Correlation of Loss of Heterozygosity at Chromosome 9q with Histological Subtype in Medulloblastomas

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Patients with the nevoid basal cell carcinoma syndrome (NBCCS) are at increased risk for medulloblastomas as well as for basal cell carcinomas. The gene for NBCCS has been mapped to chromosome 9q22.3-q31 by linkage analysis, and loss of heterozygosity (LOH) in this region has been demonstrated in approximately one-half of sporadic basal cell carcinomas. In the present study, LOH for chromosome 9q22.3-q31 microsatellite markers was investigated in medulloblastomas occurring among children with NBCCS and in sporadic medulloblastomas. Histologically, all 3 NBCCS medulloblastomas were noted to have a desmoplastic phenotype, and LOH was detected in both of the 2 cases for which microsatellite markers were heterozygous in normal tissues. LOH was also detected in a subset of sporadic medulloblastomas, each of which were found to display the desmoplastic phenotype. In all, 3 of the 6 sporadic desmoplastic tumors showed LOH, whereas LOH was not seen in any of the 11 sporadic, non-desmoplastic medulloblastomas studied. Additionally, desmoplastic tumors lacking detectable LOH each showed histological features of so-called cerebellar neuroblastoma, a subgroup of desmoplastic medulloblastoma with extensive neuroblastomatous differentiation. The data are consistent with a role for inactivation of a tumor suppressor gene at chromosome 9q in the development of medulloblastomas in patients with NBCCS and of sporadic medulloblastomas characterized by a desmoplastic phenotype similar to that found in patients with NBCCS.

Restriction of chromosome 9q loss to non-neuroblastomatous desmoplastic tumors suggests that this variant of medulloblastoma maybe pathogenetically distinct from tumors having other histological phenotypes. (Am J Pathol 1995, 146:472–480)

Patients with the nevoid basal cell carcinoma syndrome (NBCCS) are predisposed to developing numerous tumors, especially basal cell carcinomas, fibromas of the heart and ovary, and medulloblastomas. Recently, the gene for NBCCS has been localized to bands q22.3–31 of chromosome 9 by linkage analysis of affected kindreds. In addition, loss of heterozygosity (LOH) for markers in this region has been documented in one-half of sporadic basal cell carcinomas, supporting the hypothesis that this region contains a tumor suppressor gene. As NBCCS patients also tend to develop medulloblastomas, we analyzed a group of these tumors, including three occurring in children with NBCCS, for a similar loss of genetic material. A variety of histological subtypes of medulloblastomas, including desmoplastic medulloblastomas and cerebellar neuroblastomas, were represented in the study group.

Materials and Methods

All medulloblastomas surgically resected and treated at The Children’s Hospital of Pittsburgh between 1974 and 1985 were identified. Histological sections stained with hematoxylin and eosin (H&E) were reviewed and those cases for which control DNA from normal tissue could be obtained (for instance, from
separable normal cerebellar tissue within resection specimens) were selected for analysis (15 of 38 total cases fit this criterion). Also, 3 cases of medulloblastoma occurring in patients with NBCCS and surgically resected at The Children's Hospital of Boston between 1986 and 1994 were included in the initial group of tumors. Based upon the findings in these first 18 cases, 2 additional cases of desmoplastic medulloblastoma (diagnosed in 1989 and 1993) for which normal DNA could be obtained were collected from the files of the two hospitals, completing the study group of 20 tumors.

**Histology**

After cases were identified and the H&E-stained slides reviewed, a representative block of paraffin-embedded tumor was selected for all subsequent studies. Histologically, the tumor tissue showed diagnostic features of medulloblastoma, including sheets of undifferentiated, relatively homogeneous cells with round to angulated nuclei, variable numbers of mitoses, and occasionally, necrosis (Figure 1). Sections of the tumor were also stained for reticulin and examined under the microscope. Tumors found to be rich in reticulin and to contain distinct nodules that were reticulin free were classified as desmoplastic medulloblastomas (Figure 2). Desmoplastic tumors in which the reticulin-free regions were the predominant component, separated by less prominent desmoplastic regions, were subcategorized as cerebellar neuroblastomas (Figure 3). In contrast to the other desmoplastic medulloblastomas, the nuclei within the reticulin-free islands of neuroblastomas were generally round and regular and often organized in linear arrays associated with neuropil formation, bearing a striking resemblance to the peripheral (extracranial) neuroblastoma.

**Microsatellite Analysis**

In all sporadic medulloblastomas, DNA was extracted from tumor and from non-neoplastic tissue present in the block selected for evaluation of microsatellite marker heterozygosity. The source of normal DNA for two of the children with NBCCS was whole blood obtained from the patient (cases 2 and 3) and the patient's parents (case 3). In the third child with NBCCS (case 1), normal DNA was extracted from a separate block of tissue comprised entirely of non-neoplastic cerebellum.

In all cases, DNA was extracted from formalin-fixed, paraffin-embedded tissue by the method described by Levi et al.9 and detailed by Rodgers.7 In cases 2 and 3, after isolation of nuclei from peripheral blood, (normal) DNA was extracted by standard techniques.8 Microsatellite loci in the region of 9q22-3.31 were chosen for LOH analysis based upon data published in earlier linkage analysis studies of kindreds with NBCCS.2,2 Analysis of loci D9S12,9 D9S196,10 D9S180,10 D9S127,11 D9S109,12 D9S53,13 and D9S5814 was performed by polymerase chain reaction amplification after labeling of one primer at its 5’ end with γ-32P]ATP (New England Nuclear, Boston, MA) using T4 kinase ( Gibco BRL, Gaithersburg, MD). Fifty-microliter reactions were carried out, containing 200 µmol/L dNTPs, 20 pmol of each primer, and 2.5 U of DNA polymerase (AmpliTaq, Perkin-Elmer Cetus, Emeryville, CA). Each sample was amplified for 40 cycles with annealing temperatures of 64 C (D9S12), 66 C (D9S58), and 60 C (D9S196, D9S180, D9S127, D9S109, and D9S53) for 20 seconds in a Perkin-Elmer Cetus 9600 thermal cycler. Denaturation and extension temperatures of 94 C and 75 C for 20 seconds each were used for all reactions. Polymerase chain reaction products were separated by electrophoresis in a 6%/7 mol/L urea polyacrylamide gel in 1X Tris-borate/EDTA buffer.

**Fluorescence in Situ Hybridization**

Chromosome 9 copy number was determined by FISH with a pericentromeric probe, D9Z1, obtained from Oncor (Gaithersburg, MD, catalog No. P5016). Hybridization was performed on slides of disaggregated, intact nuclei prepared from the same paraffin block from which tumor LOH was assessed.15,16 Results were visualized and photographed on a Zeiss

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![Figure 1](image-url)  
*Figure 1. Sheets of relatively homogeneous cells with small angulated nuclei characterize the classic medulloblastoma (H&E stain, magnification, ×200).*
Axiophot fluorescent microscope (Carl Zeiss, Oberkochen, Germany) with a BP450–490 excitation filter, an FT 510 beam splitter, and an LP520 barrier filter.

D9Z1 primary hybridization signals were clear, distinct, and easily counted. Hybridization efficiency ranged from 50 to >95%. An aberrant population of cells was defined as the observation of a nondisomic number of signals in >20% of hybridizing nuclei.

Results

20 cases of medulloblastoma were studied, of which seventeen were sporadic and 3 occurred in children with NBCCS. Nine of the twenty tumors, including all three from patients with NBCCS, were desmoplastic. Three of the desmoplastic tumors were subclassified as cerebellar neuroblastomas. The remaining eleven tumors were characterized by classic histology. The clinical and histological features are summarized in Table 1.

Characteristics of the microsatellite loci analyzed are summarized in Table 2. They span a region of approximately 26 centimorgans at chromosome 9q22.3–9q31.3.2,3,4 and have reported or estimated incidences of heterozygosity >60%. Loci D9S109 and D9S127 are close and it is possible that the actual order may be reversed.17

Microsatellite analysis results were interpretable in 126 of 140 polymerase chain reactions and representative examples are illustrated in Figure 4. Loss of constitutional heterozygosity was not observed in any of the sporadic, nondesmoplastic medulloblastomas. Data for the desmoplastic medulloblastomas are summarized in Figure 5. LOH was demonstrated in each of two desmoplastic medulloblastomas re-
moved from children who had NBCCS and were heterozygous in normal tissue at the majority of microsatellite loci tested. There is a possibility that the third hereditary medulloblastoma (case 1, Figure 5), which arose in a 2-year-old male with NBCCS, may not have lost heterozygosity. However, adequate assessment of this case was precluded by a lack of sufficient informative markers as five of the seven microsatellites assessed, including four loci situated in the most likely region of involvement in NBCCS, were constitutionally homozygous.

In addition to those desmoplastic medulloblastomas occurring in the setting of NBCCS, loss of constitutional heterozygosity was documented in three of six sporadic desmoplastic medulloblastomas that were studied. Within this subgroup of desmoplastic tumors, however, LOH was confined to those tumors with the usual pattern of desmoplasia; it was not documented in those with a striking neuroblastomatous pattern (Figures 2, 3, and 5).

All desmoplastic medulloblastomas were characterized by at least two D9Z1 signals in >85% of hybridizing nuclei. In one tumor (case 4, Table 1 and Figure 5), 48% of hybridizing nuclei had three primary hybridization signals (Figure 6).

**Discussion**

Medulloblastomas are the most common primary malignant brain tumor in the pediatric age group. Other than their location in the posterior fossa of the skull, the single unifying feature of these tumors is the microscopic appearance of sheets of undifferentiated, small round cells. However, within this background, foci of neuronal, glial, or ependymal differentiation are...
occasionally observed, leading some to regard these tumors as primitive neuroectodermal tumors with neuronal, glial, and/or ependymal differentiation.

In addition to variable degrees of differentiation, some tumors histologically have a nodular appearance and abundant reticulin. These tumors have been referred to as desmoplastic medulloblastomas. The nature of these tumors is uncertain, but the hypothesis has been advanced that at least some of these are otherwise "classic" medulloblastomas that have infiltrated the meninges. However, the fact that the reticulin-free islands (nodules) within these desmoplastic tumors are frequently characterized by the expression of neural markers, such as synaptophysin or neuron-specific enolase, argues against this interpretation.

Reticulin-free nodular foci of neuroblastic differentiation within a background of less differentiated cells are also a hallmark of what has been termed cerebellar neuroblastoma. The histological similarities between the desmoplastic medulloblastoma and the cerebellar neuroblastoma are so great that it is unclear whether the two entities should be considered different lesions or simply reflect a spectrum of neuroblastic differentiation among medulloblastomas. Evidence of differentiation as well as desmoplasia have been inconsistently reported as either good, poor, or indifferent prognostic features in medulloblastomas. However, it has been those tumors illustrated and classified as cerebellar neuroblastomas that have occasionally matured into benign gangliogliomas, suggesting that they may indeed be separable from other tumors in the posterior fossa.

Approximately 1 to 2% of medulloblastomas are thought to arise in patients with NBCCS. NBCCS is inherited as an autosomal dominant disorder characterized by malformations (odontogenic keratocysts, palmar/plantar pits, and rib abnormalities) and a predisposition to the development of various tumors. The most common tumor seen among affected individuals is basal cell carcinoma, followed by medulloblastomas and cardiac and ovarian fibromas. The estimated incidence of medulloblastoma occurring in patients with NBCCS ranges from 5 to 20%. The inheritance of tumor predisposition as an integral component of NBCCS is underscored by the tendency for the associated tumors, particularly basal cell carcinomas, to arise relatively early in life and at multiple sites.

The gene for NBCCS has been mapped to chromosome 9q22.3–31 by linkage analysis. Subsequent to this work, LOH in this region was demonstrated in each of two hereditary basal cell carcinomas examined and in approximately one-half of the sporadic basal cell carcinomas. The deletions detected spanned at least 17 centimorgans by microsatellite analysis. Most recently, an expanded linkage analysis study was performed that further localized the putative NBCCS gene to a region of 10 centimorgans distal to D9S196 and proximal to D9S109.

Table 1. Clinical Features

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<td>1</td>
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<td>Y</td>
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</tr>
<tr>
<td>2</td>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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Table 2. Microsatellite Characteristics

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<th>Microsatellite*</th>
<th>Location</th>
<th>Number of alleles</th>
<th>Reported incidence of heterozygosity**</th>
<th>Observed incidence of heterozygosity</th>
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<tr>
<td>D9S12 (2 cM)</td>
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<td>74%</td>
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<td>D9S196 (5 cM)</td>
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<td>9q31</td>
<td>6</td>
<td>70%</td>
<td>14/20 (70%)</td>
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<td>D9S127 (3 cM)</td>
<td>9q31</td>
<td>6</td>
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<td>18/20 (90%)</td>
</tr>
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<td>D9S53 (10 cM)</td>
<td>9q31</td>
<td>8</td>
<td>87%</td>
<td>15/20 (75%)</td>
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<tr>
<td>D9S58</td>
<td>9q31–32</td>
<td>13</td>
<td>88%</td>
<td>19/20 (95%)</td>
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</table>

*Loci are listed in postulated order from centromeric to telomeric. The estimated, sex-averaged, genetic distance between each locus and the adjacent locus listed below it is given in parentheses and expressed in centimorgans (cM).

†Varying reports concerning the number of possible alleles.

**Heterozygosity is based on the observed number of alleles at each locus.
Examination of the microsatellite analysis data resulted in three main observations. First, as expected, LOH for chromosome 9q loci was present in each of two medulloblastomas occurring in children with NBCCS and constitutionally heterozygous for microsatellite markers analyzed. Most microsatellite loci analyzed in the third medulloblastoma occurring in this setting were homozygous in normal tissue, although LOH for a heterozygous locus just proximal to the proposed critical region was not documented, raising the possibility that tumorigenesis occurred by a different mechanism (or at least one without LOH at 9q) in this case. Not expected, however, was the observation that the remaining three cases in which LOH was documented and which were sporadic in origin were desmoplastic medulloblastomas; none of the cases with LOH showed the “classic” histology. Furthermore, blind review of histological sections from the tumors initially classified as desmoplastic revealed that LOH was confined to the non-neuroblastomatous tumors. Therefore, within the group of desmoplastic medulloblastomas from patients with informative polymorphisms at the microsatellite loci, LOH was documented in two of two hereditary tumors, three of three sporadic tumors, and none of three tumors subclassified as cerebellar neuroblastomas.

The large region of common LOH among these tumors spans at least 26 centimorgans (and probably much more) and is similar to that reported previously in basal cell carcinomas. LOH is likely due to a deletion in most cases, as FISH performed with a chromosome 9-specific, pericentromeric probe (D9Z1) indicated that, with the exception of case 4, all cases were disomic.

The retention of constitutional heterozygosity at the most distal locus in three of five informative cases would further suggest that the deletion is interstitial. A submicroscopic deletion in most cases could account for the paucity of reported cytogenetic abnormalities of chromosome 9 in medulloblastomas.31–34

In case 4, approximately one-half of the nuclei contained three D9Z1 primary hybridization signals (Figure 6). Whether trisomy in this tumor arose from duplication of the chromosome carrying the deletion or the chromosome carrying the presumptive mutant gene cannot be determined from our data. This finding is not unique as examples of loss of genetic material at a molecular level that are accompanied by trisomy of the associated chromosome (or chromosomal region) at a karyotypic level have been reported.35–37

As in all studies of LOH based upon DNA polymorphisms, interpretation of our results must be con-

The increased incidence of medulloblastomas in NBCCS led us to search for a similar LOH on chromosome 9q in medulloblastomas from three patients with NBCCS and in sporadic medulloblastomas. While reviewing the H&E-stained sections of the original 18 study cases, it was noted that those medulloblastomas occurring in children with NBCCS could all be classified as desmoplastic, a previously unreported observation to our knowledge. Because of this finding, two additional sporadic desmoplastic medulloblastomas were collected for study. In total, analyses were performed on 11 cases with “classic” histology and 9 cases that were desmoplastic. Of the latter, 3 occurred in patients with NBCCS, and the remaining cases were sporadic.

Figure 4. Representative examples of microsatellite analyses illustrating loss of heterozygosity for the D9S53 (size range of microsatellite repeats, 116 to 150 base pairs) and D9S127 (size range of microsatellite repeats, 149 to 159 base pairs) loci in cases 3 and 4, respectively. In case 3, DNA extracted from paraffin-embedded tumor tissue (right lane, T3) is compared with DNA extracted from nucleated peripheral blood cells obtained from the patient’s father (left lane, N(F)3) and mother (middle lane, N(M)3). In case 4, analysis was performed on tumor (right lane, T4) and normal (left lane, N4) DNA extracted from paraffin-embedded tissue.
considered in light of the resolution permitted by the set of microsatellite loci analyzed. It may be that smaller deletions falling between the loci examined do occur in some medulloblastomas. However, the failure to detect deletions among any cases of medulloblastomas other than non-neuroblastomatous desmoplastic tumors would suggest that this is not highly likely. Also, as examples of the various histological subtypes of medulloblastomas are not common, our study was limited to small numbers of cases. Consequently, a larger set of medulloblastomas containing tumors of different subtypes should be investigated to confirm the findings of this work. With this in mind, results of a recent, similar study performed on 19 medulloblastomas (occurring in 16 patients) revealed LOH on chromosome 9q in two nondesmoplastic medulloblastomas. However, there are two basic differences between the tumors in that study and the tumors described here. First, desmoplastic tumors were excluded from the study group of tumors. Second, many of the tumors analyzed occurred in adults, and it is unclear whether medulloblastomas occurring in adults are biologically or genetically the same tumor as those occurring in children. The two tumors in which LOH on chromosome 9q was demonstrated occurred in 31- and 34-year-old patients.

The specificity of LOH at chromosome 9q can be assessed by comparison with results of previous studies of LOH in medulloblastomas. Analysis of microsatellite and restriction length polymorphism for alleles on chromosomes 1p, 6q, 7q, 10, 11p, 13q, 16q, 17p, and 22q has been performed. None of these studies have attempted to separate tumors by histological subtype. The highest incidence of LOH (approximately 30%) was observed for alleles on chromosome 17p, in agreement with the karyotypic finding of an isochromosome 17q in up to 40% of medulloblastomas. LOH for alleles from the long arms of chromosomes 6 and 16 was observed in approximately 15 to 25% of cases, again in agreement with karyotypic analyses. In contrast, LOH was not observed when polymorphic markers from chromosomes 1p, 7q, 10, 11p, 13q, and 22q were examined.

<table>
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Figure 5. Chromosome 9 LOH in desmoplastic medulloblastomas. *Patient with NBCCS; †cerebellar neuroblastoma; ‡α-satellite locus assessed by fluorescence in situ hybridization; D, disomic; D/T, disomic and trisomic; O, LOH, ●, no LOH; U, uninformative; –, results not interpretable.

Figure 6. FISH with a biotinylated D9Z1 probe on nuclei disaggregated from case 4 revealed a mixture of two and three primary hybridization signals (hybridization efficiency was 50%).
Therefore, even among medulloblastomas as a whole, LOH at chromosome 9q would seem not to be a random event attributable, for example, to general genomic instability.

On the basis of our observations, we conclude that medulloblastomas observed in patients with NBCCS usually have a desmoplasic phenotype. Moreover, in children, chromosome 9q LOH may largely be restricted to desmoplasic medulloblastomas, providing independent evidence that they may indeed be pathogenetically distinct from their “classic” histology counterparts. Similarly, desmoplasic medulloblastomas classified as cerebellar neuroblastosomas may also constitute a pathogenetically separable group of tumors lacking LOH in DNA at chromosome 9q.

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References

23. Russell DS, Rubinstein LF: Pathology of Tumors of the Nervous System. Baltimore, Williams and Wilkins,
1989, pp 261–263, 265–266