the 9 cases (Table 1). The correlation between *MYCN* amplification and 1p deletion was significant ($P < 0.001$; Table 1).

Children older than 1 year at diagnosis with 1p deletions were affected by amplification of *MYCN* in 66% (8 of 12) of the cases. In contrast, younger children with 1p deletions showed a low incidence of amplification [1 (20%) of 5; Table 2].

Survival Analysis. Children with tumors in which both *MYCN* was amplified and 1p was deleted had a significantly lower survival rate than children with only 1p deletions ($P = 0.02$) or children without any of these aberrations ($P < 0.001$). Six of eight patients with 1p deletions but without *MYCN* amplification are still alive and, therefore, revealed no significantly reduced survival rate compared with the patients lacking both 1p deletions and amplification of *MYCN* ($P = 0.803$). The median follow-up time for 1p-normal patients was 28 months; the median follow-up time for patients with 1p deletions without *MYCN* amplification was 25 months; individual follow up times are given in Fig. 1. Survival rates of the three subgroups: (a) tumors without apparent aberrations in 1p or *MYCN*, (b) 1p deletions without *MYCN* amplification, and (c) 1p deletions plus *MYCN* amplification, are summarized in Fig. 1.

DISCUSSION

In the present study, we found that 32% of the neuroblastomas have LOH at 1p, which is in good agreement with most of the previous deletion studies using RFLP markers (5–7, 26, 27). All deletions involved the distal portion of 1p; the commonly deleted region

spanned 1p36-pter, but some tumors had much more extended deletions. In previous studies (5, 28, 29), most of the deletions found in neuroblastoma were also terminal. These results suggest that 1p36-pter may be the location of one or more tumor suppressor genes, which could be involved in neuroblastoma. In a recent study (30), some tumors showed small interstitial deletions within 1p36, whereas others had large terminal deletions. Children with interstitial deletions had tumors of nonadrenal origin, which progressed to stage IV rarely. In contrast, patients with terminal deletions had tumors of adrenal origin, which progressed to stage IV. The authors, therefore, proposed the presence of two tumor suppressor loci at 1p, each of which identified a biologically distinct subtype of neuroblastoma with either a good or bad outcome, respectively. Despite the high density and degree of polymorphism of the probes that we used, in this study, we did not detect interstitial deletions in 51 cases analyzed. Therefore, it seems as if terminal deletions are the most prominent aberration at 1p in neuroblastoma.

Statistical evaluation of our data revealed that children with both *MYCN* amplification and 1p deletions had a significantly lower survival rate than children with 1p-undeleted tumors. *MYCN* amplification, with the exception of one tumor, was always associated with 1p deletion. On the other hand, eight tumors which had 1p deletions revealed no *MYCN* amplification. Six of these patients are still alive, whereas only 1 of the 10 patients with *MYCN* amplification survived. These results show clearly that 1p deletion alone is not a good parameter to assess prognosis and at the same time reinforce previous data that *MYCN* amplification is correlated with rapid tumor progression and poor outcome. In contrast, independent 1p deletions were not associated with the same aggressive type of tumor. In previous reports the prognostic value of 1p deletions was discussed controversially. In a cytogenetic study analyzing 1p deletion in comparison to clinical parameters, all but one patient with 1p deletion died as a result of disease progression (31). The prognostic significance of both parameters, 1p deletion and *MYCN* amplification, was evaluated by Fong *et al.* (5). Both 1p deletions and *MYCN* amplification were correlated with poor outcome, but when cases with only 1p deletions were considered, the prognostic value was lost. *MYCN* amplification, however, did retain its prognostic value after correcting for 1p deletion. The same result emerged from a study involving 377 patients in which *MYCN* amplification turned out to be the only relevant molecular prognostic factor (32).

Although the basis of the apparently contradicting conclusion of the various studies is not totally clear, it is possible that the different approaches of chromosome *versus* DNA analysis have different sensitivity for detecting a loss of genetic information from 1p. Aside from the possibility that a bias may be introduced into chromosome analyses by individual capabilities of tumor cells to grow in short-term *in vitro* culture and to yield chromosome preparations suitable for analysis, it is obvious that small deletions escape detection through cytogenetic inspection. Large deletions that are readily detectable by cytogenetics appear preferentially in conjunction with *MYCN* amplification (33; this study) and are, therefore, often associated with aggressive tumors, which could again result in a bias introduced by cytogenetic analyses.

Altogether, our results demonstrate that the prognostic significance of 1p deletion and *MYCN* amplification has to be evaluated by independent comparison of these parameters with clinical data. It seems that of the two genetic alterations, only *MYCN* amplification is an independent prognostic parameter. Our findings might also be interpreted to suggest that the deletion of 1p presents an early event in the development of neuroblastoma and precedes *MYCN* amplification. Future studies have to show whether a functional correlation of

genes at 1p36 and *MYCN* amplification exists or if the 1p deletion signals simply a genetic instability of the tumor cell, which may be a prerequisite for the amplification process.

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