**Loss of heterozygosity on long arm of chromosome 22 in sporadic colorectal carcinoma**

Chong-Zhi Zhou, Zhi-Hai Peng, Fang Zhang, Guo-Qiang Qiu, Lin He

**INTRODUCTION**

Colorectal cancer is one of the three leading causes of worldwide cancer mortality. The progression of the cancer is thought to result from an accumulation of genetic alteration at numerous loci controlling growth and proliferation. As a model for both multistep and multipathway carcinogenesis, colorectal neoplastic progression provides paradigms of both oncogenes and tumor suppressor genes \(^1,2\). The loss of heterozygosity (LOH) on tumor suppressor genes is believed to be one of the key steps to carcinogenesis of colorectal cancer \(^3,4\). The loss of one allele at a specific locus is caused by a deletion mutation or loss of a chromosome from a chromosome pair \(^5,6\). When this occurs at a tumor suppressor gene locus where one of the alleles is already abnormal, it can result in neoplastic transformation. In colorectal cancers, frequent allelic loss has been identified in chromosome 5q (30 %), 8p (40 %), 17p (75-80 %), 18q (80 %), and 22q (20-30 %) \(^5,6\). Indeed, much has been published on tumor suppressor genes APC, p53, and DCC, which have been localized to chromosome 5q, 17p, and 18q, respectively. The LOH analysis became an effective way to find informative loci and then to find candidate tumor suppressor genes \(^7,8\). In this study we analyzed the LOH at 5 loci on chromosome 22 in sporadic colorectal cancer to identify additional loci involved in colorectal tumorigenesis.

**MATERIALS AND METHODS**

**Materials**

This study was based on 83 consecutively collected tumors, including 40 males and 43 females, from unrelated patients with colorectal cancer, treated at the surgical department in Shanghai First people’s hospital, China, between 1998 and 1999. The patients’ ages ranged from 31 to 84 years with a median of 66. All patients were confirmed by pathology, and were staged by Dukes criterion. Dukes stage A, B, C, D were 8, 21, 40, 14 cases respectively. Well-differentiated adenocarcinoma was 23 cases, moderate differentiated adenocarcinoma was 39, poorly differentiated adenocarcinoma was 23 cases, mucinous adenocarcinoma was 15. HNPCC patients were ruled out by Amsterdam criteria \(^9,10\). Each patient gave his or her informed consent for the use of his or her tissue in this study.

**Methods**

**DNA Extraction**

The cancerous and adjacent normal tissues were fresh frozen within 30 min after removal. These tissues were then cut into cubes of approximately 2 mm\(^2\) and immediately frozen in liquid nitrogen. DNA was extracted using standard methods with protease K digestion and phenol/chloroform purification.

**Microsatellite Markers and PCR**

Five fluorescence-labeled primers for polymorphic microsatellite markers (PE Applied Biosystems Foster city CA, USA), at a density of approximately 20 pmol/μl. The PCR products were electrophoresed on an ABI 3700 (PE Applied Biosystems Foster city CA, USA), at a density of approximately 20 pmol/μl. The PCR products were electrophoresed on an ABI 3700's ABI PRISM 3700 Genetic Analyzer (PE Applied Biosystems Foster city CA, USA), at a density of approximately 20 pmol/μl. The PCR products were electrophoresed on an ABI 3700 Genetic Analyzer and were analyzed in 83 cases of colorectal and normal DNA by PCR. PCR products were eletrophoresed on an ABI 377 DNA sequencer; Genescan 3.1 and Genotype 2.1 software were used for LOH scanning and analysis. Comparison between LOH frequency and clinicopathological data were performed by χ\(^2\) test. P <0.05 was considered as statistically significant.

**RESULTS**

The average LOH frequency on chromosome 22q was 28.38 %. The region between markers D22S280 and D22S274 (22q12.2-q13.3) exhibited relatively high LOH frequency. The two highest LOH loci with frequencies of 35.09 % and 34.04 % was identified on D22S280 (22q12.2-12.3) and D22S274 (22q13.32-13.33). 8 cases showed LOH at all informative loci, suggesting that one chromosome 22q had been completely lost. On D22S274 locus, LOH frequency of rectal cancer was 50 % (9/18), which was higher than that of proximal colon cancer (12 %, 2/17) (P=0.018). The frequency of distal colon cancer was 42 % (5/12), also higher than that of proximal colon cancer. But there was no statistical significance. Putting both the tumors in distal colon and rectum together into consideration, the frequency, 47 % (14/30), was higher than that of proximal colon cancer (P=0.015), suggesting the mechanism of carcinogenesis was different in both groups.

**CONCLUSIONS**

This study provided evidence for the involvement of putative tumor suppressor genes related to the sporadic colorectal carcinoma on chromosome 22q. The tumor-suppressor-gene(s) might locate on the 22q12.2-12.3 and/or 22q13.32-13.33.

Zhou CZ, Peng ZH, Zhang F, Qiu GQ, He L. Loss of heterozygosity on long arm of chromosome 22 in sporadic colorectal carcinoma. World J Gastroenterol 2002;8(4):668-673

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one marker every 8 cM (Figure 1), was used to amplify matched pairs of normal and tumor DNAs for LOH analysis. Polymorphic microsatellite markers were analyzed in each patient’s tumor and normal DNAs by PCR (GeneAmp PCR System 9700, PE Applied Biosystems Foster city CA, USA). PCR conditions[11] were as follows: 5 ml total volume with approximately 1.4 ng of DNA as a template with 10× standard buffer, 0.3 µl Mg²⁺, 0.8 µl deoxynucleotide triphosphates, 0.3 unit of Hot-start taq polymerase and 0.06 ml of each oligonucleotide primer, with the forward primer fluorescence labeled with HEX, FAM or NED. Cycling conditions consisted of 3 stages: an initial denaturation at 96 degrees for 12 min in Stage I; 14 cycles each at 94 degrees for 20 sec, 63-56 degrees for 1 min (0.5 degrees decreased per cycle), 72 degrees for 1 min in Stage II; 35 cycles each at 94 degrees for 20 sec, 56 degrees for 1 min, 72 degrees for 1 min in stage III.

**LOH Analysis**

A portion of each PCR product (0.5 µl) was combined with 0.1 µl of Genescan 500 size standard (PE Applied Biosystems Foster city CA, USA) and 0.9 µl of formamide loading buffer. After denaturation at 96 degrees for 5 min, products were eletrophoresed on a 5 % polyacrylamide gels on an ABI 377 DNA sequencer (PE Applied Biosystems Foster city CA, USA) for 3 hours. Genotype 2.1 software displayed individual gel lanes as electropherograms with a given size, height, and area for each detected fluorescent peak. Stringent criteria were used to score the samples. Alleles were defined as the two highest peaks within the expected size range. A ratio of T1:T2/N1:N2 of less than 0.67 or greater than 1.50 was scored as a loss of heterozygosity (Figure 2). Most amplification of normal DNA produced two PCR products indicating heterozygosity. A single fragment amplified from normal DNA (homozygote) and those PCR reactions in which fragments were not clearly amplified were scored as not informative. The LOH frequency of a locus was equal to the ratio of the number between allelic loss and informative cases. The average LOH frequency of chromosome 22 long arm was the average value of each locus LOH frequency.

**Statistics analysis**

Comparison between LOH and clinicopathological data were performed by χ² test. P<0.05 was considered as statistically significant.

**RESULTS**

**LOH of 5 microsatellite markers on chromosome 22q**

The average LOH frequency at chromosome 22q was 28.38 %. The region between markers D22S280 and D22S274 (22q12.2-q13.33) exhibited relatively high LOH frequency, the two highest LOH loci with frequencies of 35.09 % and 34.04 % was identified on D22S280 (22q12.2-12.3) and D22S274 (22q13.32-13.33). Of these 83 cases, 8 cases had behaved LOH in all informative loci, suggesting that one chromosome 22q had been completely lost (Table 1-2).

**Table 1** LOH frequency of 5 microsatellite markers on the long arm of chromosome 22

| Locus      | Location     | LOH case | Normal case | LOH rate(%) | Informative rate(%) |
|------------|--------------|----------|-------------|-------------|---------------------|
| D22S315    | 22q12.1      | 12       | 56          | 17.65       | 81.93               |
| D22S280    | 22q12.2-12.3 | 20       | 37          | 35.09       | 68.67               |
| D22S283    | 22q12.3-13.1 | 17       | 43          | 28.33       | 72.29               |
| D22S423    | 22q13.2      | 15       | 41          | 26.79       | 67.47               |
| D22S274    | 22q13.3-13.3 | 16       | 31          | 34.04       | 56.63               |

**The relationship of clinicopathological features and LOH on chromosome 22**

On D22S274 locus, LOH frequency of rectal cancer was 50 % (9/18), which was higher than that of proximal colon cancer (12 %, 2/17) (P=0.018). The frequency of distal colon cancer
was 42 % (5/12), which was also higher than the frequency of proximal colon cancer. But there was no statistical significance. Putting both the tumors in distal colon and rectum together into consideration, the frequency, 47 % (14/30), was higher than that of proximal colon cancer (P=0.015). There was no association between LOH of each marker on chromosome 22q and other clinicopathological data (patient sex, age, tumor size, growth pattern or Dukes stage). It indicated that LOH of 22q was a

Table 2 Clinicopathological features of 8 cases of sporadic colorectal carcinoma who behaved LOH in all informative loci

| No | Gender  | Age | Location            | Gross Pattern | Size (cm) | Differentiation | Dukes stage |
|----|---------|-----|---------------------|---------------|-----------|-----------------|-------------|
| 125| Female  | 52  | Sigmoid Colon       | Ulcerative    | 5.5×4     | Moderately      | A           |
| 128| Male    | 70  | Descending Colon    | Ulcerative    | 4×4.5     | Moderately      | C           |
| 134| Female  | 70  | Ascending Colon     | Massive       | 5×5.5     | Moderately      | C           |
| 137| Female  | 76  | Sigmoid Colon       | Ulcerative    | 6×6       | Moderately      | C           |
| 138| Female  | 66  | Rectum Colon        | Ulcerative    | 3×3       | Well            | A           |
| 210| Female  | 41  | Ascending Colon     | Massive       | 5×4       | Well            | A           |
| 220| Female  | 79  | Ascending Colon     | Massive       | 7×4       | Well            | B           |
| 223| Male    | 63  | Rectum              | Encroaching   | 6×6.5     | Moderately      | D           |

Table 3 The relationship between clinicopathological features and LOH of 5 loci on chromosome 22

|                  | D22S315 | D22S280 | D22S283 | D22S423 | D22S274 |
|------------------|---------|---------|---------|---------|---------|
| Gender Male      | 28      | 6       | 19      | 7       | 22      | 5       | 13      | 8       |
| Gender Female    | 28      | 6       | 18      | 13      | 22      | 10      | 19      | 10      | 18      | 8       |
| Age ≥60          | 41      | 9       | 24      | 19      | 31      | 15      | 30      | 11      | 22      | 13      |
| Age ≤60          | 15      | 3       | 13      | 1       | 12      | 2       | 11      | 4       | 9       | 3       |
| Location Proximal Colon | 21      | 4       | 13      | 7       | 18      | 5       | 14      | 6       | 15      | 2       |
| Location Distal Colon | 13      | 4       | 12      | 4       | 11      | 5       | 12      | 6       | 7       | 9*      |
| Location Rectum  | 22      | 4       | 12      | 9       | 14      | 7       | 15      | 3       | 9       | 3*      |
| Gross Pattern Massive | 23      | 4       | 16      | 8       | 19      | 7       | 16      | 6       | 11      | 5       |
| Gross Pattern Ulcerative | 21      | 7       | 15      | 9       | 14      | 7       | 18      | 7       | 14      | 9       |
| Gross Pattern Encroaching | 12      | 1       | 6       | 3       | 10      | 3       | 7       | 2       | 6       | 2       |
| Gross Pattern Poorly | 3       | 3       | 4       | 2       | 3       | 1       | 1       | 2       | 3       | 3       |
| Gross Pattern Mucinous | 10      | 3       | 8       | 2       | 8       | 3       | 5       | 3       | 6       | 1       |
| Size ≥5(cm) | 25      | 7       | 14      | 11      | 20      | 8       | 18      | 10      | 17      | 5       |
| Size <5(cm) | 31      | 5       | 23      | 9       | 23      | 9       | 23      | 5       | 14      | 11      |
| LN Metastasis LN(+) | 36      | 9       | 26      | 13      | 31      | 11      | 26      | 11      | 24      | 7       |
| LN(-) | 20      | 3       | 11      | 7       | 12      | 6       | 15      | 4       | 7       | 9       |
| Differentiation Well | 15      | 3       | 8       | 6       | 13      | 3       | 11      | 5       | 7       | 5       |
| Moderately | 28      | 3       | 17      | 10      | 19      | 10      | 24      | 5       | 15      | 7       |
| Poorly | 3       | 3       | 4       | 2       | 3       | 1       | 1       | 2       | 3       | 3       |
| Mucinous | 10      | 3       | 8       | 2       | 8       | 3       | 5       | 3       | 6       | 1       |
| Dukes stage A | 3       | 3       | 1       | 3       | 3       | 2       | 3       | 2       | 2       | 4       |
| B | 17      | 1       | 10      | 4       | 9       | 4       | 12      | 2       | 5       | 5       |
| C | 26      | 4       | 18      | 11      | 22      | 9       | 19      | 7       | 16      | 5       |
| D | 10      | 4       | 8       | 2       | 9       | 2       | 7       | 4       | 8       | 2       |

*p=0.018, the LOH frequency of rectal cancer vs. that of proximal colon cancer
bP=0.015, the LOH frequency of cancer in distal colon and rectum vs. that of proximal colon cancer

DISCUSSION

During tumorigenesis, loss of the wild-type allele (inherited from the non-mutation-carrying parents) is frequently observed at the appropriate locus. To date, loss of heterozygosity (LOH) on tumor suppressor genes plays a key role in colorectal cancer transformation\[^3\]. And LOH analysis of sporadic colorectal cancer can promote the discovery of unknown tumor suppressor genes\[^13\]. In this study, LOH scanning was carried out in 83 sporadic colorectal cancer samples with 5 highly polymorphic markers and analyzed by Genotyper software, that is, by the ratio of the fluorescence intensity of allele, with an effort to identifying additional loci involved in colorectal tumorigenesis.

In this study, the average LOH frequency of chromosome 22q is 28.38 %, which is consistent with previous observations\[^5,6\]. D22S280 (22q12.2-12.3) and D22S274 (22q13.32-13.33) exhibited highest LOH frequency, indicating that colon cancer related tumor suppressor gene(s) located in this region and perhaps near D22S280 or/and D22S274. The previous study showed that 22q13.1-13.3 behaved high LOH frequency in
sporadic colorectal cancer. This study is consistent with the finding and also showed that 22q12.2-12.3 existed obvious LOH phenomenon, which was similar to the pancreatic adenocarcinomas.

By database referring, there are three candidate tumor-suppressor genes related to colon cancer, NF2 (22q12.2) [15], EP300 (22q13) [16], NBK/BIK (22q13.3) [17] on 22q12.2-13.33. NF2 gene was confirmed to be a tumor-suppressor-gene in neurofibromatosis type 2 syndrome [18-21]. And NF2 gene inactivation was also reported in NF2-associated tumor and some sporadic colorectal cancer [22-28]. NF2 gene encodes a 587-amino acid protein with striking similarity to several members of the ERM family of proteins proposed to link cytoskeletal components with proteins in the cell membrane, including moesin, ezrin, and radixin. Because of the resemblance to these 3 proteins, Trofatter et al. called the NF2 gene product Merlin [29]. Stokowski et al [30] found that 80% of the melanin mutants significantly altered cell adhesion by causing cells to detach from the substratum. They stated that such changes in cell adhesion might be an initial step in the pathogenesis of NF2. And some scholars also studied the relationship between NF2 gene and sporadic colorectal cancer and found that NF2 gene was probably involved in some colorectal tumors, but was not the critical chromosome 22q tumor suppressor gene involved in colon tumorigenesis [31,32]. The results of this study suggested that there might be colon cancer related candidate tumor-suppressor-gene(s) on 22q12.2 and NF2 was the only known tumor-suppressor-gene in this region. So it was needed to evaluate the effect of NF2 gene on colorectal carcinogenesis, and the new tumor suppressor gene involved in colorectal tumorigenesis can not be excluded. However, there were 2 putative tumor-suppressor genes on 22q13.2-13.31. EP300 and NBK/BIK [33]. P300 is the number of the retinoblastoma protein family. Stein et al [34] and suggested that p300 acted as a tumor suppressor firstly. Recently, Hasan et al [35] proposed the p300 might participate in chromatin remodeling at DNA lesion sites to facilitate proliferating cell nuclear antigen (PCNA) function in DNA repair synthesis. Muraoka et al [36] raised the possibility that inactivation of EP300 gene was involved in the genesis or progression of colorectal cancer. And Gayther et al [37] described EP300 mutations that predicted a truncated protein in 6 (3%) of 193 epithelial cancers analyzed and provided the first evidence that it behaved as a classic tumor suppressor gene. But EP300 mutation was rare in colorectal cancer tissue. So Castells et al [42] presumed that NBK/BIK gene, a proapoptotic BCL-2 family member [38-41], acted as a candidate gene in that region. However, SSCP sequencing analysis excluded mutations of this gene. The results of this study showed that the LOH frequency was also high on 22q13, especially on 22q13.32-13.33, suggesting that colorectal cancer associated candidate tumor-suppressor genes are likely to locate on chromosome 22q13.

Yama et al [11] indicated that loss of heterozygosity correlated with Dukes staging. Iino et al [42] suggested that allelic loss on 22q was significantly associated with the presence of lymph node metastasis. However, Castells et al [11] did not support their opinion. This result also agreed with Castells’ study and suggested that there was no association between LOH of each marker on chromosome 22q and Dukes staging. However, we found on D22S274 locus, LOH frequency of rectal cancer was higher than that of proximal colon cancer. And the frequency of the tumors in distal colon and rectum was also higher than that of the tumors in proximal colon cancer. Now it was admitted that the mechanism of carcinogenesis in distal colon was different from that in proximal colon [43-45]. And the mechanism in rectal cancer was also different from that in the common phenomenon in sporadic colorectal cancer (Table 3). Proximal colon [46]. Distal colon cancer displayed a higher frequency of 17p and 18q allelic loss, p53 accumulation [47], c-myc expression and aneuploidy [48]. Right-sided tumors are more often diploid [49] and of the microsatellite instability (MSI) phenotype. Rectal cancers showed significantly more expression of p53 than that in proximal colon cancer [46], which was similar with distal colon cancer. This study showed the D22S274 LOH was more frequent in distal colon and rectal cancer than in proximal colon ones, which proved the mechanism of carcinogenesis in distal colon and rectum was not completely same as that in the proximal colon.

Allelic loss on chromosome 22q is present not only in colorectal cancer but also in carcinomas of the ovary (55 %) [50,51], breast (40 %) [52-55], pancreatic endocrine (30 %) [56], oral cavity (40 %) [57], stomach, liver, lung, head and neck [60], and insulinoma. After microsatellite DNA analysis, several attempts were made to identify a region of deletion and eventually the tumor suppressor genes responsible for these neoplasms. Allelic deletions were restricted to D22S444 and D22S922 (22q13.2-q13.3). In the study, the locations of tumor suppressor genes that may contribute to the development of pancreatic cancer [7]. Considering these results, it is tempting to hypothesize that the same putative tumor suppressor genes might be involved in these different neoplastic processes. Further LOH scanning with high-density microsatellite markers in the region and the study of the relationship between these genes and the carcinogenesis of sporadic colorectal cancer may provide much more genetic information and find the potential tumor suppressor genes.

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Edited by Zhang JZ