Evidence for a Tumor Suppressor Gene on Chromosome 19q Associated with Human Astrocytomas, Oligodendrogliomas, and Mixed Gliomas

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Abstract

Previous studies have shown frequent allelic losses of chromosomes 9p, 10, 17p, and 22q in glial tumors. Other researchers have briefly reported that glial tumors may also show allelic losses of chromosome 19, suggesting a putative tumor suppressor gene locus on this chromosome (D. T. Ransom et al., Proc. Am. Assoc. Cancer Res., 32: 302, 1991). To evaluate whether loss of chromosome 19 alleles is common in glial tumors of different types and grades, we performed Southern blot restriction fragment length polymorphism analysis for multiple chromosomes in 122 gliomas from 116 patients. Twenty-nine tumors had loss of constitutional heterozygosity of 19q, and four tumors had partial deletions of 19q. Allelic losses on 19q were restricted to grade III anaplastic astrocytomas (4/9) and grade IV glioblastomas (11/46), grade II oligodendrogliomas (2/5) and grade III anaplastic oligodendrogliomas (2/2), and grade II (5/8) and grade III (5/7) mixed oligoastrocytomas. These data demonstrate genetic similarities between astrocytomas, oligodendrogliomas, and mixed gliomas and indicate the presence of a glial tumor suppressor gene on chromosome 19q.

Introduction

LOH studies have been widely used to identify regions of chromosomal loss in human tumors (1, 2). The loss of one chromosomal allele is thought to unmask a mutant tumor suppressor gene on the remaining allele, thus fulfilling the paradigm of recessively acting tumor suppressor genes (3). In glial tumors LOH on chromosome 17p has been associated with mutations of the p53 tumor suppressor gene on the remaining 17p allele (4–6). In addition to chromosome 17p, LOH studies in human glial tumors have revealed frequent allelic losses on chromosomes 9p, 10, and 22q, suggesting the presence of a tumor suppressor gene on these chromosomes that are involved in the pathogenesis of gliomas (7, 8). Cytogenetic studies initially suggested that loss of portions of the long arm of chromosome 19 occur in anaplastic astrocytomas and glioblastomas (9, 10). Recently, Ransom et al. (11) reported loss of chromosome 19 in 6 of 22 astrocytomas, 3 of 4 oligodendrogliomas, and 1 of 4 mixed oligoastrocytomas; one of their oligodendrogliomas had a homozygous deletion at the locus D19S8 on the long arm of chromosome 19 (11). To evaluate whether 19q loss is unique to fibrillary astrocytomas and oligodendrogliomas, and whether a putative tumor suppressor gene locus exists on the long arm of chromosome 19, we evaluated 122 glial tumors for LOH events on chromosome 19.

Materials and Methods

Tissue Specimens and Histopathology. Tumor and blood samples were obtained from 116 patients treated at the Massachusetts General Hospital (Boston, MA) and at the University Hospital (Zürich, Switzerland). All tumors were classified by the same neuropathologists and graded according to the guidelines of the WHO (12). The group of 122 gliomas consisted of six grade II astrocytomas, nine grade III anaplastic astrocytomas, 54 grade IV GBM, 20 pilocytic astrocytomas, five grade II oligodendrogliomas, three grade III anaplastic oligodendrogliomas, nine grade II oligoastrocytomas, seven grade III anaplastic oligoastrocytomas, two pleomorphic xanthoastrocytomas, two malignant brainstem gliomas, two ependymomas, and three gangliogioblastomas. In four cases of GBM and one case each of anaplastic oligodendroglioma and anaplastic ependymoma, recurrent tumors were also examined.

DNA Probes and RFLP Analysis. We used a panel of DNA probes for the long and short arms of chromosomes 19: pJCZ3.1 (D19S20) and p13-1-25 (D19S11) for the short arm; and p19 (D19S19), pMPS1 (CYP2A), p1T7.1 (D19S8), p12 (APC2), p92CK-M (CKM), pKEI2 (ERG2), p134C (D19S51), and pFED42 (D19S22) for the long arm. The loci are illustrated in Fig. 1. All probes were purchased from the American Type Culture Collection. The following combinations of DNA markers and restriction enzymes were used: pJCZ3.1 (Hinf1, MspI, or BglII), p13-1-25 (TaqI), p19 (D19S19), pMPS1 (SacI), p1T7.1 (MspI), p12 (APC2), p92CK-M (TaqI), pKERR2 (RsaI), p134C (PstI), and pFED42 (TaqI). Restriction fragment length polymorphism analysis was performed as described elsewhere (13).

Results and Discussion

The findings are summarized in Table 1. LOH for loci on 19q was demonstrated in 4 of 9 grade III anaplastic astrocytomas (44%) and in 11 of 46 GBMs (24%), but not in the six cases of grade II astrocytomas. LOH was also seen in 2 of 5 grade II oligodendrogliomas and 2 of 2 grade III anaplastic oligodendrogliomas (57% of pure oligodendrogliial tumors). Of the mixed oligoastrocytomas, 5 of 8 grade II tumors and 5 of 7 grade III tumors had LOH (67% of mixed tumors). In four cases (one anaplastic astrocytoma and three GBMs), partial deletions were found on the long arm of chromosome 19; these are illustrated in Figs. 1 and 2. No LOH was detected in the other gliomas (20 pilocytic astrocytomas, two pleomorphic xanthoastrocytomas, two malignant brainstem gliomas, two ependymomas, and three gangliogioblastomas). LOH on the short arm of chromosome 19 was seen in only one case, a recurrent GBM in which the primary tumor did not show allelic loss on 19p.
area of homozygous deletion reported by Ransom et al., at the D19S8 locus falls within the overlap regions of our partial deletions. Our results further demonstrate that 19q loss in gliomas appears to be restricted to diffuse astrocytic and oligodendrogial tumors.

The common region of overlap for the observed deletions involves an area of chromosome 19 that contains a number of cloned genes, including ERCC1, ERCC2, XRCC1, and CKM (14, 15). The ERCC and XRCC genes are of particular interest as tumor suppressor gene candidates, since they code for DNA repair enzymes, and because ERCC2 has been recently shown to reverse the UV radiation-sensitive phenotype of xeroderma pigmentosa cells (16). It remains to be shown, however, whether this locus is abnormal in glial tumors. The CKM gene, encoding muscle creatine kinase, could also be involved in a tumor suppressor pathway, since recent studies have shown that the upstream enhancer region of the murine CKM gene contains a locus which can be activated by the murine p53 tumor suppressor gene product (17). Numerous studies have implicated the p53 gene in glial tumorigenesis (4–6, 18, 19). If CKM plays a role in a cellular pathway involving p53, perhaps in control of the cell cycle, mutations in the CKM gene itself may be important in oncogenesis. In these four cases, however, relatively large areas of 19q were not informative or not examined (Fig. 1, shaded areas), and we cannot therefore exclude other regions of 19q as sites for this putative tumor suppressor gene.

Studies of allelic loss have shown that certain chromosomal losses are more common in some tumors than in others and that patterns of allelic loss may characterize individual tumors. Loss of chromosome 19 is an uncommon finding in human tumors (20) and has been reported, to our knowledge, only in glial tumors (11). The histogenesis of mixed oligoastrocytomas has long been a source of debate. Clinical, immunohistochemical, electron microscopic, and experimental data have hinted that the oligodendrogial and astrocytic components in mixed oligoastrocytomas may arise from a common stem cell and that mixed tumors are related to "pure" oligodendrogliomas (21–23). The common loss of portions of the long arm of chromosome 19 in mixed oligoastrocytomas, oligodendrogliomas, and
 astrocytomas, but not in other gliomas, adds further evidence that these three entities are biologically related. It will be of interest to determine whether astrocytomas with 19q loss respond to the same chemotherapeutic regimens that have recently been shown to be effective in the treatment of oligodendrogliaoma and mixed oligoastrocytoma (24, 25). In pure astrocytic tumors, LOH of 19q appears to be restricted to grade III and IV tumors, while in oligodendroglial and mixed astrocytic-oligodendroglial tumors, LOH also occurs in grade II tumors. This may imply that loss of a tumor suppressor gene on 19q is important in the progression of pure astrocytic tumors from lower-grade to higher-grade lesions but that this same tumor suppressor gene may be important in the early stages of oligodendroglial and mixed oligoastrocytic tumorigenesis.

References

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