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Detection of Chromosomal Imbalances in Spinal Meningiomas by Comparative Genomic Hybridization

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Abstract

Little is known about genetic mutations during the malignant progression of spinal meningiomas. This study investigated genomic changes across the entire genome in spinal meningioma samples to determine possible mechanism(s) of tumorigenesis. Paraffin-embedded tissue sections of 16 spinal meningiomas were analyzed by the comparative genomic hybridization (CGH) technique. Lymphocytes of the patients were evaluated as controls. Genomic change was detected in 11 samples. Complete or partial loss of chromosome 22 was the most commonly seen abnormality in eight cases. Chromosome losses on 1p, 9p, and 10q and gains on 5p and 17q were the other abnormalities. These changes are all frequently seen in meningiomas, but are mostly specific to atypical and anaplastic meningiomas. However, in the present study, copy number changes on chromosomes 9p (3 samples), 17q (2 samples), and 1p (2 samples) were seen even in the benign tumors. Our results suggest that in addition to the neurofibromatosis type 2 tumor suppressor gene, other cancer-related genes located on 1p, 9p, 10q, and 17q might be involved in the etiology of spinal meningiomas.

Key words: meningioma, comparative genomic hybridization, chromosome 22q, tumor suppressor gene

Introduction

Meningiomas are common tumors of the central nervous system, with an annual incidence of approximately 6 per 100,000 individuals, and constitute approximately 15% of all intracranial and 25% of all spinal tumors.[20] Spinal meningiomas are a commonly encountered entity in practice. The important properties of spinal meningiomas are the slow rate of growth and the rapid recovery of neurological deficits after early diagnosis and treatment.[19]

Meningiomas were among the first solid tumors studied by cytogenetics. Loss of chromosome 22 is the most common aberration and has been detected in 40% to 70% of cases.[4,16,25,30,31] Recent studies have demonstrated that the neurofibromatosis type 2 (NF2) gene, a tumor suppressor gene, is located at the 22q12 locus[21,27] and is the gene involved in the etiology of meningiomas, since most cases have mutations in this region.[9,22] The presence of mutations and/or loss of NF2 gene in meningiomas of all malignancy grades indicates that inactivation of this tumor suppressor gene represents an early genetic event in the pathogenesis of meningiomas. However, cytogenetic and molecular analyses have failed to detect 22q12 mutations in about 40% of all tumors. Tumors without 22q12 mutations have no distinct clinical and histological features from the meningiomas with deletions on 22q, but cases without 22q aberrations have other nonrandom chromosome abnormalities and putative tumor suppressor genes located on these chromosomal regions.[3,5,12,14,17,29] These observations suggest an alternative mechanism(s) is responsible for the development of some meningiomas. Therefore, other molecular mechanisms that may be involved in the tumorigenesis of meningiomas are important to elucidate.

No detailed investigation has evaluated genomic mutations in spinal meningiomas. In our previous study,[8] chromosome 22q13 deletion was found in a patient with intracranial and spinal meningiomas, and some cytogenetic abnormalities have been

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Table 1 Summary of histological examination and genome analysis of 16 spinal meningiomas

Case No.	Age	Sex	Histological diagnosis	Tumor location	WHO grade	CGH results	
						Loss	Amplification
1	35	F	transitional	T-6	I		17q23
2	55	F	transitional	T9–10	I	normal	
3	65	F	transitional	T2–3	I	22	
4	39	F	transitional	C7–T1	I	normal	
5	67	F	transitional	T-4	I	22q12, 9p23-pter	
6	52	M	transitional	C7–T1	I	normal	
7	60	F	transitional	T5–6	I	22q12	
8	29	F	psammomatous	T-9	I	1p35-pter	
9	52	F	meningothelial	C-3	I	9p23-pter	
10	61	F	transitional	T-10	I	22q12, 1p35-pter	
11	42	F	transitional	T2–3	I	normal	
12	70	F	transitional	T4–5	I	22	
13	39	F	transitional	T-6	I	normal	
14	41	M	transitional	T-5	I	22q12	
15	60	F	transitional	T2–3	I	22	
16	35	M	atypical	T2–4	II	22q12, 10q25-qter, 9p23-pter	5p15-pter, 17q23

CGH: comparative genomic hybridization, WHO: World Health Organization.

reported.[6] However, it is not known whether there are specific aberrations involved in the etiology of the spinal meningiomas.

The present study evaluated the presence of mutations in the entire genome of a series of spinal meningiomas to determine the possible mechanisms of tumorigenesis.

Materials and Methods

The present study investigated 16 spinal meningiomas from adult patients with the comparative genomic hybridization (CGH) method for nonrandom quantitative genomic changes. Thirteen patients were females and three males, with a median age at diagnosis of 50.12 ± 13.02 years.

The samples were classified according to the World Health Organization system[13] as 15 grade I meningiomas and one grade II meningioma. A paired blood sample was drawn from each patient and used as the control. Isolation of high- molecular weight deoxyribonucleic acid (DNA) from the paraffin-embedded tissue samples, the blood samples from the patients and a healthy male donor, and chromosome preparations from the healthy male donor followed standard methods.

Degenerate oligonucleotide-primed polymerase chain reaction (DOP-PCR) was used to uniformly amplify the DNA as previously described[26] using the primer 6MW (5' CCGACTCGAGNNNNNNATGTGG-3'). Tumor and normal DNA probes were generated in a secondary labeling DOP-PCR reaction by incorporation of spectrum green (Vysis, Inc., Downers Grove, Ill., U.S.A.) and spectrum red (Vysis, Inc.) directly conjugated nucleotides, respectively. After PCR labeling, DNA size was reduced to below 500 bp using a controlled deoxyribonuclease I digestion for 10 minutes at room temperature and then the reaction was stopped by 2–3-minute incubation at 95°C. Diploid metaphase spreads were obtained from peripheral blood lymphocyte cultures of normal male donors. Slide preparation was optimized to minimize residual cytoplasm and generate well-spread metaphases as described previously.[10] The test and reference DNA samples, labeled in different colors, were precipitated together in the presence of 40 μg unlabeled Cot1 DNA (Gibco BRL, Life Technologies, Ltd., Paisley, U.K.), resuspended in 12 μl hybridization mixture (50% formamide/2 × SSC), denatured at 70°C for 10 minutes, and preannealed for 1 hour at 37°C. The probe was hybridized to a normal denatured metaphase spread for 3 days, followed by stringency washes adapted from a standard fluorescence in-situ hybridization protocol.

Slides were viewed on an Zeiss Axiophot fluorescence microscope (Carl Zeiss, Oberkochen, Germany). For each hybridization, at least 10 metaphases were captured and analyzed with MacProbe version 4.11 software (Perceptive Scientific International, Chester, U.K.). Interpretation of the profiles accorded to published guidelines.[11] Any shifts in the mean green-to-red ratio value above 1.25 were considered

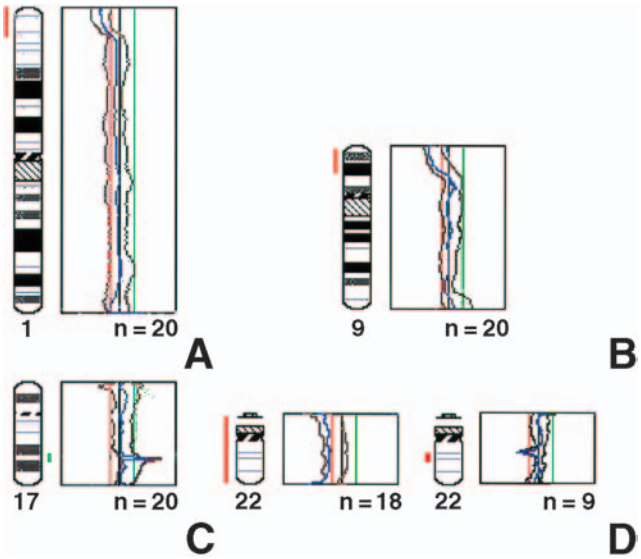


Fig. 1 Comparative genomic hybridization analyses of chromosomes 1, 9, 17, and 22. A, B: Fluorescence ratio profiles of the chromosomes 1p35-pter (A) and 9p23-pter (B) regions, respectively, were lower than the lower threshold level (<0.85), showing that grade I spinal meningiomas have copy number losses in these chromosomal regions. C: Fluorescence ratio profile of the chromosome 17q23 region was higher than the upper threshold level (>1.25), showing that this chromosomal region was amplified. D: Fluorescence ratio profile showing complete chromosome 22 deletion or chromosome 22q12 deletion. The ratio profiles represent the mean fluorescence ratios obtained from 5–10 metaphases. The center (*black*) line indicates the ratio value (1.0) for a balanced state of chromosomal material. The left (*red*) and the right (*green*) lines depict upper and lower 90% thresholds. Deviations beyond the right threshold indicate gains and those beyond the left threshold indicate losses of chromosome segments. These copy number alterations are indicated by the lines on the right and left sides of the chromosome idiograms.

to indicate gains of chromosomal material and any shifts below 0.85 to indicate losses.

Procedures followed in experiments on samples used in this study were in accordance with the Helsinki Declaration of 1975.

Results

Table 1 summarizes the age, sex, clinical data, histological diagnosis, and genomic mutations detected by CGH in the 16 sporadic spinal meningiomas.

The tumors were located in the thoracic region in 13 patients and in the cervical region in three. All spinal meningiomas were located intradurally and extramedullary. Thirteen of the tumors were transitional meningiomas, and the other two were the psammomatous and the meningothelial subtypes.

The patients were followed up for 6 months to 9 years (mean follow up 2.4 years) and no cases of recurrence were encountered. There was no relationship between genomic abnormality and tumor location. The lymphocytes of each case were also analyzed by CGH as controls and no chromosomal abnormality was seen.

There was no chromosomal abnormality in five grade I tumor samples but CGH detected genomic abnormalities in the other 10 grade I and one grade II samples. The most common aberration was complete or partial loss of chromosome 22 in eight cases, seven grade I and the grade II tumors. Three of these eight tumors had complete chromosome loss, but only chromosome 22q12 loss in five samples (Table 1, Fig. 1). Monosomy 22 or loss of 22q12 was the only abnormality in seven tumors.

Other aberrations were losses on 1p, 9p, and 10q and gains on 5p and 17q (Fig. 1). There were three cases of 9p deletion, two in grade I and the other in the grade II tumors. Chromosome 9p deletion was the only abnormality detected in Case 9 with a benign tumor. Chromosome 1p deletion was the only abnormality in Case 8, but was detected together with chromosome 22q12 loss in Case 10. Chromosome 17q amplification appears to be an important molecular mechanism for progression from grade II to grade III, but was also detected in our grade I and grade II tumors. Amplification of 17q23 was the only abnormality in Case 1 but was one of multiple abnormalities in Case 16. Multiple genomic abnormalities were determined in the grade II tumor (Fig. 2). Chromosome 10q25-qter deletion and amplification of 5p15-pter were only seen in this sample. Although the first abnormality is specific for grade II meningiomas, 5p amplification might be a random abnormality. However, this abnormality is clearly specific to the tumor sample because no copy number changes were seen in the lymphocytes of this patient. The specificity of the abnormality could not be evaluated since the sample with 5p amplification was the only grade II tumor and no other atypical or anaplastic meningiomas were present in this series.

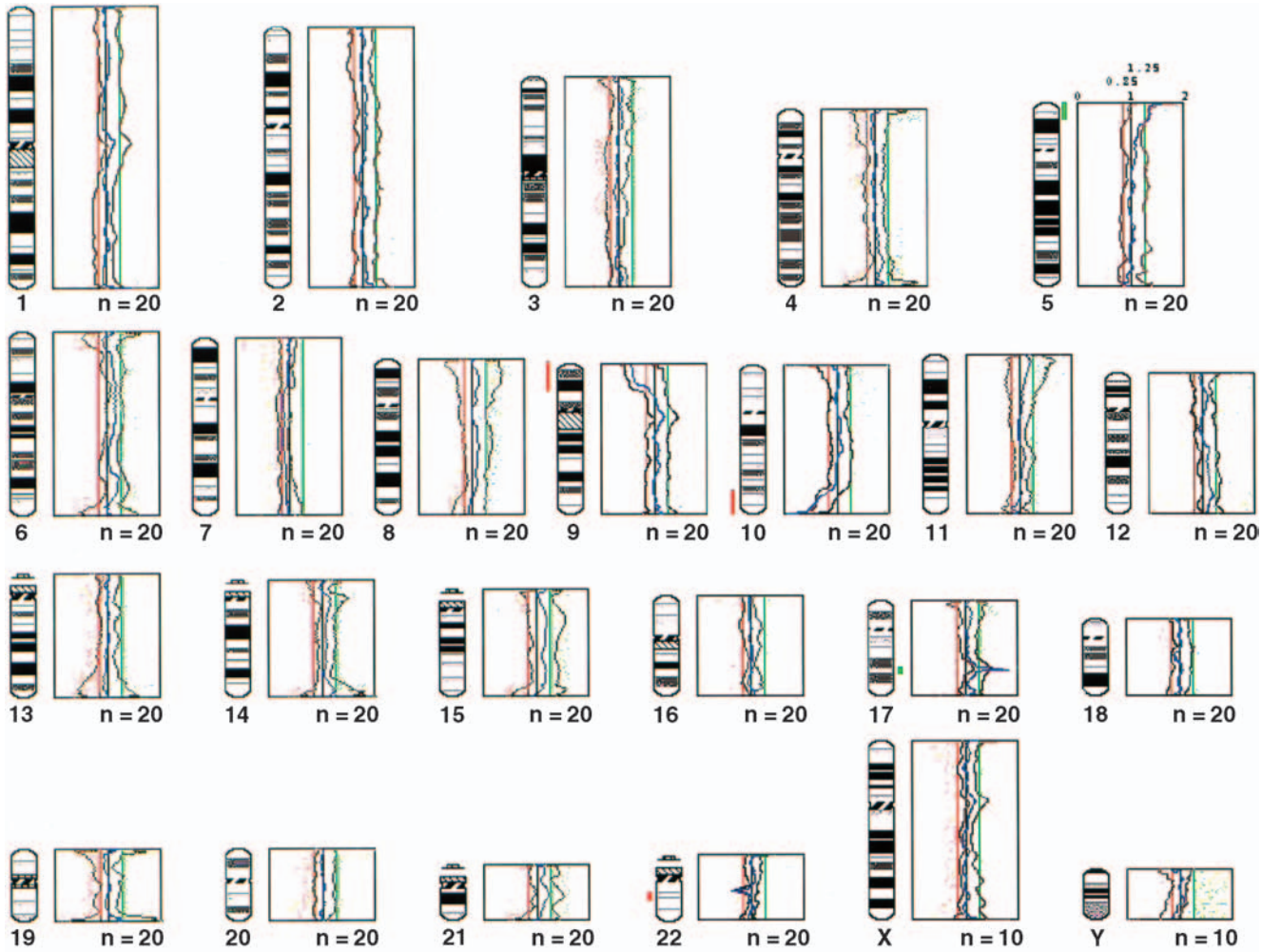


Fig. 2 Comparative genomic hybridization ratio karyotype from Case 16 (grade II) with gains of 5p15-pter and 17q23, and losses of 9p21-pter, 10q, and 22q12. Lines on the left (*red*) and right (*green*) of the chromosomes indicate losses and gains of these chromosomal regions, respectively.

Discussion

Knudson's two hit hypothesis suggests that inactivation of a tumor suppressor gene occurs in two steps: mutation of the first allele followed by the loss of the other one. The NF2 gene located at 22q12 is a tumor suppressor gene. The product *merlin* (moesin-ezrin-radixin-like protein) is a 590 amino acid protein that shares 45–47% identity with the cytoskeleton-associated proteins.[21,27] Since complete or partial loss of chromosome 22 is the most common genetic aberration in meningiomas of all malignancy grades, tumorigenesis of the majority of meningiomas involves the inactivation of both alleles of NF2, which supports Knudson's two hit hypothesis. However, MN1, BAM22, and INI1 are other genes located on chromosome 22q of which inactivation has been reported in meningiomas, but the roles of these genes in the genesis of meningiomas are not clear yet.[14,24,29]

The prevalence of chromosome 22 mutation detected in the present study is in the reported range of 40–70%.[12,29] The 22q deletion was detected in grade I tumors but also in the grade II sample, demonstrating that chromosome 22q mutation is the most commonly occurring early genetic event in the pathogenesis of meningiomas. This finding is in agreement with the other cytogenetic and molecular genetic studies.[5–7,12,14,17,23,25,28,29]

The present study also identified losses on chromosome 9p (9p23-pter) and 1p (1p35-pter), and amplification of 17q (17q23). Deletion of 9p and amplification of 17q are frequent abnormalities in grade III tumors but rarely detected in grade I and II tu-

mors.[15] In our study, 9p21-pter deletion was detected in two grade I tumors and in one grade II tumor. The tumor suppressor gene, CDKN2A, is located at the 9p21 locus and loss of inactivation would be an alternative mechanism for the progression of meningiomas.

Chromosome 17q amplification was detected in one grade I tumor and the grade II tumor in our series. PS6K, a putative oncogene mapped to chromosome 17q23, encodes a serine/threonine kinase that is involved in the phosphorylation of ribosomal subunit 6 and is part of the insulin receptor signal transduction pathway. Amplification of 17q23 is frequently seen in grade II and III meningiomas and seems to be an important molecular mechanism for tumor progression from grade II to grade III.[2,29] No 17q23 amplifications were detected in benign (grade I) and atypical (grade II) meningiomas in a previous study,[2] but amplification of 17q occurs in 5% of grade II meningiomas.[29] Our case of 17q23 amplification in a grade I tumor is the first known case.

Chromosome 1p deletion was detected in two grade I tumors. This abnormality is rarely seen in grade I but often in grade II and grade III meningiomas, and thus may contain a tumor suppressor gene associated with meningioma progression. Although both samples with 1p chromosomal mutation were grade I, our results are consistent with this suggestion because loss of chromosome 1p35-pter was determined in the samples without chromosome 22q deletions, which is the most common abnormality associated with meningiomas. We suggest that another genetic abnormality may be present in all benign tumors without chromosome 22q deletion. The p73 gene at 1p36.3, and the tissue non-specific alkaline phosphatase Alpl gene at 1p36.1-p34 are candidate tumor suppressor genes in meningiomas.[1,15,18] Since the common deleted region on 1p in our series was located at 1p35-pter, we suggest that 1p should be a primary focus of detailed assessment of tumorigenesis, and also this candidate tumor suppressor gene may be involved in tumor progression as well as initiation of meningioma. Other authors[3,17] have made this suggestion for losses of both 1p and 3p which were detected in benign meningiomas.

Chromosomes 10q deletion and amplification of 5p were detected in grade II tumors. Chromosome 10q mutations are seen in 27-50% of grade II meningiomas.[29] The PTEN (MMAC1) gene cloned at 10q23.3 is a tumor suppressor gene and is inactivated in some glioblastomas.[29] Further, germ-line PTEN mutations have been found to be responsible for Cowden's disease, which is a hereditary syndrome predisposing to multiple tumors, including meningiomas. Chromosome 10q25-qter might be an important region for the progression of meningiomas because of the deactivation of the PTEN gene or another, as yet unknown, tumor suppressor gene.

Gain on chromosome 5p was the other abnormality detected in the grade II meningioma. Chromosome 5p amplification has not been found previously in grade II meningiomas. The individual target gene(s) for this gain is not known. However, the presence of this abnormality in a tumor sample, but not present in the control, may indicate the participation of gene(s) on chromosome 5p15-pter in the progression of meningiomas.

Most of the chromosomal aberrations detected in grade I spinal meningiomas in our series coincide with the genetic mutations seen in meningiomas at different anatomical locations but in higher tumor grades. The only previous study of cytogenetic changes in spinal meningiomas found various chromosomal changes.[6] Our other CGH study of a series of benign and malignant meningiomas (in preparation) also detected chromosome 1p as an alternative initiator of meningioma other than chromosome 22q deletion. However, the other chromosome aberrations such as 17q amplification and 9p deletion detected in this study were specific abnormalities in atypical and anaplastic meningiomas of our other series. Therefore, we suggest that presence of these abnormalities in benign samples might be specific for spinal meningiomas. Further studies of larger series and different tumor grades are necessary to clarify the molecular mechanisms of spinal meningiomas.

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Commentary on this paper appears on the next page.

Commentary

The authors analyzed genomic alterations in 16 spinal meningioma samples using a comparative genomic hybridization technique. In addition to frequent loss on chromosome 22, they documented chromosome losses for 1p, 9p, and 10q and gains on 5p and 17q in their series, observations that are frequently made in malignant type meningiomas. Their suggestion of a possible relationship with the tumorigenesis of spinal meningiomas is interesting. Tumor suppressor genes other than NF2 are relevant in the tumorigenesis of intracranial meningiomas: 1p deletion was commonly observed in tumors without 22q-deleted populations. Although both intracranial and spinal meningiomas may follow a common pathway in the course of tumor formation, comparative studies may reveal the existence of variations between them. The total number of samples used in this study is too small to allow such an important conclusion. Further studies using larger series are essential for an understanding of the molecular mechanism(s) underlying the tumorigenesis of spinal meningiomas.

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Although there have been a number of studies evaluating chromosomal abnormalities in meningiomas affecting the brain, there have been very few studies directed toward spinal meningiomas. This study looks very carefully at a series of 16 meningiomas occurring in the spinal compartment. These tumors were analyzed for genetic composition using the comparative genomic hybridization technique. The authors detected genomic changes in 11 of the 16 patients. The most common abnormality was complete loss of chromosome 22, similar to that seen in cerebral meningiomas. They also noted additional chromosome losses and two instances of chromosome gains. Once again, these types of changes are fairly common in meningiomas elsewhere, but tend to be more common in those tumors that are more aggressive. These presumably aggressive chromosomal changes were seen even in very benign appearing spinal meningiomas. Although the data do not support a definite conclusion of a causative relationship, they are certainly provocative and add in a significant way to our knowledge of the molecular biology of meningiomas.

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The authors extended their genetic analysis of meningioma, based on their previous study and presently on-going investigations of malignant progression, into the molecular genetic analysis of the intraspinal location. The material is relatively extensive for a basic study of the clinical cases and the methodology is updated. This paper is a significant contribution with the conclusions of involvement of the cancer-related genes located on 1p, 9p, 10q and 17q in the tumorigenesis of spinal meningiomas.

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