Clinical Investigation of Neuroblastoma with Partial Deletion in the Short Arm of Chromosome 1

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ABSTRACT
Several loci on the short arm of chromosome 1 (1p) have been reported as the consensus deleted regions for the putative suppressor genes of neuroblastoma by deletion mapping. The significance of deletion in 1p on the clinical features of neuroblastoma remains controversial. To clarify the relationship between the clinical features of neuroblastoma cases and genetic status of 1p, we performed deletion mapping on 1p on samples obtained from 58 cases with neuroblastoma using 12 highly polymorphic microsatellite or minisatellite loci. Loss of heterozygosity of 1p was detected in 19 cases (33%) of primary tumors and in 21 cases (36%) when metastatic and recurrent sites were included. They were classified into two groups according to the 1p deletion pattern: interstitial deletion (group I, n = 11) and terminal deletion (group T, n = 10). The shortest region of overlap in group I ranged between FGR and DIS170 (1p36.1-2). Clinically, all group I cases survived disease free, and none of these cases showed MYCN amplification. However, in group T, eight (80%) cases showed a large terminal deletion from DIS162 (1p32-pter), including the shortest region of overlap of group I, and two (20%) showed a very terminal deletion from DIS160 (1p36.3). Of the group T cases, only two survived disease free, and seven (70%) showed MYCN amplification. Thus, the candidates for the locations of neuroblastoma suppressor genes on 1p may involve at least two regions, which demonstrate different clinical features.

INTRODUCTION
Neuroblastoma, a childhood malignant tumor arising from neural crest, shows various clinical behaviors from spontaneous regression to unfavorable prognosis due to aggressive growth despite multimodal therapy. The prognosis mainly depends upon the biological characteristics of the tumor cells, especially amplification of the MYCN gene (1, 2), NTRK1 expression (3–7), telomerase activity (8), and DNA ploidy pattern (9–11). Alterations of chromosome 1p have been reported in 30–80% of clinical samples and cell lines that have been successfully karyotyped (12–16). Studies of the LOH on chromosome 1p, using RFLPs and/or microsatellite markers, have found that Ip LOH occurs in 30–40% of neuroblastoma tumor specimens (17–23) and that the SRO of 1p deletions maps to the chromosomal region 1p36.1–3. These data suggest that suppressor genes associated with neuroblastoma development may be located in this region, whereas recent more detailed analyses of 1p deletions have suggested the involvement of multiple different neuroblastoma suppressor genes on 1p (24–27). Although several prognosis-associated factors have been reported, data on the relationship between 1p deletion and patient prognoses have remained contradictory (18, 25, 26, 28–31).

Microsatellites and simple sequence repeats are ideal markers for highly informative DNA polymorphisms, because they are widely dispersed throughout eukaryotic genomes (32) and are easily detectable using the PCR (33–36), thus enabling a representative survey of the genome to be studied. In the present study, detailed deletion mapping of chromosome 1p, mainly using microsatellite loci, was carried out for neuroblastoma tumor specimens resected from 58 patients, and the clinical outcomes of these patients and biological behaviors of the tumors were analyzed.

MATERIALS AND METHODS
Patients. In the patients who underwent operation or surgical biopsy between 1984 and 1995 in our hospital or other institutions in Japan (listed in the “Acknowledgments”), both primary neuroblastoma tissue and normal tissue samples could be obtained from 58 patients at the time of the operation with informed consent. We enrolled these 58 patients in this study and also investigated eight metastatic samples (one bone marrow, three liver, and four lymph node metastatic lesions) and two relapse samples (one bone marrow and one intraabdominal relapse sample). Seven of the primary tumor samples were obtained after chemotherapy, and the remaining samples were resected before chemotherapy. All tumor samples contained more than 60% of tumor cells in specimens examined. In each case, normal tissue was sampled from peripheral blood, normal adrenal gland, or appendix to obtain constitutional DNA. These tumors and normal tissues were stored at −80°C until DNA isolation was performed. In these 58 patients, the ages at diagnosis ranged between 2 months and 20 years, and 36 patients

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3 The abbreviations used are: LOH, loss of heterozygosity; SRO, the shortest region of overlap; DI, DNA index.
were detected by a mass screening program for neuroblastoma that has been performed for infants aged 6 months in Japan. The disease staging was classified using the standard clinical and pathological criteria of Evans et al. (37). Stage III patients who were 1 year or older when their tumors were diagnosed and all stage IV patients were treated postoperatively with the protocol of the Study Group of Japan; they received cyclophosphamide, vincristine, doxorubicin, cis-dichlorodiamine platinum, and etoposide (38). Other patients underwent an operation and received postoperative chemotherapy consisting of cyclophosphamide, vincristine, and doxorubicin [the James’ (39) or Saint-Jude protocol (40)].

Isolation of DNAs. High molecular genomic DNA was isolated from tumor and normal frozen tissue specimens using proteinase K and SDS, followed by phenol/chloroform extractions as described previously (41). Genomic DNA was isolated from constitutional blood samples using a DNA Extractor WB kit (Wako, Osaka, Japan). Matched tumor and constitutional DNAs were used as templates for PCR amplification.

PCR Conditions. PCR procedure was performed with specific sets of primers at two minisatellite loci (D1S76 and D1S80, 1p36.3; Ref. 21), nine microsatellite loci (D1S160, 1p36.3; D1S170, 1p36.2; FGR, 1p36.2-1; CRTM and D1S168, 1p35; MYCLI, 1p32-34; D1S162 and D1S188, 1p32; and F13B, 1q31-32; Refs. 42–45), and one single strand conformational polymorphism locus (TNFR2, 1p36.2; Ref. 46). The PCR procedure for minisatellite loci was performed with 2–10 ng of template DNA in a reaction mixture containing 200 μM of each deoxynucleotide triphosphate, 1.5 mm MgCl2, 0.25 μM of each primer, and 1 unit of Taq DNA polymerase (Wako). PCR amplification protocol was performed using a Program Temp Control System PC-800 (Aste, Fukuoka, Japan) for 35 cycles of 60 s at 95°C, 70 s at 63°C or 57°C for D1S76 and D1S80, respectively, and 180 s at 74°C. Extension during the final cycle was continued for 10 min. The amplified fragments were examined by 2% agarose gel electrophoresis and ethidium bromide staining. In analysis for microsatellite loci, we performed with 2–10 ng of template DNA as the control of heterozygosity. We diagnosed LOH only when the observed intensity of one allele in the tumor DNA was less than 70% of expected intensity, which was calculated from the control, to minimize the effects of aneuploidy.

Southern Blot Hybridization. MYCN amplification and LOH of the MYCLI (RFLP) locus were investigated by Southern blot analysis as reported previously (8). Briefly, 2 μg of genomic DNA were digested to completion with 10 units of the restriction enzyme EcoRI. The DNA fragments were separated by electrophoresis on 0.8% agarose gels and then blotted onto nitrocellulose filters. The filters were hybridized with an MYCN probe (PN-myc.1, Oncor Inc., Gaithersburg, MD) or an MYCLI probe (JCRB CO049) and subjected to autoradiography.

Flow Cytometric Analysis of the Cellular DNA Content. Cellular DNA content was analyzed as reported previously (47–49). Briefly, tumor samples were thawed to 20°C and disrupted mechanically using scissors. After treatment with trypsin to isolate bare nuclei, the samples were stained with propidium iodide using a modified method of Vindeløv et al. (50) and analyzed with a FACSscan flow cytometer (Becton Dickinson, San Jose, CA). Results for 20,000 nuclei were plotted as histograms. The DI was determined by calculating the ratio of modal channel numbers of the tumor G0-G1 peak to that for normal diploid cells. Hence, the DI of diploid neuroblastoma cells was 1.0; tumors with a distinct population from DI = 1.0 were defined as aneuploid. Tumors were considered tetraploid if a peak occurred with a DI of 1.90–2.10 in at least 20% of the analyzed cells and if a peak corresponding to a G2-M tetraploid cell population was also present. When more than two different aneuploid G0-G1 cell populations were present, the tumor was classified as polyploid.

Statistical Analysis. Correlations between 1p LOH and each of the other factors were analyzed using χ2 or Fisher’s exact test where appropriate. The overall survival curves for each group of patients were estimated by the Kaplan-Meier method, and the resulting curves were compared using the Cox-Mantel test. Differences were considered significant at P ≤ 0.05.

RESULTS

Deletion Mapping of Chromosome 1p. All 70 tumors including recurrent and metastatic tumors from 58 cases were informative for more than 3 of the 12 loci on chromosome 1p. The observed heterozygosity indices of 10 microsatellite markers ranged from 0.54 to 0.82, and those of two minisatellite markers were 0.52 and 0.68, respectively, which were similar to the reports described previously (21, 36, 42–46). Among the 58 primary tumors, including 7 samples obtained after chemotherapy, 19 (33%) showed LOH on at least one locus. In these primary tumor samples with LOH, only one (N145) was obtained after chemotherapy. Moreover, two cases (N30 and N199) showed LOH in recurrent or metastatic sites without detectable LOH in the primary tumor. Thus, 1p LOH was detected in 21 of 58 cases (36%), and representative LOH patterns were shown in Fig. 1. Results of deletion mapping on 1p in these 21 cases were shown in Fig. 2. On the basis of the deletion patterns, we classified these cases into two groups: interstitial deletion (group I, n = 11) and terminal deletion (group T, n = 10). In group I, the SRO encompassed the locus of the observed intensity of one allele in the tumor DNA was
proximal to *FGR* and distal to *D1S170* (1p36.1–2). In group T, the SRO encompassed the locus distal from *D1S160* (1p36.3-pter), and eight of these cases showed a large deletion encompassing the locus distal from *D1S162* (1p32-pter). We classified the cases without detectable LOH on any locus examined in 1p as group N (*n* = 37).

**Clinical Aspects of Cases with 1p LOH.** We compared age at diagnosis, result of mass screening, stage, primary site, and outcome among three groups (Table 1). Although 8 of 11 group I patients were diagnosed at under 12 months of age, more than one-half of the group T patients were older than 12 months old. LOH on 1p was observed in 8 of 36 patients detected by...
mass screening and in 13 of 22 remaining patients. There was a significant difference in the incidence of 1p LOH between the patients detected by mass screening and other patients ($\chi^2 = 6.57$, df = 1, $P = 0.011$). In the patients (excluding those detected by mass screening), the incidence of group T was not significantly different between the cases under 12 months and in the cases older than 12 months at diagnosis [4 of 6 (66%) vs. 22 (59%) of 37 in group N were stage I, II, or III.](56)

According to the stage classification of Evans et al. (37), six cases (55%) of 11 in group I, two (20%) of 10 in group T, and 22 (59%) of 37 in group N were stage I, II, or III. Group T cases were in significantly more advanced stages of disease ($P = 0.030$). There was no significant difference in the primary tumor sites among these three groups.

The outcomes of the 58 patients are shown in Fig. 3. All 11 Group I patients have survived disease free, whereas only 2 (20%) group T patients and 29 (78%) group N patients have. The overall survival rates at 3 years in groups I, T, and N were 100, 33.3, and 90.7% (Fig. 3A), respectively. There were significant differences in the overall survival rates between groups I and T ($P < 0.01$) and between groups T and N ($P < 0.01$).

**Biological Aspects of Cases with 1p LOH.** Table 1 shows the relationships between 1p LOH patterns and two other biological factors, DNA ploidy pattern and MYCN amplification. In 55 cases, 23 cases were diploid (2n), 28 cases were aneuploid (3n), three cases were tetraploid (4n), and one case was polyploid (Pn). There were no significant differences in ploidy patterns among these three groups.

MYCN amplification was detected in 9 (14%) of 58 cases, and 1p LOH was detected in seven of those nine cases; all seven cases were in group T with large 1p deletions on D1S162-pter as the SRO. MYCN amplification was significantly detected in group T ($\chi^2 = 22.28$, df = 2, $P < 0.001$), especially with large 1p deletions. The outcomes of cases with or without MYCN amplification are shown in Fig. 3B. The overall survival rate of the cases with MYCN amplification was significantly poorer than those without MYCN amplification ($P < 0.01$). Both patients (N145 and N160) with deletions in the very distal region (1p36.3-pter) had lack of MYCN amplification but were unlikely to have a favorable outcome because of the evidence of tumor recurrence and difficulty in controlling liver metastases, respectively. As shown in Fig. 3C, the outcomes of the cases with MYCN amplification or 1p terminal deletion were poor, whereas the remaining cases have survived except for one case.

**Tumors Samples at Different Sites or Times.** For eight cases, we examined 1p LOH analysis at the different sites or times in the same case, and in four cases, we observed different results on 1p LOH analysis among tumors (Table 2). In case N199, both a large deletion of 1p32-pter and MYCN amplification were detected in his recurrent tumor but were not detectable in his primary tumor. In case N186, whose primary tumor consisted of two morphologically and histologically different portions, neuroblastoma and ganglioneuroblastoma, a large deletion of 1p (1p32-pter) was detected in the neuroblastoma portion but not in the ganglioneuroblastoma portion. In cases N30 and N66, all specimens obtained from their primary tumors and metastatic tumors showed the same copy number of the amplified MYCN gene (50 and 40 copies, respectively). However, a large deletion on 1p32-pter was detected in the lymph node metastasis of case N30 and in the primary tumor and lymph node metastasis of N66 but was undetectable in other specimens. Moreover, the primary and metastatic tumors in case N30 were considered to contain multiple clones, demonstrating a different combination of MYCN gene rearrangement (51) and the 1p32-pter LOH pattern, but all these clones had the same.
Genomic Instability in Neuroblastoma. Differences between tumor and constitutional DNA banding patterns at several microsatellite loci indicate genomic instability (52, 53). In the present study, only 1 of 58 cases (1.7%) showed genomic instability at more than two microsatellite loci. In this case, the disease was at stage I, and the patient survived disease free. This low frequency suggests that genomic instability does not play a major role in neuroblastoma carcinogenesis (53, 54).

DISCUSSION

In the present study, we examined 58 neuroblastoma cases for 1p LOH using several markers in the distal 1p region. LOH for 1p occurred with a frequency of 33% in primary neuroblastomas and with a frequency of 36% when metastatic and recurrent sites were included. The two cases (N30 and N199) with LOH detected in only recurrent or metastatic sites indicated the possibility of induction or selection of tumor cells with 1p LOH during tumor progression and/or chemotherapy. Although our series contained a large proportion of stage I tumors detected by mass screening and the incidence of 1p LOH in the cases detected by mass screening was significantly lower than that of other cases, the overall frequency of 1p LOH in the present study is similar to those reported in previous studies (17, 23, 26, 55).

Except for two cases (N145 and N160), the SRO in our series was at FGR-D1S170. This region on 1p36.1–2 was indicated as being the site of a candidate neuroblastoma suppressor gene. The results of many studies using RFLP analysis also indicate that a candidate location for neuroblastoma suppressor gene(s) may be located on 1p36 (17–23). A recent study using microsatellite markers by Takeda et al. (25) reported the SRO on FGR-DIS47, which contains our SRO, although White et al. (56) reported that the SRO of neuroblastoma was on 1p36.2–3 (TNFR2-DIS80), which is distal to the site identified in our study. Moreover, the two cases (N145 and N160) in the present study showed very distal 1p deletions at DIS160-pter, which is more distal portion of the SRO reported by White et al. (56). These apparently contradictory results of SRO might indicate the existence of multiple neuroblastoma suppressor genes.

Because multiple neuroblastoma suppressor genes may be located in 1p, we tentatively classified the cases with 1p LOH into two groups according to the deletion patterns: interstitial deletion (group I) and terminal deletion (group T). The SRO in group I was located on FGR-D1S170 (1p36.1–2), whereas that in group T was located at the more terminal locus, DIS160-pter. Therefore, we mapped at least two consensus deleted regions on chromosome 1p. FGR-D1S170 (1p36.1–2) and DIS160-pter (1p36.3), by their deletion patterns. In group T, two cases (N145 and N160) with distal 1p deletion (DIS160-pter) did not contain the SRO of group I, whereas the remaining eight cases had large terminal deletions from 1p32. The 1p32–35 locus might be an additional consensus deleted region in neuroblastoma reported previously (24).

Studies on the relationships between 1p LOH and clinical prognoses have produced conflicting results (18, 25, 26, 28, 29, 55). These controversial results seem to suggest the existence of biological heterogeneity in tumors with 1p deletion. In our study, almost all group I cases had favorable outcomes, whereas
group T cases had unfavorable outcomes. Moreover, all 1p LOH cases detected by mass screening were group I. Significant differences in prognoses between groups I and T suggested that the suppressor genes associated with prognosis might be located at 1p32-pter. Takeda et al. (25) reported that small interstitial deletions in 1p36 do not correlate with a poor prognosis, whereas the large 1p deletions extending to 1p32 were found in cases with poor prognoses. We also reported previously that a 1p proximal deletion detected by RFLP analysis of the MYCN gene was related to a poor prognosis (8), and 46 cases of them were included in the present study. Our present study suggested that the proximal region (1p32-pter), including the MYC/1 locus, also correlated with a poor outcome because seven of eight cases with a large deletion containing 1p32 died. Considering the different outcomes of cases N151 (good outcome without LOH in 1p32) and N66 (poor outcome without LOH in 1p32), we suspect that the 1p32-pter MYC/1 locus (1p32-34) may contribute to the prognosis and/or MYCN amplification. Thus, the clinical outcomes of the 1p LOH patients suggest the existence of three regions of neuroblastoma suppressor genes. Deletions in the regions 1p32-36.1 (1p32-pter) and 1p36.3 (1p316.3) were correlated with the prognoses of the patients, but deletions at 1p36.1-2 (FGR-1p316.7) were not.

Recently, several studies using detailed deletion mapping in clinical cases have also suggested the existence of multiple tumor suppressor genes located in 1p32 to 1p36 (24, 26, 27) and agree that deletion of the proximal region correlates with a poor outcome and/or MYCN amplification. In our study, MYCN amplification was also detected in seven of eight cases with large terminal deletions. Possibly the poor outcomes of cases with large 1p deletions containing 1p32-pter may depend on MYCN amplification. However, only one case (N186) with lack of MYCN amplification died of recurrence of tumor. This case suggests that LOH on 1p32-pter is a candidate for a poor prognostic factor that does not usually depend on MYCN amplification.

The study of human breast cancer has suggested that inactivation of the putative suppressor gene located at the 1p32-pter locus controls MYCN amplification in various cancers including neuroblastoma (57). Caron et al. (23, 26) have described a case in which 1p LOH and lack of MYCN amplification occurred at the time of diagnosis, but MYCN amplification was detected during tumor progression. Their case suggests that 1p LOH preceded MYCN amplification. However, we observed the opposite order of MYCN amplification before 1p LOH in two cases, N30 and N66. Thus, although 1p32-pter LOH is frequently concomitant with MYCN amplification, we conclude that 1p32-pter LOH does not always control MYCN amplification. In the recent report by Schleiermacher et al. (30), cases with 1p LOH limited to distal loci were most frequently metastatic with rare association of MYCN amplification. Similarly, both patients (N145 and N160) with deletions in the very distal region (1p36.3-pter) had lack of MYCN amplification but were likely to have an unfavorable outcome. These cases with very distal deletion and poor prognosis also suggest the existence of another suppressor gene affecting tumor progression not associated with MYCN amplification at this site. Thus, the clinical outcomes of the 1p LOH patients suggest that deletions in the regions 1p32-36.1 (1p32-pter) were correlated with the poor prognosis and/or MYCN amplification and that deletions in the regions 1p36.3 (1p316.3) were also correlated with the poor prognosis of the patients but not with MYCN amplification. Because MYCN amplification was detected in some cases without 1p deletion (group N), the combination of MYCN amplification.
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Clinical investigation of neuroblastoma with partial deletion in the short arm of chromosome 1.

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