A Specific Genetic Alteration on Chromosome 6 in Ulcerative Colitis-associated Colorectal Cancers

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ABSTRACT

Various genetic alterations in ulcerative colitis (UC)-associated colorectal cancers (CRCs) have been reported. However, almost all studies have shown abnormalities of the known genes that have been demonstrated in sporadic CRCs. To identify novel genetic alterations, we selected unintentionally 35 microsatellite markers, and performed allelotype study in CRCs or dysplastic lesions from UC. High frequency of loss of heterozygosity (LOH; 62.5%) was detected on chromosome 6 (D6S468) but not on other chromosomes. With four additional microsatellite markers around the D6S468 locus, we determined the commonly deleted region between two loci, D6S1543 and D6S1580, in UC-associated CRCs and dysplasia. Interestingly, there was no LOH in this region in sporadic CRCs and severely inflamed lesions of longstanding and extensive UC without cancer. These results indicated the presence of novel tumor suppressor genes on chromosome 6 related to the carcinogenesis of UC but not to sporadic CRCs.

INTRODUCTION

UC is a chronic inflammatory bowel disease with unknown etiology. It is well known that longstanding and extensive UC is high-risk for CRCs (1). Although the adenoma-carcinoma sequence is known as the molecular mechanism for carcinogenesis of sporadic CRCs (2), it is not solely applied to UC-associated CRCs. In sporadic CRCs, mutation of the APC gene is an early event, and mutation of p53 is a late event in their carcinogenesis. In contrast, mutation of APC gene is rare and mutation of p53 is an early event in the carcinogenesis in UC-associated CRCs (2–5). MSI is another important mechanism of carcinogenesis (6–8). Two phenotypes, MSI-H and low frequency of MSI (MSI-L), have been described in sporadic CRCs (9). In CRCs of hereditary nonpolyposis colon cancer with MSI-H phenotype, the MSI (MSI-L), have been described in sporadic CRCs (9). In CRCs, MSI is an early event in the carcinogenesis of UC and not to sporadic CRCs. These results indicated the presence of novel tumor suppressor genes on chromosome 6 related to the carcinogenesis of UC but not to sporadic CRCs.

RESULTS

Allelotype Study. The results of allelotype study using paired samples of CRCs or dysplastic lesions and corresponding noncancerous lesions from UC are summarized in Fig. 1. LOH was found at 16 of 35 loci and was distributed in 12 chromosomes. At the D6S468 locus on chromosome 6, 8 of 12 cases were informative, and 5 (62.5%) of 8 cases showed LOH. In contrast, the frequency of LOH was extremely low and was <25% on other chromosomes. LOH on chromosome 6 was detected in four of six CRCs. Four cases with LOH on chromosome 6 consisted of one case with well-differentiated adenocarcinoma and three with moderately or poorly differentiated adenocarcinomas. Interestingly, one case of dysplastic lesions also showed LOH. It means there is no significant relationship with pathological diagnosis of neoplasia. Besides there was no association with clinical courses such as duration of disease, location of tumor, or resistant properties for medication.

Deletion Mapping on Chromosome 6. We then performed LOH analysis on chromosome 6 using the same samples from UC according to the results of the allelotype study. An additional four microsatellite markers were selected around the D6S468 locus (see the deletion map of chromosome 6 in Fig. 2A). We determined the commonly deleted region between two loci, D6S1543 and D6S1580. The distance of these two loci is ~6 cM apart. Typical patterns of LOH analysis were also shown in Fig. 2B. LOH (arrowhead) was detected in the tumor at the loci of D6S1543, D6S468, and D6S283, but not at the loci of D6S1606 and D6S1580.

LOH Analysis at the D6S283 Locus in Sporadic CRCs. We then assessed whether the genetic alteration on chromosome 6 was specific to UC-associated CRCs or not. We investigated LOH analysis in paired samples of cancer and corresponding noncancerous lesions from 20 sporadic CRCs at the D6S283 locus. The reason we used this locus was that the D6S283 locus is the commonly deleted region and showed clear bands of alleles in UC-associated CRCs. In any cancerous lesions of the 20 sporadic CRCs, no LOH was detected at the D6S283 locus (Table 1). Even in three patients with moderately or poorly differentiated adenocarcinoma, no LOH was detected.

LOH Analysis at the D6S283 Locus in Longstanding and Extensive UC without CRC. To investigate whether the genetic alteration occurred in the chronic inflammation process, we carried out...
LOH analysis at the D6S283 locus in inflammatory lesions of 20 extensive and longstanding UCs in patients who belonged to the high-risk group of CRCs but had not developed CRCs. All 20 patients showed severe inflammatory lesions of UC in the study. Among the 20 cases, 8 of them were a chronic continuous type. Six patients had suffered from UC for less than 5 years, eight for 5–10 years and six for >10 years. In none of the patients, was there a genetic alteration at the D6S283 locus (Table 2). Even in three cases of the chronic continuous type that had continued for more than 10 years, no LOH was detected.

DISCUSSION

We performed allelotype study of human chromosome 1 to 22 and X for UC-associated CRCs or dysplastic lesions, and we defined the commonly deleted lesion between D6S1543 and D6S1580 on chromosome 6. To clarify the alteration specific for UC-associated cancers, we investigated LOH analysis for sporadic CRCs by D6S283. No LOH was detected in any sporadic CRCs. This result is consistent with a previous report (16). These findings, therefore, indicated that LOH on chromosome 6 is specific in the carcinogenesis of UC-associated CRCs but not with sporadic CRCs. In addition, we carried out LOH analysis by D6S283 in 20 severe inflammatory lesions of UC
Table 2. LOH study in 20 severely inflamed UCs without CRC

<table>
<thead>
<tr>
<th>Type</th>
<th>Duration (yr)</th>
<th>Frequency of LOH</th>
</tr>
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<tbody>
<tr>
<td>Totala</td>
<td>&lt;5</td>
<td>0/4</td>
</tr>
<tr>
<td></td>
<td>5–10</td>
<td>0/6</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>0/2</td>
</tr>
<tr>
<td>Left sideb</td>
<td>&lt;5</td>
<td>0/2</td>
</tr>
<tr>
<td></td>
<td>5–10</td>
<td>0/2</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>0/4</td>
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a Total, total colitis.
b Left side, left-sided colitis.

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REFERENCES


