

Nicholas J. Patronas, MD
Nikos Courcoutsakis, MD
Christina M. Bromley, PhD
Gregory L. Katzman, MD
Mia MacCollin, MD
Dilys M. Parry, PhD

Index terms:

Genes and genetics
Neurofibromatosis, 30.1831
Spinal cord, MR, 30.121411,
30.12143
Spinal cord, neoplasms, 30.363,
30.364, 30.366

Radiology 2001; 218:434–442

Abbreviations:

NF2 = neurofibromatosis 2
NST = nerve sheath tumor

¹ From the Department of Diagnostic Radiology, Clinical Center, National Institutes of Health, 10 Center Dr, MSC 1182, Rm 1C660, Bethesda, MD 20892-1182 (N.J.P.); Xenokratous 33, Athens, Greece (N.C.); the Department of Radiology, Northwestern Memorial Hospital, Chicago, Ill (G.L.K.); the Genetic Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Md (C.M.B., D.M.P.); and the Department of Neurology, Massachusetts General Hospital, Boston (M.M.). Received February 17, 2000; revision requested April 3; revision received June 20; accepted July 14. M.M. supported by a grant from the U.S. Army Research Command. Address correspondence to N.J.P. (e-mail: npatronas@nih.gov).

© RSNA, 2001

Author contributions:

Guarantors of integrity of entire study, D.M.P., N.J.P.; study concepts and design, D.M.P., N.J.P.; definition of intellectual content, D.M.P., N.J.P.; literature research, D.M.P., N.J.P.; clinical studies, N.C., G.L.K., D.M.P., N.J.P.; data acquisition, D.M.P., N.J.P., N.C., G.L.K.; data analysis, D.M.P., N.J.P.; statistical analysis, C.M.B.; manuscript preparation and review, D.M.P., N.J.P.; manuscript editing, all authors; manuscript final version approval, D.M.P., N.J.P.

Intramedullary and Spinal Canal Tumors in Patients with Neurofibromatosis 2: MR Imaging Findings and Correlation with Genotype¹

PURPOSE: To determine the appearance of spinal tumors on magnetic resonance (MR) images of patients with neurofibromatosis 2 (NF2), to assess the biologic behavior of these tumors, and to determine the correlation between NF2 germline mutations and these tumors.

MATERIALS AND METHODS: Spinal MR images in 49 patients with NF2 were reviewed retrospectively. Intramedullary and intradural extramedullary tumors were counted, and imaging features and growth patterns of intramedullary tumors were determined. Medical records were reviewed for spinal tumor surgery. Data on spinal tumors and NF2 germline mutations in 37 patients from 19 families were analyzed for genotype-phenotype correlation.

RESULTS: Thirty-one patients (63%) had spinal tumors: Twenty-six (53%) had intramedullary tumors, 27 (55%) had intradural extramedullary tumors, and 22 (45%) had at least one tumor of each type. Three (12%) patients with intramedullary tumors versus 16 (59%) with extramedullary tumors had undergone surgery for the respective types of tumors. Compared with patients with all other types of mutations, a higher percentage of patients with nonsense and frameshift mutations had intramedullary tumors ($P < .025$); these patients also had higher mean numbers of all tumors ($P < .001$), intramedullary tumors ($P < .001$), and nerve sheath tumors (NSTs) ($P < .001$).

CONCLUSION: In patients with NF2 and spinal tumors, extramedullary tumors (predominantly NSTs) were present in higher numbers and were associated with more surgery than were intramedullary tumors. Our data suggest that the association between nonsense and frameshift mutations and severe NF2 may extend to specific categories of spinal tumors.

Neurofibromatosis 2 (NF2) is a rare autosomal dominant disorder characterized by the development of multiple nervous system tumors. The presence of bilateral vestibular schwannomas is a defining feature, but patients with NF2 also develop other cranial, spinal, and peripheral schwannomas, cranial and spinal meningiomas, and cataracts (1–3). Recent reports (2–4) of series of patients with NF2 screened with magnetic resonance (MR) imaging of the neuraxis have focused attention on the occurrence of spinal tumors. Among patients in whom the entire spine was imaged, spinal tumors were documented in 75%–89%, and 25%–35% of patients with these tumors reported symptoms caused by them (2,4). The histologic findings of excised extramedullary tumors were usually schwannoma or meningioma, and most excised intramedullary tumors were ependymomas, although astrocytomas and schwannomas occurred (4–6). Because spinal tumors often develop in NF2, their presence raises issues about appropriate management strategies (7),

since the natural history of NF2-associated tumors may differ from that of their sporadic counterparts (8).

The NF2 gene was cloned from chromosome 22q in 1993 (9,10); since then, germline NF2 mutations have been reported (3,11–14) in several series of patients with NF2. These study findings support a genotype-phenotype correlation in which nonsense and frameshift mutations are usually associated with severe disease, in which missense mutations and large gene deletions are found with mild phenotypes, and in which splice-site mutations lead to variable clinical manifestations. The data of Evans et al (14) demonstrated that NF2 genotype influences the mean number of spinal tumors per patient, but to our knowledge, the effect of different types of mutations on spinal tumor histologic characteristics or location has not been examined.

Previously, we described clinical findings in more than 60 patients with NF2 (2,3), many of whom had spinal tumors. In the present study, we determined the anatomic abnormalities detected within the spinal cord and canal on MR images of 49 patients; we used the number of operations for intramedullary and extramedullary spinal tumors as a measure of disease burden. In addition, because germline NF2 mutations were identified in 37 of these individuals (3,12,15), we looked for correlations between specific categories of mutations and different types of spinal tumors in this subset of patients.

MATERIALS AND METHODS

Patient Population

Patients with NF2 were enrolled between August 1987 and February 1994 in a protocol (78-C-0039) approved by the institutional review board of the National Cancer Institute, Bethesda, Md. After informed consent was obtained, clinical evaluation was performed and included physical examination, complete eye examination, audiometry, evaluation of auditory brainstem-evoked responses, and MR imaging of the brain and spine. Blood was obtained for molecular studies.

This study was based on 49 patients from 26 unrelated families who underwent spinal MR imaging at the Clinical Center, National Institutes of Health, Bethesda, Md, between August 1987 and January 1998. Spinal imaging findings in 41 patients were reported previously (3).

The diagnosis of NF2 was based on standard clinical criteria in 48 patients (16) and on DNA test results in one. Medical records of these 26 male and 23 female patients were reviewed (D.M.P.). Abstracted information included age at onset of initial symptoms related to NF2, age at diagnosis of this disorder, and age at which the last spine MR images were examined for this study.

The number of operations and regimens of radiation therapy undertaken for spinal tumors was also recorded. No patient underwent chemotherapy for NF2-related tumors. The data on treatment were used as a measure of disease burden associated with spinal tumors. Available surgery and pathology reports of the tumors removed at surgery were reviewed. We also reviewed the autopsy reports of two patients who died after participating in the study to determine the histologic characteristics of the examined spinal tumors.

MR Imaging

The entire spine was examined in 44 patients, the cervical and thoracic spine were imaged in four patients, and only the cervical spine was evaluated in one patient. The examinations were performed by using a 0.5-T (Picker, Cleveland, Ohio) or 1.5-T (GE Medical Systems, Milwaukee, Wis) unit. T1-weighted (repetition time msec/echo time msec, 400–600/8–22) and intermediate- and T2-weighted (2,000–3,500/20–104) spin-echo images were obtained in the sagittal plane with a 4–5-mm section thickness. Images in the transverse plane were obtained in any area of the spine in which sagittal images demonstrated an abnormality. Contrast material-enhanced images were obtained in all patients after the administration of 0.1 mmol of gadopentetate dimeglumine per kilogram of body weight (Magnevist; Berlex Laboratories, Wayne, NJ) by using the same T1-weighted pulse sequences as in the non-enhanced studies.

Spinal MR images were evaluated by two radiologists (N.J.P., N.C.) who identified and characterized the abnormalities by consensus. Each spinal lesion in the 49 patients was identified; its location, morphologic characteristics, signal intensity characteristics, and enhancement were assessed. The greatest diameter of each intramedullary tumor was measured on the contrast-enhanced images, and the presence of focal cord engorgement, cord displacement, and cord compression were also noted. A subset of

five patients had two or more intramedullary lesions in proximity. In these patients, we counted each lesion as a separate tumor, provided that intervening normal cord tissue was identified between such lesions.

Spinal tumors were classified as intramedullary or extramedullary on the basis of their location with respect to the spinal cord and their morphologic characteristics. We classified extramedullary tumors that were round and located near a nerve root as nerve sheath tumors (NSTs), and we designated extramedullary tumors that exhibited a flat surface of dural attachment as meningiomas. Tumors in the paraspinal soft tissues without appreciable extension into the spinal canal were excluded from this analysis.

In 16 patients with intramedullary lesions, two or more consecutive sets of spinal MR images were reviewed for this study. The interval between the first and last studies ranged from 17 to 96 months (mean, 49 months). The diameter of each intramedullary lesion was measured on consecutive contrast-enhanced T1-weighted images and was compared between the first and last examinations. Because the number of extramedullary tumors was large, the diameter of each tumor was not measured on sequential images.

Mutation Data

NF2 mutations were identified in a subset of 37 patients in this study; these patients were from 19 unrelated families. The mutations in patients from 18 of these families were determined at exon scanning of the genomic DNA extracted from peripheral lymphocytes or Epstein-Barr virus-transformed lymphoblasts (3,12,15). The mutation in patients from the 19th family was identified by means of Southern blot analysis (3,9). The patients with known NF2 mutations included 13 from 10 families with nonsense or frameshift mutations, 15 from seven families with splice-site mutations, six from one family with an in-frame deletion, and three from one family with a missense mutation.

Statistical Analysis

Standard statistical tests such as the χ^2 test or analysis of variance assume independence of the study subjects. This assumption may not always apply when study subjects are related (eg, blood relatives) because observations may be correlated. Therefore, we used a family (group)-specific adjustment method with

the standard χ^2 test (17) to test for differences in proportions of patients with spinal tumors among the different types of mutations. In this method, a clustering adjustment factor C_i is used in the calculations of the χ^2 test that we performed for each of the i families.

Ages at onset of symptoms, at diagnosis of NF2, and at last spinal MR imaging were adjusted to 5-year intervals, and family-specific mean ages were calculated. The associations between mutation type and mean ages were analyzed by using PROC GLM of the SAS program (version 6.12 for Windows; SAS Institute, Cary, NC). Both this approach and the χ^2 method described before are more conservative than methods that do not take family membership into account.

We analyzed the associations between mutation type and numbers of tumors by using PROC GENMOD of the SAS program (SAS Institute), with a regression analysis approach. Because of the relatively small number of patients with data available for analysis, direct adjustment of the model for family size resulted in the loss of degrees of freedom. Therefore, we used as the dependent variable the ratio of the number of tumors in each family member divided by the total number of tumors in the family. This method is used to adjust for bias that might arise in the number of tumors because of large family size without the use of additional degrees of freedom. Since this approach may not fully account for correlations between family members, we selected one patient from each family at random and conducted a second set of analyses by using the number of tumors in each patient as the dependent variable. The results from the second approach (data not shown) were consistent with the results from our original data set.

In all analyses, data in patients with nonsense and frameshift mutations were compared with those of patients with all other types of mutations and patients with splice-site changes. The last was the only mutation category that included more than 10 patients.

RESULTS

MR Imaging Findings

Spinal MR images demonstrated spinal cord and/or canal tumors in 31 (63%) of 49 patients. Twenty-six patients (53%) had intramedullary lesions, 27 patients (55%) had intradural extramedullary tumors, and 22 patients (45%) had at least one tumor of each type. Data on the type and numbers of tumors are summarized in Table 1.

TABLE 1
Spinal Tumors Depicted on MR Images in Patients with NF2

Patients	No. of Tumors		
	Intramedullary	NST*	Meningioma [†]
All ($n = 49$)	107	177	24
With intra- and extramedullary tumors ($n = 22$)	101	167	24
With only intramedullary tumors ($n = 4$)	6	0	0
With only extramedullary tumors ($n = 5$)	0	10	0
Without spinal tumors ($n = 18$)	0	0	0

* These tumors were classified on the basis of their rounded appearance and proximity to nerve roots on MR images.
[†] These tumors were classified as on the basis of their flat surface of attachment to the dura on MR images.

Solid intramedullary tumors were either isointense or slightly hyperintense with respect to normal cord parenchyma on nonenhanced T1-weighted images. Cavitory tumors were hypointense with this technique and demonstrated a faint hyperintense rim around the cavity. On T2-weighted images, intramedullary tumors appeared hyperintense. Small tumors that ranged between 4 and 7 mm in diameter were not identified on the T2-weighted or nonenhanced T1-weighted images. All intramedullary tumors were enhanced on the contrast-enhanced images; contrast-enhanced imaging was the best method for the detection of these lesions regardless of size (Figs 1–4). Both sagittal and transverse sections demonstrated that these tumors were located in the center of the cord (Figs 1,2). Eight (7%) of 107 intramedullary tumors were in the cervicomedullary junction, 60 (56%) were in the cervical cord, and 39 (36%) were in the thoracic cord. The greatest diameter of these tumors measured 4–44 mm.

Nine patients had a total of 12 intramedullary tumors, with cavitation in at least part of each tumor. These tumors were among the largest encountered (20–44 mm in diameter). The 12 cavitory tumors and five solid tumors produced focal cord engorgement (Figs 1,3,4). One cavitory tumor had an associated syrinx located proximally to it that enlarged the cord beyond the tumor margins (Fig 4).

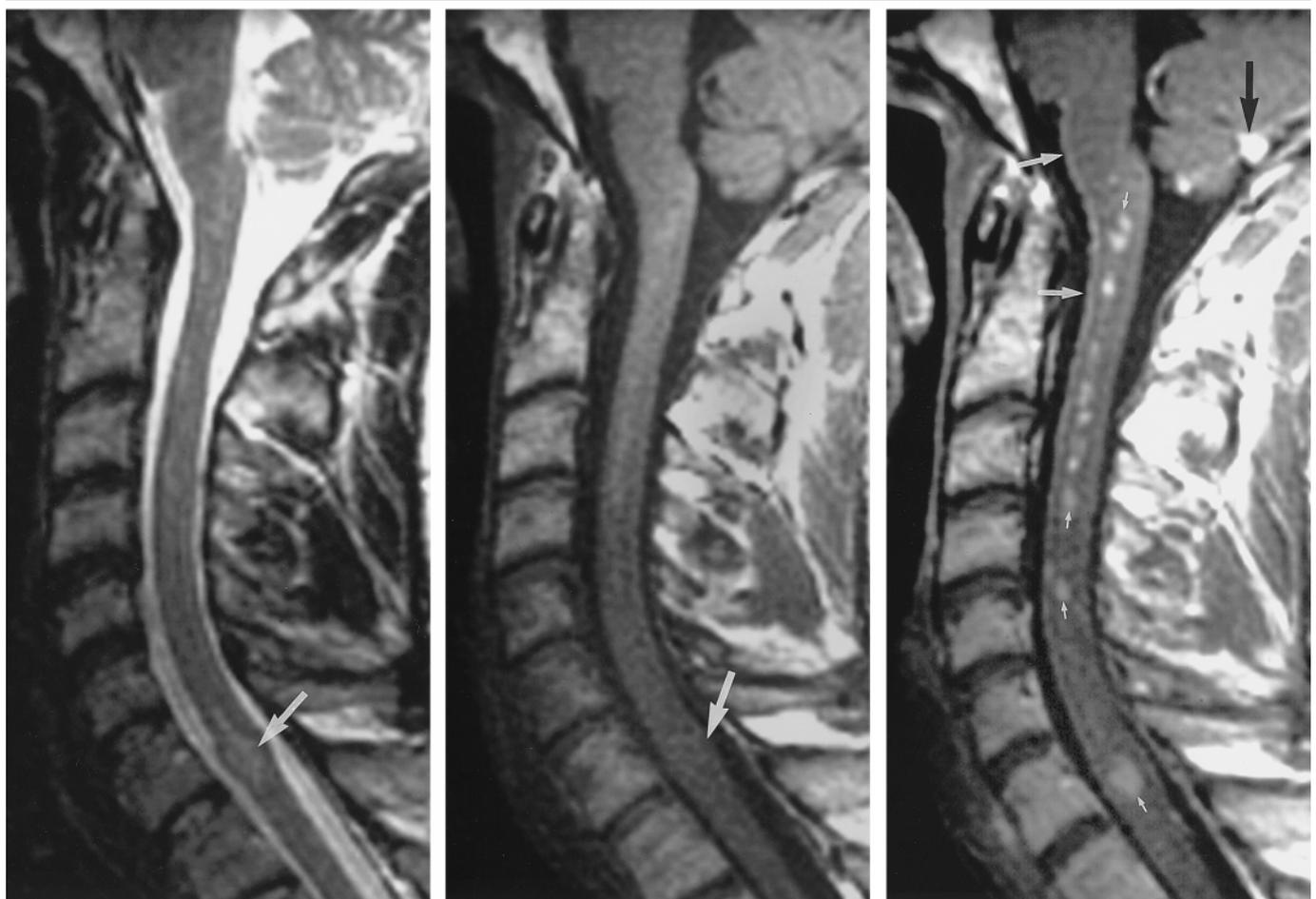
Fifteen patients had two or more intramedullary tumors. In five of these patients, the tumors seen on sagittal contrast-enhanced images were in proximity. Because none of these patients had undergone surgery for any of these tumors, we could not rule out the presence of a tumor bridge connecting some of these lesions at a microscopic level. Among patients with intramedullary tu-

mors, the mean and median numbers of these tumors were 4.1 and two, respectively, with a range of one to 17.

Sixteen patients had 84 intramedullary tumors that were evaluated on serial contrast-enhanced MR images of comparable quality that were obtained with comparable techniques. The diameter of 83 of these tumors remained essentially unchanged during a mean interval of 49 months. The single tumor that showed progressive growth was in a patient whose initial MR images of the cervical cord obtained at age 11 years were negative. A mass lesion appeared in the cervical cord on follow-up MR images at age 12 years; the lesion grew slowly during 2 years and then remained stable during the last year of observation.

Twenty-seven patients had a total of 201 extramedullary tumors (Table 1). This number is an underestimation because three patients had so many tumors in the lumbar canal that they could not be counted individually. In 177 (88%) of the 201 extramedullary tumors, imaging characteristics were consistent with those of NSTs (Fig 2), and 24 (12%) were classified as meningiomas (Fig 4). One hundred sixty-seven (94%) of the NSTs and all meningiomas occurred in 22 patients who also had intramedullary tumors (Table 1). Among patients with NSTs, the mean and median numbers of these tumors were 6.8 and five, respectively, with a range of one to 28. The corresponding numbers of meningiomas among patients with them were 2.6 and one, respectively, with a range of one to 11.

Twelve (44%) of the 27 patients with extramedullary tumors exhibited cord compression caused by some of these tumors. In seven patients, the cord was compressed by a total of 10 NSTs; in four patients, it was compressed by a total of 10 meningiomas, six of which were in a



a.

b.

c.



d.

Figure 1. (a) Sagittal T2-weighted MR image (3,500/100) of the cervical spine. A focal abnormality at the C7 level demonstrates slight hyperintensity (arrow) with focal cord engorgement. (b) Sagittal nonenhanced T1-weighted image (400/11). There are no signal abnormalities in the cord, but a mild focal engorgement is seen again at the C7 level (arrow). (c) Sagittal contrast-enhanced T1-weighted image (400/11) shows multiple enhancing tumors (small white arrows) in proximity within the cord parenchyma. A small mass posterior to the cerebellar vermis is thought to represent an intracranial meningioma (black arrow). The linear enhancing structure on the ventral aspect of the cord and medulla represents a draining vein (large white arrows). (d) Transverse contrast-enhanced T1-weighted image (400/15) demonstrates the central location of one intramedullary enhancing tumor (arrow).

single individual. In one other patient, two NSTs and two meningiomas compressed the cord.

Tumor Treatment and Histologic Findings

Three (12%) of the 26 patients with intramedullary tumors had been treated for

symptomatic tumors. All three were treated prior to being enrolled in our study. Two of the patients underwent subtotal surgical resection followed by radiation therapy. Surgery in the first patient was performed for an ependymoma at age 25 years; the second patient underwent operations for astrocytomas at two separate sites at ages 34 and 36 years. In the third patient, an intramedullary schwannoma was removed at age 26 years, with no further treatment. These patients were evaluated at the National Institutes of Health at ages 45, 49, and 41 years.

We obtained information on the histologic findings of other intramedullary tumors from autopsy reports of two pa-

tients in the study who later died of causes related to NF2. One was the third patient described previously, who died at age 43 years; microscopic examination of the spinal cord revealed two ependymomas that were not contiguous and an intervening low-grade astrocytoma. The other was the patient with the only intramedullary lesion that demonstrated progressive growth in this study; when he died at age 15 years, that lesion was found to be a solitary ependymoma. In addition to these tumors, autopsy in both patients revealed extensive spinal meningiomatosis.

Sixteen (59%) of the 27 patients with intradural extramedullary tumors under-

went a total of 30 operations for these tumors. No patient underwent adjuvant radiation therapy for extramedullary tumors. Pathology reports of the 49 excised tumors described 26 as schwannomas, 17 as meningiomas, and six as neurofibromas. The number and type of intramedullary and intradural extramedullary tumors removed at surgery or examined at autopsy are listed in Table 2.

We were able to compare our MR imaging classifications of 15 extramedullary tumors with the histologic findings reported after these tumors were removed from eight patients. On the basis of the MR images, we designated nine tumors as NSTs and six as meningiomas. The MR imaging classification and pathology reports agreed for all 15 tumors; of the nine NSTs, eight were reported to be schwannomas, and one was described as a neurofibroma. We did not detect one small meningioma on the MR images obtained prior to surgery in one of the patients. This patient had two large meningiomas that compressed the cord; these two tumors and an adjacent small meningioma were removed during a single operation.

Correlations between Genotype and Clinical Findings

Clinical data from the 37 patients with identified NF2 mutations are summarized in Table 3. The patients are grouped according to type of mutation. When the spinal imaging findings in patients with nonsense and frameshift mutations were compared with those of patients with all other types of mutations, a significantly higher percentage of patients with nonsense and frameshift mutations had intramedullary tumors but not any other type of tumor (Table 3, analysis 1). A similar pattern was seen in the comparison of patients with nonsense and frameshift mutations with patients with splice-site mutations, but the difference in the percentage of patients with intramedullary tumors was not statistically significant (Table 3, analysis 2).

Patients with nonsense and frameshift mutations had significantly higher numbers of all spinal tumors ($P < .001$), intramedullary tumors ($P < .001$), NSTs ($P < .001$), and extramedullary tumors (NSTs and/or meningiomas, $P < .001$). However, they did not have a higher number of meningiomas alone ($P = .54$), compared with patients in the other two mutation groups. With respect to the age variables, patients with nonsense or frameshift mutations were significantly younger at the onset of symptoms and at

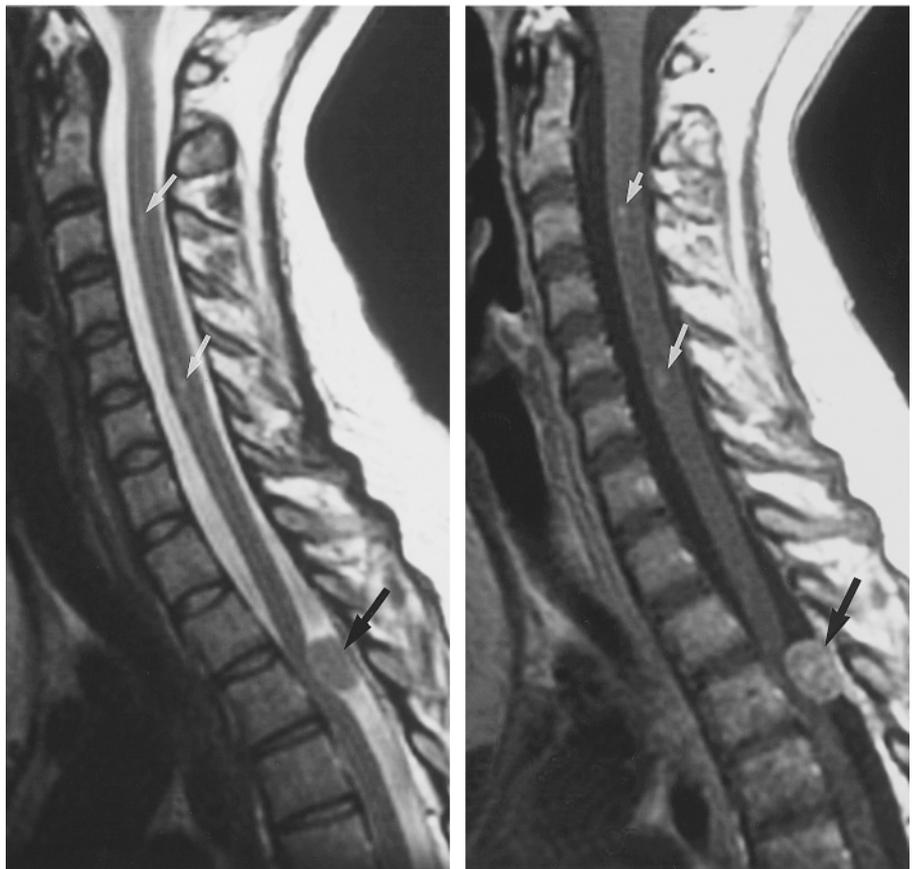


Figure 2. (a) Sagittal T2-weighted MR image (3,500/100) of the cervical and upper thoracic spine. A rounded extraaxial mass is depicted in the spinal canal at the level of T3 and compresses the cord (black arrow). Two small focal hyperintense areas (white arrows) are also identified in the cord near the central canal at the C3 and C5-C6 levels. (b) Sagittal contrast-enhanced T1-weighted image (500/8). Mass lesion (black arrow) at T3 demonstrates homogeneous enhancement and represents an NST. Two additional lesions (white arrows) identified within the cord are also enhanced; they represent intramedullary tumors.

diagnosis of NF2 than the patients in the other two mutation groups (Table 3, analyses 1 and 2). They were also significantly younger when the last reviewed spinal MR images were obtained.

DISCUSSION

In this article, we describe the tumors detected on gadolinium-enhanced MR images of the spine of 49 patients with NF2 from 26 unrelated families. The results confirm those of previous reports (4,6,18), namely, the high percentage of patients with spinal tumors, the variety of spinal tumors associated with this disorder, and the frequent occurrence of multiple tumors. With similar numbers of patients with any intramedullary or extramedullary tumors in those studies and ours, a higher percentage of our patients underwent surgery for extramedul-

lary tumors. Analyses of the correlations between specific categories of mutations and different types of spinal tumors in a subset of 37 patients revealed that patients with nonsense and frameshift mutations had more spinal manifestations of NF2 than did patients with all other types of mutations or the group with splice-site mutations. These spinal manifestations included the more frequent occurrences of intramedullary tumors and higher mean numbers of all spinal tumors, intramedullary tumors, NSTs, and extramedullary tumors. These results suggest that genotype-phenotype correlations may extend to specific categories of spinal tumors.

Imaging and Pathologic Findings

Our imaging data are qualitatively similar to those described in 73 patients with

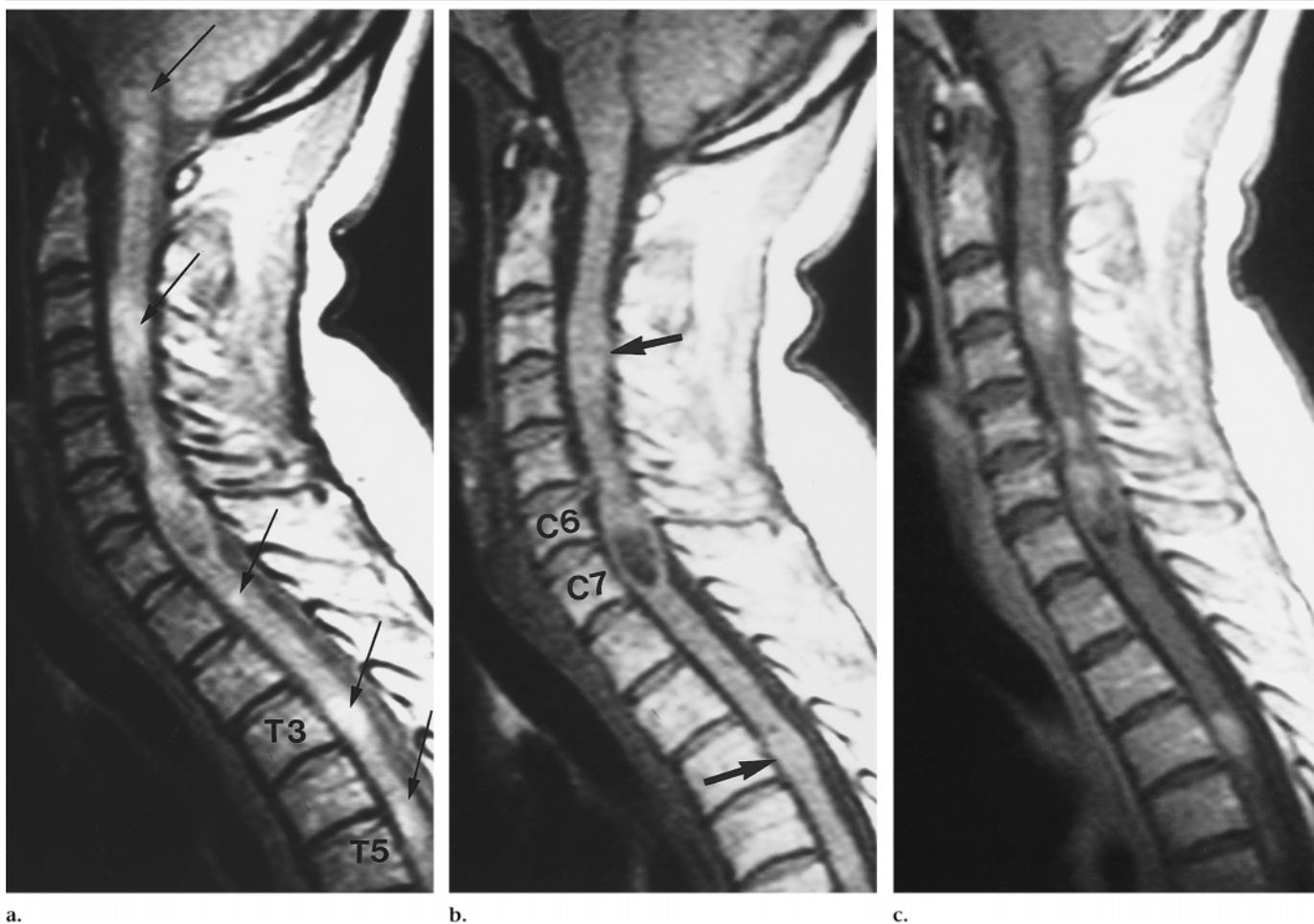


Figure 3. (a) Sagittal intermediate-weighted MR image (2,500/20) of the cervical spine. Several hyperintense tumors (arrows) are present at the level of the medulla, C3–C4, C6 to C7, T1, T3, and T5. The tumor at the C6–C7 level is large and partially cavitary, and it produces cord engorgement. Less obvious cord engorgement is also caused by the tumors at the C3–C4 and T3 levels. (b) Sagittal nonenhanced T1-weighted image (417/16) clearly demonstrates the cavitary tumor at the C6–C7 level. Two of the solid tumors at the C3–C4 and T3 levels appear slightly hyperintense with respect to the normal cord (arrows). (c) Sagittal contrast-enhanced T1-weighted image (417/16). All intramedullary tumors are enhanced.

NF2 by Mautner et al (4), but they differ quantitatively. We documented spinal tumors in 63% of our patients, which is lower than the 89% reported by Mautner et al. We observed a higher percentage of patients with no spinal tumors (37% [18 of 49 patients] vs 11%), and, among patients with spinal tumors, we observed a higher percentage with intramedullary tumors (84% [26 of 31 patients] vs 37%). The percentages of patients with extramedullary tumors were the same in the two studies (87% [27 of 31 patients] vs 92%), but the data of Mautner et al included those of patients with intradural and extradural tumors; the latter were excluded from our study.

The higher percentage of patients in our study without spinal tumors may reflect our inclusion of 12 patients from two large families with mild NF2; only one of these patients had spinal tumors.

Other differences may be explained, in part, by the fact that our results are based on findings of imaging studies of the entire spine in 90%, rather than 100%, of patients. Since our results suggest that the development of different categories of spinal tumors may be influenced by the type of NF2 mutation, the disparities in imaging findings between the two studies also likely reflect differences in the distribution of different types of NF2 mutations in the studied populations, as well as in patient ascertainment.

We identified three cardinal features of intramedullary tumors in our patients: (a) central location within the cord parenchyma, (b) intense enhancement, and (c) multiplicity. The presence of multiple intramedullary tumors is a feature of both metastatic tumors and hemangioblastomas. However, these tumors usually originate from the leptomeninges

and are eccentrically placed; only rarely are they located in the center of the cord. None of the patients with multiple contiguous intramedullary tumors underwent surgery for them after the imaging studies were performed, so we could not determine whether these tumors represented nodules of a single large lesion or independently occurring multicentric tumors.

The reported histologic findings in the intramedullary tumors removed from patients or examined at autopsy have all been described before in NF2 (4–6,19). That different types of intramedullary tumors can occur within an individual with NF2 was demonstrated with the autopsy findings in one patient from this study of two ependymomas separated by an astrocytoma. None of the MR images or surgery or autopsy reports suggested that any of the intramedullary tumors were

holocord tumors similar to those described (20) infrequently in children and young adults.

Few of the 26 patients in our study with intramedullary tumors had undergone any therapeutic intervention for these tumors. Only three (12%) patients underwent surgery for them, a percentage similar to that reported by Mautner et al (4). In addition, of the 84 intramedullary tumors that we evaluated on consecutive MR images of 16 patients, only one demonstrated appreciable growth during a mean follow-up of 49 months. Taken together, these results suggest that many intramedullary tumors associated with NF2 remain quiescent over a long period of time. Therefore, surgical intervention may not be necessary for most of them.

Our data and the observations of others (8) support an approach to NF2-associated intramedullary tumors of watchful waiting during which tumor growth is monitored with regular imaging studies and appropriate clinical correlations. This approach differs from the treatment implemented for a symptomatic intramedullary tumor in an individual in the general population. Because these tumors usually behave aggressively, standard of care mandates attempted total resection and adjunct radiation therapy and/or chemotherapy for residual disease (21). In the setting of NF2 in which both the relatively indolent course of most NF2-associated intramedullary tumors and the anticipated burden from other spinal and intracranial tumors must be considered, such aggressive management may not be warranted, even in a symptomatic patient (8).

In contrast to the indolent behavior of most of the intramedullary tumors in our patients, the presence of extramedullary tumors led frequently to surgical intervention. A higher percentage of patients underwent surgery for extramedullary tumors than for intramedullary tumors. When we included operations performed to remove extramedullary tumors both before and after patients entered our study, the percentage of patients with extramedullary tumors who underwent such surgery was about five times higher than the percentage of patients with intramedullary tumors who underwent surgery for them (59% vs 12%). Furthermore, with similar numbers of patients, 30 operations were performed to remove extramedullary tumors compared with four operations for intramedullary tumors, a 7.5-fold increase. The higher surgical burden associated with extramedullary tumors in our patients may be the

TABLE 2
Pathologic Findings in Spinal Tumors

Type of Tumor	No. of Tumors (N = 57*†)
Intramedullary	
Astrocytoma	3*
Ependymoma	4†
Schwannoma	1
Subtotal	8*†
Extramedullary	
Schwannoma	26
Meningioma	17
Neurofibroma	6
Subtotal	49

Note.—Spinal tumors were removed from 16 patients and were examined at autopsy in two patients.

* Includes one tumor examined at autopsy.

† Includes three tumors described in the autopsy reports of two patients.

result of a combination of factors, including the relatively high mean number of these tumors and frequent occurrence of cord compression.

An important corollary to these observations is that a large proportion of the patients with NF2 in our study who had spinal tumors did not undergo any surgery related to them: specifically, 23 (88%) of 26 patients with intramedullary tumors and 11 (41%) of 27 patients with extramedullary tumors did not undergo surgery for these tumors either prior to or during our study.

We were able to distinguish meningiomas from NSTs on the basis of MR imaging characteristics in the small number of patients on whom we performed imaging studies prior to spinal tumor surgery. Extrapolation of these correlations to all the patients in our study allows us to compare the morbidity associated with meningiomas and that associated with NSTs at both the radiographic and clinical levels. The results of these comparisons suggest that meningiomas were more aggressive.

We observed meningiomas on the MR images in a smaller proportion of patients (18% vs 53%), and their total and mean numbers were lower (24 vs 177, and 2.6 vs 6.8, respectively), compared with patients with NSTs. However, the percentage of patients with meningiomas who underwent surgery specifically for these tumors was higher than the percentage of patients with NSTs who underwent surgery for NSTs, namely, 56% (five of nine patients) versus 38% (10 of 26 patients). One other patient underwent separate operations for both types of tumors. Although meningiomas com-

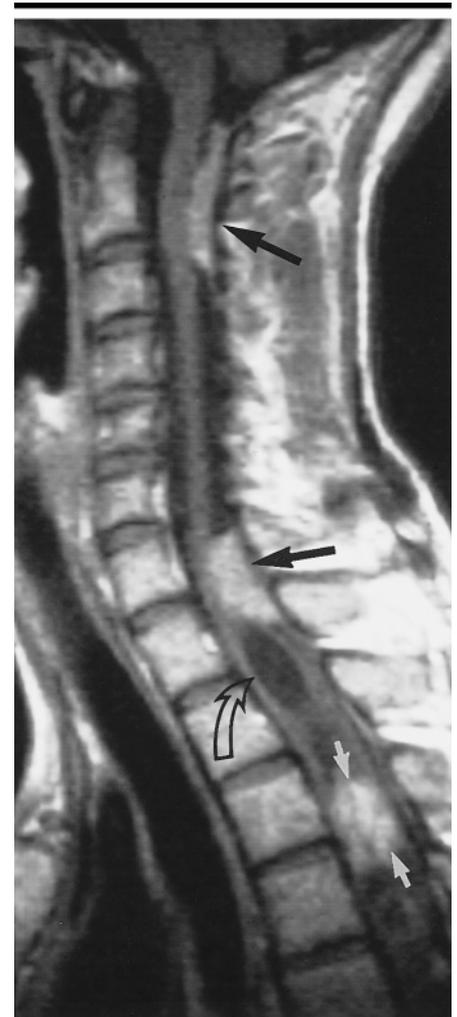


Figure 4. Sagittal contrast-enhanced T1-weighted MR image (550/22) of the cervical spine. Extramedullary enhancing dural-based tumors (meningiomas) are seen at the C2 and C7-T1 levels (black solid arrows). The tumor at the C7-T1 level results in cord compression. In addition, an enhancing intramedullary tumor (white solid arrows) at the T3-T4 level causes focal cord engorgement. An associated syrinx (open arrow) is seen in a small segment of the cord proximal to this tumor.

prised only 12% of all extramedullary tumors on the MR images, 37% of extramedullary tumors that were excised after the patients entered our study were meningiomas. These results, which are based on small numbers of patients and tumors, suggest that the presence of meningiomas should raise the level of vigilance in the clinicians who care for patients with NF2 and meningiomas.

Genotype-Phenotype Correlations

Ever since NF2 germline mutations were reported (9,10), investigators have

TABLE 3
Clinical Findings in Patients with NF2: Nonsense and Frameshift Mutations versus Other Mutations

Feature	Mutation				P Value*	
	Nonsense and Frameshift	Splice-Site	In-Frame	Missense	Analysis 1†	Analysis 2‡
No. of patients	13	15	6	3	NP	NP
No. of families	10	7	1	1	NP	NP
Percentage of patients§						
With any spinal tumors	92 (11.3 ± 8.0)	60 (6.8 ± 8.2)	0	100 (1.7 ± 1.5)	.25	.47
With intramedullary tumors	92 (3.3 ± 4.8)	53 (3.7 ± 4.7)	0	67 (1.3 ± 1.5)	<.025	<.075
With NSTs	85 (6.5 ± 6.1)	47 (2.7 ± 4.7)	0	33 (0.3 ± 0.6)	<.15	<.4
With meningiomas	46 (1.4 ± 3.0)	20 (0.4 ± 0.9)	0	0	<.3	<.4
With NSTs and/or meningiomas	85 (7.9 ± 6.7)	53 (3.1 ± 4.8)	0	33 (0.3 ± 0.6)	<.2	<.4
Age (y)¶						
At onset	12 ± 7.9	21 ± 7.8	25 ± 3.1	30 ± 14.6	<.009	<.032
At diagnosis	17 ± 6.6	32 ± 13.6	30 ± 6.9	31 ± 13.1	0	0
At last MR imaging	31 ± 12.9	40 ± 15.2	42 ± 12.2	41 ± 13.9	<.025	<.04

* NP = not performed.

† Data in patients with nonsense and frameshift mutations were compared with those in patients with the three other types of mutations.

‡ Data in patients with nonsense and frameshift mutations were compared with those in patients with splice-site mutations.

§ Data in parentheses are the mean number of tumors plus or minus the SD.

¶ Data are the mean plus or minus the SD. Mean ages at onset, at diagnosis, and at last MR imaging in the entire set of 49 patients were 18.9 years (range, 4–46 years), 25.9 years (range, 7–67 years), and 39.1 years (range, 10–72 years), respectively. Only four patients were younger than 15 years at entrance into this study. Three patients were asymptomatic when NF2 was diagnosed.

looked for correlations between different categories of mutations and specific clinical manifestations. These study findings have demonstrated that, in general, patients with nonsense or frameshift mutations have disease that is more severe than that of most patients with splice-site mutations, missense mutations, or large gene deletions. Manifestations of severe disease include onset of symptoms before age 20 years; presence of intracranial meningiomas, spinal tumors, and skin tumors; and higher numbers of these tumors (14).

In previous studies, the variable spinal tumors included all spinal tumors without regard to their location or histologic characteristics (3,14). The results presented here suggest that genotype-phenotype correlations may extend to specific categories of spinal tumors. In particular, patients with nonsense and frameshift mutations may be more likely to have intramedullary tumors and to have higher numbers of all spinal tumors, intramedullary tumors, NSTs, and extramedullary tumors, compared with patients with other types of mutations. They may also have higher numbers of tumors in these categories than do patients with splice-site mutations.

However, the results of the number of tumors must be viewed with caution. Because our study was based on a small number of patients and families with identified mutations, we could not directly adjust the analytic model for family size. Therefore, these analyses should be repeated in a data set large enough to

accommodate this adjustment. With respect to the age variables, our results are consistent with those of previous reports (3,11–14) of the younger ages at onset and at diagnosis of NF2 in patients with nonsense and frameshift mutations.

In conclusion, we have confirmed that a high proportion of patients with NF2 have multiple intramedullary and/or intradural extramedullary spinal tumors that often have different histologic types. Although the numbers of patients in this study with intramedullary or extramedullary tumors were similar, the patients underwent far more surgical procedures for extramedullary tumors. NSTs were present more often and in higher numbers than were meningiomas, and they were associated with more surgical procedures overall. However, a higher percentage of patients with meningiomas underwent surgery specifically for these tumors.

Overall, these results suggest that the frequency of follow-up of patients with spinal tumors should be based on knowledge of tumor location, number, and suspected histologic type. Regular assessment at MR imaging and neurologic examination should allow the clinician to establish appropriate indications for surgery on intramedullary tumors and should facilitate early removal of rapidly growing or symptomatic extramedullary tumors.

Our results also suggest that patients with nonsense and frameshift mutations may be more likely to develop intramedullary tumors and to have higher numbers of intramedullary tumors and NSTs compared with patients with other types

of mutations. If confirmed, these observations would extend genotype-phenotype correlations in NF2 to specific types of spinal tumors.

Glossary of Terms

Exon.—A region of a gene that is transcribed into mature messenger RNA. After translation, the exon corresponds to a sequence of amino acids in the resulting protein. The NF2 gene has 17 exons.

Exon scanning.—A method used to look for base changes in the NF2 gene. Exon scanning was used to identify sequence changes in single-stranded DNA from each exon that altered its conformation and hence its mobility on a gel matrix. DNA strands that migrated abnormally were sequenced to identify specific base-pair changes.

Frameshift mutation.—A deletion or insertion of one or more bases that is not an exact multiple of three. A frameshift mutation changes the reading frame of the gene. All coding sequences that follow the mutation are read as gibberish, and a chain termination codon usually results. Usually, translation of the resulting messenger RNA results in a shortened or truncated protein.

In-frame deletion.—The loss from a gene of three bases or a multiple of three contiguous bases. This type of mutation does not alter the reading frame beyond the point of the mutation. Translation of the resulting messenger RNA beyond the mutation results in an amino acid sequence that is unchanged.

Intron.—A segment of a gene that is transcribed into messenger RNA but then is removed from it by splicing together the sequences (exons) on either side of it.

Missense mutation.—A single base substitution in DNA that changes a codon specific for one amino acid so that it specifies a different amino acid.

Nonsense mutation.—A single base substitution in DNA that results in a chain-termination codon and, presumably, a truncated protein.

Splice-site mutation.—Usually a deletion or insertion of one or more bases that alters a DNA sequence involved in the splicing out of introns and the splicing together of exons from the primary RNA transcript to generate a mature messenger RNA. By interfering with normal splicing, such mutations usually result in either a premature stop codon and a truncated protein or an abnormal protein from which an exon has been deleted.

Acknowledgments: We are greatly indebted to the patients and family members whose cooperation made this study possible. We acknowledge the helpful discussions with Alisa M. Goldstein, PhD, National Cancer Institute, Bethesda, Md, on the statistical analyses.

References

1. Evans DGR, Huson SM, Donnai D, et al. A clinical study of type 2 neurofibromatosis. *Q J Med* 1992; 84:603–618.
2. Parry DM, Eldridge R, Kaiser-Kupfer MI,

3. Bouzas EA, Pikus A, Patronas N. Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. *Am J Med Genet* 1994; 52:50–461.
4. Parry DM, MacCollin, Kaiser-Kupfer MI, et al. Germ-line mutations in the neurofibromatosis 2 gene: correlations with disease severity and retinal abnormalities. *Am J Hum Genet* 1996; 59:529–539.
5. Mautner VF, Tatagiba M, Lindenau M, et al. Spinal tumors in patients with neurofibromatosis type 2: MR imaging study of frequency, multiplicity and variety. *AJR Am J Roentgenol* 1995; 165:951–955.
6. Lee M, Rezai AR, Freed D, Epstein FJ. Intramedullary spinal cord tumors in neurofibromatosis. *Neurosurgery* 1996; 38:32–37.
7. Egelhoff JC, Bates DJ, Ross JS, Rothner AD, Cohen BH. Spinal MR findings in neurofibromatosis types 1 and 2. *AJNR Am J Neuroradiol* 1992; 13:1071–1077.
8. Elster AD. Occult spinal tumors in neurofibromatosis: implications for screening. *AJR Am J Roentgenol* 1995; 165:956–957.
9. Jones RM, MacCollin M. The natural history of ependymoma in patients with neurofibromatosis 2 (abstr). *Neurology* 1997; 48:A35.
10. Trofatter JA, MacCollin MM, Rutter JL, et al. A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. *Cell* 1993; 72:791–800.
11. Rouleau GA, Merel P, Lutchman M, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. *Nature* 1993; 363:515–521.
12. Merel P, Hoang-Xuan K, Sanson M, et al. Screening for germ-line mutations in the NF2 gene. *Genes Chromosom Cancer* 1995; 12:117–127.
13. Ruttledge MH, Andermann AA, Phelan

14. CM, et al. Type of mutation in the neurofibromatosis type 2 gene (NF2) frequently determines severity of disease. *Am J Hum Genet* 1996; 59:331–342.
15. Kluwe L, Bayer S, Baser ME, et al. Identification of NF2 germ-line mutations and comparison with neurofibromatosis 2 phenotypes. *Hum Genet* 1996; 98:534–538.
16. Evans DGR, Trueman L, Wallace A, Collins S, Strachan T. Genotype/phenotype correlations in type 2 neurofibromatosis (NF2): evidence for more severe disease associated with truncating mutations. *J Med Genet* 1998; 35:450–455.
17. MacCollin M, Mohny T, Trofatter J, Wertelecki W, Ramesh V, Gusella J. DNA diagnosis of neurofibromatosis 2. *JAMA* 1993; 270:2316–2320.
18. Gutmann DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA* 1997; 278:51–57.
19. Donner A, Klar N. Methods for comparing event rates in intervention studies when the unit of allocation is a cluster. *Am J Epidemiol* 1994; 140:279–289.
20. Li MH, Holtas S. MR imaging of spinal neurofibromatosis. *Acta Radiologica* 1991; 32:279–285.
21. Rodriguez HA, Berthrong M. Multiple primary intracranial tumors in von Recklinghausen's neurofibromatosis. *Arch Neurol* 1966; 14:467–475.
22. Epstein F. Spinal cord astrocytomas of childhood. *Adv Tech Stand Neurosurg* 1986; 13:135–169.
23. McCormick PC, Torres R, Kalmon DP, Stein BM. Intramedullary ependymoma of the spinal cord. *J Neurosurg* 1990; 72:523–532.