PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2004;10(10):1431-1435
World Journal of Gastroenterology
 ISSN 1007-9327

• COLORECTAL CANCER •

Loss of heterozygosity on hromosome 1 in sporadic colorectal carcinoma

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

Chong-Zhi Zhou, Guo-Qiang Qiu, Fang Zhang, Zhi-Hai Peng, Department of General Surgery, Shanghai Jiaotong University, First People' s Hospital, Shanghai 200080, China
Lin He, Shanghai Institute for Biological Science, Chinese Academy of Sciences, Shanghai 200031, China
Supported by the National Natural Science Foundation of China, No. 30080016
Correspondence to: Dr. Zhi-Hai Peng, Department of General Surgery, Shanghai Jiaotong University, First People' s Hospital, 85 Wujin Road, Shanghai 200080, China. pengpzhb@online.sh.cn
Telephone: +86-21-63240090 Ext 3102
Received: 2003-06-10 **Accepted:** 2003-08-16

Abstract

AIM: Loss of heterozygosity (LOH) on tumor suppressor genes is believed to play a key role in carcinogenesis of colorectal cancer. When it occurs at a tumor suppressor gene locus with abnormal allele, neoplastic transformation happens. In this study, we analyzed the LOH at 21 loci on chromosome 1 in sporadic colorectal cancer to identify additional loci involved in colorectal tumorigenesis.

METHODS: Twenty-one polymorphic micro-satellite DNA markers were analyzed with PCR both in 83 cases of colorectal cancer and in normal tissues. 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. χ^2 test was used to compare LOH frequency with clinicopathological data. $P<0.05$ was considered as statistically significant.

RESULTS: The average LOH frequency of chromosome 1, short arm and long arm was 19.83%, 18.00% and 21.66%, respectively. The 2 highest LOH loci with a frequency of 36.54% and 32.50% were identified on D1S468 (1p36.33-p36.31) and D1S413 (1q31.3), respectively. On D1S2726 locus, LOH frequency of rectal cancer was 28.57% (6/21), which was higher than that of colon cancer (0.00%, 0/33) ($P=0.002$), suggesting that the mechanism of carcinogenisis was different in both groups.

CONCLUSION: Putative tumor suppressor genes on chromosome 1 may relate to sporadic colorectal carcinomas. Tumor-suppressor-genes might locate on 1p36.33-36.31 and/or 1q31.3.

Zhou CZ, Qiu GQ, Zhang F, He L, Peng ZH. Loss of heterozygosity on hromosome 1 in sporadic colorectal carcinoma. *World J Gastroenterol* 2004; 10(10): 1431-1435
http://www.wjgnet.com/1007-9327/10/1431.asp

INTRODUCTION

Colorectal cancer is one of the three leading causes of cancer mortality worldwide. The progression of the cancer is due to an accumulation of genetic alteration in controlling growth and proliferation at numerous loci. 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 as one of the key steps to carcinogenesis of colorectal cancer[3]. The loss of one allele at a specific locus is caused by a deletion mutation or loss of a chromosome from a chromosome pair[4]. When this occurs at a tumor suppressor gene with an abnormal allele, neoplastic transformation occurs. 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]. Tumor suppressor genes APC, p53, and DCC were found to be located on chromosome 5q, 17p, and 18q, respectively. LOH analysis became an effective way to find informative loci candidate tumor suppressor genes afterwards[7,8]. In this study we analyzed the LOH at 21 loci on chromosome 1 in sporadic colorectal cancers to identify additional loci involved in colorectal tumorigenesis.

MATERIALS AND METHODS

Materials

From 1998 to 1999, 83 consecutively collected tumors were treated surgically at Surgical Department of First People' s Hospital in Shanghai Jiaotong University. There were 40 males and 43 females with a median age of 66 years (range 31-84). The diagnosis was verified pathologically. The number of Dukes stages A, B, C, D was 8, 21, 40 and 14, respectively. The number of proximal colon cancer, distal colon cancer, and rectal cancer was 33, 21 and 29, respectively. Well-differentiated adenocarcinomas, moderately differentiated adenocarcinomas and poorly differentiated adenocarcinomas were 23, 39 and 6, respectively, and mucinous adenocarcinomas were 15. HNPCC patients were ruled out by Amsterdam criteria[9,10]. Informed consent to use surgical specimens in this study was obtained from patients.

Methods

DNA extraction Thirty min after surgery, fresh cancerous and adjacent normal tissues were cut into approximately 2 mm^3 and immediately frozen in liquid nitrogen. DNA was extracted using standard method with proteinase K digestion and phenol/chloroform purification.

Microsatellite markers and PCR Twenty-one fluorescence-labeled primers for polymorphic microsatellite markers (Perkin-Elmer, USA), at a density of approximately one marker every 10 cm (Figure 1), were used to amplify DNAs from normal and tumor tissues for LOH analysis. PCR for DNAs from normal and tumor tissue was done to analyze the polymorphic microsatellite markers. PCR conditions were as follows: 5 μL total volume with approximately 1.4 ng of DNA as a template with 10×standard buffer, 0.3 μL Mg^{2+}, 0.8 μL deoxynueleotide triphosphetes, 0.3 unit of Hot-start taq polymerase and 0.06 μL 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 ℃ for 12 min in stage I; 14 cycles each at 94 ℃ for 20 s, at 63-56 ℃ for 1 min (0.5 ℃ decreased per cycle), at 72 ℃ for 1 min in stage II: 35 cycles each at 94 ℃ for 20 s, at 56 ℃ for 1 min, at 72 ℃ for 1 min in stage III [11-13].

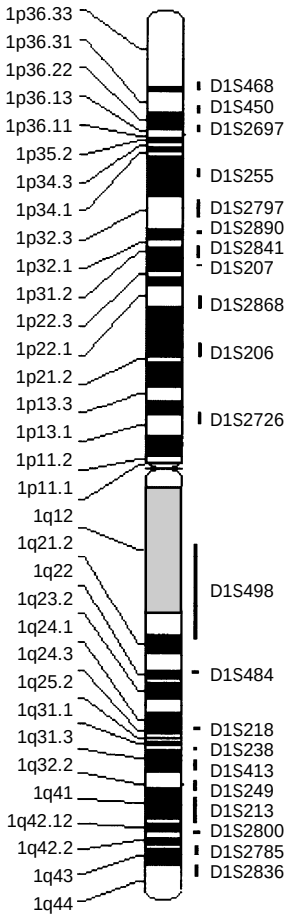

Figure 1 Twenty-one microsatellite markers on chromosome 1.

LOH analysis PCR product (0.5 μL) was mixed with 0.1 μL of Genescan 500 size standard (PE Applied Biosystems, USA) and 0.9 μL of formamide loading buffer. After denaturation at 96 ℃ for 5 min, products were eletrophoresed on 50 g/L polyacrylamide gels on an ABI 377 DNA sequencer (PE Applied Biosystems, USA) for 3 h. Genotype 2.1 software displayed individual gel lanes as electopherograms 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 less than 0.67 or greater than 1.50 was scored as a loss of heterozygosity (Figure 2). Most amplifications of normal DNA producing two PCR products indicated preserve of heterozygosity. A single fragment amplified from normal DNA (homozygote) and fragments not clearly amplified from PCR reactions 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 1 was the mean of the LOH frequency in all loci[14-17].

Statistics χ^2 test was used to compare LOH with clinicopathological data. $P<0.05$ was considered statistically significant.

RESULTS

LOH of 21 microsatellite markers on chromosome 1

The average LOH frequency at chromosome 1, short arm and long arm was 19.83%, 18.00% and 21.66%, respectively. The two highest LOH loci with a frequency of 36.54% and 32.50% were identified on D1S468 (1p36.33-36.31) and D1S413 (1q31.3). Other loci also exhibited higher LOH frequencies, including D1S255 (1p34.1-32.3), D1S2868(1p22.1), D1S218 (1q24.1-24.3), D1S249 (1q32.2), D1S2800 (1q42.12-42.2) and D1S2836 (1q43-44) (Table 1).

Relationship of clinicopathological features and LOH on chromosome 1

On D1S2726 locus, LOH frequency of rectal cancer was 28.57% (6/21), which was higher than that of colon cancer (0%, 0/33) (P=0.002). No association between LOH of each marker on chromosome 1 and other clinicopathological data (patient sex, age, tumor size, growth pattern or Dukes stage) was observed. It indicated that LOH on chromosome 1 was a common phenomenon in all kinds of sporadic colorectal cancers (Tables 2A, 2B).

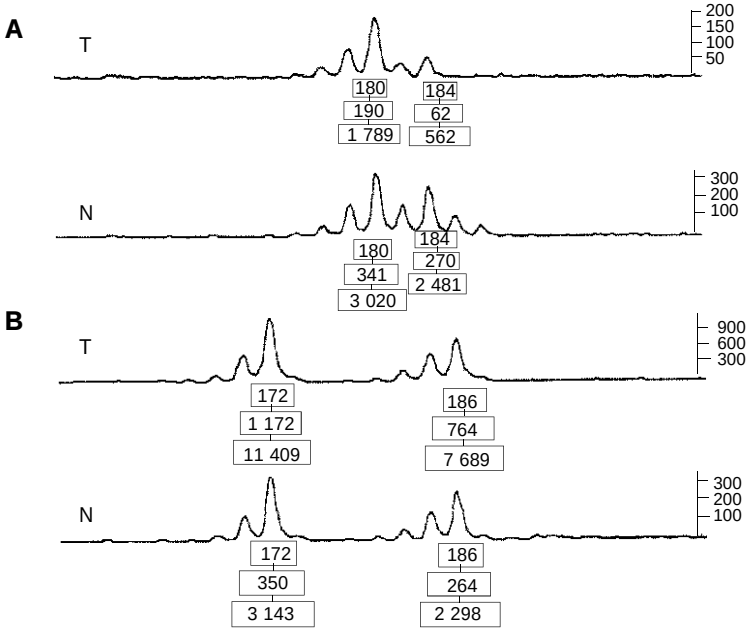

Figure 2 Typical peak and normal peak of LOH3. A: Typical peak of LOH: Allele ratio=(T1/T2)/(N1/N2)=(190/62)/(341/270) =2.43>1.5, B: The normal peak (no LOH): Allele ratio=(T1/T2)/(N1/N2)=(1172/764)/(350/264)=1.15, T: Tumor, N: Normal.

Table 1 LOH frequency of 21 microsatellite markers on chromosome 1

Locus	Location	LOH case	Normal case	LOH rate (%)	Informative rate (%)
D1S468	1p36.33-36.31	19	33	36.54	62.65
D1S450	1p36.31	7	41	14.58	57.83
D1S2697	1p36.22-36.13	5	25	16.67	36.14
D1S255	1p34.1-32.3	11	43	20.37	65.06
D1S2797	1p32.3	8	46	14.81	65.06
D1S2890	1p32.3-32.1	6	48	11.11	65.06
D1S2841	1p31.2	11	46	19.30	68.67
D1S207	1p31.2-22.3	5	63	7.35	81.93
D1S2868	1p22.1	10	39	20.41	59.04
D1S206	1p22.1-21.2	7	33	17.50	48.19
D1S2726	1p13.3-13.1	6	48	11.11	65.06
D1S498	1q12-21.2	11	48	18.64	71.08
D1S484	1q22	10	55	15.38	78.31
D1S218	1q24.1-24.3	16	42	27.59	69.88
D1S238	1q31.1	3	38	7.32	49.40
D1S413	1q31.3	13	27	32.50	48.19
D1S249	1q32.2	10	36	21.74	55.42
D1S213	1q41-42.12	8	41	16.33	59.04
D1S2800	1q42.12-42.2	12	45	21.05	68.67
D1S2785	1q43	10	48	17.24	69.88
D1S2836	1q43-44	12	36	25.00	57.83

Table 2a Relationship between clinicopathological features and LOH of 11 loci on short arm of chromosome 1

		D1S468		D1S450		D1S2697		D1S255		D1S2797		D1S2890		D1S2841		D1S207		D1S2868		D1S206		D1S2726	
		N	L	N	L	N	L	N	L	N	L	N	L	N	L	N	L	N	L	N	L	N	L
Gender	Male	18	8	20	4	13	2	19	7	20	5	21	4	20	6	31	2	15	3	17	3	19	5
	Female	15	11	21	3	12	3	24	4	26	3	27	2	26	5	32	3	24	7	16	4	29	1
Age (yr)	>60	26	13	30	7	19	4	32	8	36	7	37	6	34	11	46	5	32	7	27	5	33	6
	≤60	7	6	11	0	6	1	11	3	10	1	11	0	12	0	17	0	7	3	6	2	15	0
Location	Proximal colon	12	9	12	2	13	2	14	5	19	2	22	3	21	4	24	2	13	6	11	1	20	0
	Distal Colon	7	5	10	1	4	2	12	2	8	3	11	1	9	4	17	1	13	2	8	4	13	0
	Rectum	14	5	19	4	8	1	17	4	19	3	15	2	16	3	22	2	13	2	14	2	15	6[1]
Gross pattern	Massive	15	9	16	2	10	1	15	7	21	3	17	5	20	4	23	2	17	3	17	1	19	2
	Ulcerative	13	5	16	3	9	3	22	4	19	3	20	1	18	4	27	3	15	3	10	3	20	3
	Encroaching	5	5	9	2	6	1	6	0	6	2	11	0	8	3	13	0	7	4	6	3	9	1
Size	≥5 (cm)	18	8	21	5	13	1	19	8	24	4	27	2	23	4	31	1	19	5	13	5	24	3
	<5 (cm)	15	11	20	2	12	4	24	3	22	4	21	4	23	7	32	4	20	5	20	2	24	3
LN metastasis	LN (+)	24	10	26	5	17	4	29	4	28	6	31	5	26	9	38	5	22	8	20	5	28	4
	LN(-)	9	9	15	2	8	1	14	7	18	2	17	1	20	2	25	0	17	2	13	2	20	2
Differentiation	Well	8	7	14	1	5	1	10	3	20	1	15	0	12	4	16	2	13	2	14	3	18	0
	Moderately	16	10	19	5	12	4	21	5	14	7	19	5	22	5	31	3	16	5	13	2	18	6
	Poorly	3	0	4	1	2	0	5	0	4	0	5	0	2	0	6	0	3	1	0	2	5	0
	Mucinous	6	2	4	0	6	0	7	3	8	0	9	1	10	2	10	0	7	2	6	0	7	0
Dukes stage	A	3	3	4	0	1	0	4	1	3	2	4	0	7	0	7	0	5	0	2	1	5	0
	B	6	6	11	2	7	1	10	6	15	0	13	1	13	2	18	0	12	2	11	1	15	2
	C	17	8	20	3	11	2	21	3	20	5	23	5	18	7	26	5	16	7	18	3	20	4
	D	7	2	6	2	6	2	8	1	8	1	8	0	8	2	12	0	6	1	2	2	8	0

[1]*P*=0.002, LOH frequency of rectal cancer *vs* colon cancer.

Table 2b Relationship between clinicopathological features and LOH of 10 loci on long arm of chromosome 1

		D1S498		D1S484		D1S218		D1S238		D1S413		D1S249		D1S213		D1S2800		D1S2785		D1S2836	
		N	L	N	L	N	L	N	L	N	L	N	L	N	L	N	L	N	L	N	L
Gender	Male	25	6	25	7	22	6	20	1	14	7	16	6	17	3	19	9	25	3	19	5
	Female	23	5	30	3	20	10	18	2	13	6	20	4	24	5	26	3	23	7	17	7
Age (yr)	>60	37	10	43	6	30	14	28	3	18	10	28	7	33	6	33	10	39	10	26	9
	≤60	11	1	12	4	12	2	10	0	9	3	8	3	8	2	12	2	9	0	10	3
Location	Proximal colon	14	6	20	4	16	5	15	1	10	6	17	3	15	2	15	6	18	6	16	5
	Distal colon	14	3	14	4	14	4	10	1	7	3	4	2	12	3	14	1	14	2	6	5
	Rectum	20	2	21	2	12	7	13	1	10	4	15	5	14	3	16	5	16	2	14	2
Gross pattern	Massive	22	4	23	3	18	11	12	2	14	5	13	4	17	4	17	3	20	6	16	5
	Ulcerative	17	5	24	3	15	4	19	1	9	5	13	5	19	4	18	6	20	3	12	5
	Encroaching	9	2	8	4	9	1	7	0	4	3	10	1	5	0	10	3	8	1	8	2
Size	≥5 (cm)	21	7	27	7	22	6	18	3	11	6	16	5	21	4	21	8	23	7	17	8
	<5 (cm)	27	4	28	3	20	10	20	0	16	7	20	5	20	4	24	4	25	3	19	4
LN Metastasis	LN (+)	31	6	36	4	26	11	23	2	16	6	22	6	28	5	30	7	31	7	25	5
	LN(-)	17	5	19	6	16	5	15	1	11	7	14	4	13	3	15	5	17	3	11	7
Differentiation	Well	12	4	15	3	11	3	8	1	7	3	10	2	13	2	13	5	16	2	10	5
	Moderately	26	4	27	4	22	7	19	0	12	6	17	4	18	5	21	5	18	7	18	6
	Poorly	2	0	6	0	3	2	3	0	2	1	2	3	4	0	4	1	4	0	2	1
	Mucinous	8	3	7	3	6	4	8	2	6	3	7	1	6	1	7	1	10	1	6	0
Dukes stage	A	4	0	5	2	3	2	5	1	3	2	2	1	3	1	4	0	4	1	2	3
	B	13	5	14	4	13	3	10	0	8	5	12	3	10	2	11	5	13	2	9	4
	C	22	5	26	4	18	9	18	1	12	4	15	5	21	5	21	6	23	6	17	2
	D	9	1	10	0	8	2	5	1	4	2	7	1	7	0	9	1	8	1	8	3

DISCUSSION

During tumorigenesis, loss of wild-type alleles (inherited from the non-mutation-carrying parents) is frequently observed. Loss of heterozygosity (LOH) on tumor suppressor genes played a key role in colorectal cancer transformation, and LOH analysis of sporadic colorectal cancers could help discover unknown tumor suppressor genes[7,8]. In this study, LOH scanning was analyzed by Genotyper software in 83 sporadic colorectal cancer samples with 21 highly polymorphic markers, the ratio of the fluorescence intensity of alleles was studied to identify additional loci involved in colorectal tumorigenesis.

In this study, the average LOH frequency at chromosome 1 (19.83%), short arm (18.00%) and long arm (21.66%) was consistent with the previous study[5]. The two highest LOH loci with a frequency of 36.54% and 32.50% was identified on D1S468 (1p36.33-36.31) and D1S413 (1q31.3). There were few reports about the relationship between the long arm of chromosome 1 and colorectal cancer. But some previous studies showed that the 1q31-32 region frequently presented allelic loss in breast cancers and medulloblastomas. Pietsch *et al.*[18] found that 36% of medulloblastomas showed loss of heterozygosity (LOH) on chromosome 1q. The study of Benitez J showed more than 60% of breast tumors exhibited allelic loss in the 1q31-32 region[19]. These results suggested that putative tumor suppressor genes might locate on the 1q31-32 region. Our study also found that D1S413(1q31.3) exhibited a higher LOH frequency and that the LOH frequency of long arm of chromosome 1 was higher than that of short arm[5]. If D1S413 could be excluded, the LOH frequency of long arm was nearly equal to that of short arm. Thus, we hypothesized that the higher LOH frequency of D1S413 might be the reason why the LOH frequency of long arm of chromosome 1 was higher than that of short arm, suggesting the presence of a tumor suppressor gene in this region. This gene might be involved in the neoplastic process of colorectal cancer, breast cancer and medulloblastoma.

Previous studies showed that the 1p36 region frequently presented allelic loss in various cancers, such as colon cancer[20], neuroblastoma[21], hepatocellular carcinomas[22], lung cancer[23], and breast cancer[24]. But only NB gene was confirmed to be the tumor suppressor gene of neuroblastomas. In 1993, Tanaka *et al.* believed that a normal chromosome 1p36 might contain a tumor suppressor gene of colon carcinogenesis[25]. By database referring, we found TP73 gene (1p36) might be the known candidate tumor-suppressor genes related to colon cancer in this region. TP73, a novel family member of p53, was predicted to encode a protein with significant amino acid sequence similarity to p53[29]. TP73 could inhibit cell growth in a p53-like manner by inducing apoptosis[27]. Kaghad *et al.*[26] regarded TP73 as a tumor suppressor gene. But Sunahara found that allelic loss of p73 occurred only in 17% of colorectal carcinomas, and suggested that p73 might not play a role as a tumor suppressor in colorectal carcinoma at least not in a classic Knudson manner[28]. In our study, the highest LOH frequency was exhibited in 1p36.33-36.31, and colorectal cancer related tumor suppressor gene (s) might locate in the region. TP73gene is a member of p53 family, its effect on colorectal carcinogenisis is not certain and requires further study. Due to many genes located in the region of 1p36.33-36.31, further LOH scanning with high-density microsatellite markers in the region is necessary in order to find new candidate genes.

No association between LOH markers on chromosome 1 and the clinicopathological data was found, indicating that LOH was a common phenomenon in all sporadic colorectal cancers. However, we found that on D1S2726 locus, LOH frequency of rectal cancer was high, no LOH was found in colon cancer. In 2001, Kapiteijn *et al.*[29] proposed that rectal cancer had more significant expression of p53 and more nuclear beta-catenin than colon cancer, and considered that the mechanism of carcinogenisis in distal colon was different from that in proximal colon. Our results could show that the mechanism of carcinogenisis in distal colon and rectum was not completely the same as in proximal colon.

In conclusion, colorectal cancer associated candidate genes are likely to locate on D1S468 and D1S413. Further LOH scanning with high-density microsatellite markers in the region may provide much more genetic information and discover novel tumor suppressor genes.

REFERENCES

1 **Fearon ER**, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759-767

2 **Hardy RG**, Meltzer SJ, Jankowski JA. ABC of colorectal cancer: Molecular basis for risk factors. *BMJ* 2000; **321**: 886-889

3 **Kataoka M**, Okabayashi T, Johira H, Nakatani S, Nakashima A, Takeda A, Nishizaki M, Orita K, Tanaka N. Aberration of p53 and DCC in gastric and colorectal cancer. *Oncol Rep* 2000; **7**: 99-103

4 **Lengauer C**, Kinzler KW, Vogelstein B. Genetic instabilities in human cancers. *Nature* 1998; **396**: 643-649

5 **Vogelstein B**, Fearon ER, Kern SE, Hamilton SR, Preisinger AC, Nakamura Y, White R. Allelotype of colorectal carcinomas. *Science* 1989; **244**: 207-211

6 **Weber TK**, Conroy J, Keitz B, Rodriguez-Bigas M, Petrelli NJ, Stoler DL, Anderson GR, Shows TB, Nowak NJ. Genome-wide allelotyping indicates increased loss of heterozygosity on 9p and 14q in early age of onset colorectal cancer. *Cytogenet Cell Genet* 1999; **86**: 142-147

7 **Baker SJ**, Fearon ER, Nigro JM, Hamilton SR, Preisinger AC, Jessup JM, vanTuinen P, Ledbetter DH, Barker DF, Nakamura Y. Chromosome 17 deletions and p53 gene mutations in colorectal carcinomas. *Science* 1989; **244**: 217-221

8 **Kinzler KW**, Nilbert MC, Vogelstein B, Bryan TM, Levy DB, Smith KJ, Preisinger AC, Hamilton SR, Hedge P, Markham A. Identification of a gene located at chromosome 5q21 that is mutated in colorectal cancers. *Science* 1991; **251**: 1366-1370

9 **Vasen HF**, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum* 1991; **34**: 424-425

10 **Vasen HF,** Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 1999; **116**: 1453-1456

11 **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**: 668-673

12 **Peng Z**, Zhou C, Zhang F, Ling Y, Tang H, Bai S, Liu W, Qiu G, He L. Loss of heterozygosity of chromosome 20 in sporadic colorectal cancer. *Chin Med J* 2002; **115**: 1529-1532

13 **Zhang F**, Zhou C, Ling Y, Qiu G, Bai S, Liu W, He L, Peng Z. Allelic analysis on chromosome 5 in sporadic colorectal cancer patients. *Zhonghua Zhongliu Zazhi* 2002; **24**: 458-460

14 **Xu SF**, Peng ZH, Li DP, Qiu GQ, Zhang F. Refinement of heterozygosity loss on chromosome 5p15 in sporadic colorectal cancer. *World J Gastroenterol* 2003; **9**: 1713-1718

15 **Peng Z**, Zhang F, Zhou C, Qiu G, Bai S, Liu W, He L. Loss of heterozygosity analysis to define putative region involved in tumor differentiation and metastases in sporadic colorectal cancer patients. *Zhonghua Waike Zazhi* 2002; **40**: 776-779

16 **Peng Z**, Ling Y, Bai S. Loss of heterozygosity on chromosome 3 in sporadic colorectal carcinoma. *Zhonghua Yixue Zazhi* 2001; **81**: 336-339

17 **Zhang F**, Zhou C, Ling Y, Bai S, Liu W, Qiu G, He L, Peng Z. High frequency of LOHon chromosome 18 in Chinese sporadic colorectal cancer patients. *Zhonghua Shiyan Waike Zazhi* 2002; **19**: 320-321

18 **Pietsch T**, Koch A, Wiestler OD. Molecular genetic studies in medulloblastomas: evidence for tumor suppressor genes at the chromosomal regions 1q31-32 and 17p13. *Klin Padiatr* 1997; **209**: 150-155

19 **Benitez J**, Osorio A, Barroso A, Arranz E, Diaz-Guillen MA, Robledo M, Rodriguez de Cordoba S, Heine-Suner D. A region of allelic imbalance in 1q31-32 in primary breast cancer coincides with a recombination hot spot. *Cancer Res* 1997; **57**: 4217-4220

20 **Praml C**, Finke LH, Herfarth C, Schlag P, Schwab M, Amler L. Deletion mapping defines different regions in 1p34.2-pter that may harbor genetic information related to human colorectal cancer. *Oncogene* 1995; **11**: 1357-1362

21 **White PS**, Maris JM, Beltinger C, Sulman E, Marshall HN, Fujimori M, Kaufman BA, Biegel JA, Allen C, Hilliard C. A region of consistent deletion in neuroblastoma maps within human chromosome 1p36.2-36.3. *Proc Natl Acad Sci U S A* 1995; **92**: 5520-5524

22 **Yeh SH**, Chen PJ, Chen HL, Lai MY, Wang CC, Chen DS. Frequent genetic alterations at the distal region of chromosome 1p in human hepatocellular carcinomas. *Cancer Res* 1994; **54**: 4188-4192

23 **Nomoto S**, Haruki N, Tatematsu Y, Konishi H, Mitsudomi T, Takahashi T, Takahashi T. Frequent allelic imbalance suggests involvement of a tumor suppressor gene at 1p36 in the pathogenesis of human lung cancers. *Genes Chromosomes Cancer* 2000; **28**: 342-346

24 **Bieche I**, Khodja A, Lidereau R. Deletion mapping of chromosomal region 1p32-pter in primary breast cancer. *Genes Chromosomes Cancer* 1999; **24**: 255-263

25 **Tanaka K**, Yanoshita R, Konishi M, Oshimura M, Maeda Y, Mori T, Miyaki M. Suppression of tumourigenicity in human colon carcinoma cells by introduction of normal chromosome 1p36 region. *Oncogene* 1993; **8**: 2253-2258

26 **Kaghad M**, Bonnet H, Yang A, Creancier L, Biscan JC, Valent A, Minty A, Chalon P, Lelias JM, Dumont X, Ferrara P, McKeon F, Caput D. Monoallelically expressed gene related to p53 at 1p36, a region frequently deleted in neuroblastoma and other human cancers. *Cell* 1997; **90**: 809-819

27 **Jost CA**, Marin MC, Kaelin WG Jr. p73 is a human p53-related protein that can induce apoptosis. *Nature* 1997; **389**: 191-194

28 **Sunahara M**, Ichimiya S, Nimura Y, Takada N, Sakiyama S, Sato Y, Todo S, Adachi W, Amano J, Nakagawara A. Mutational analysis of the p73 gene localized at chromosome 1p36.3 in colorectal carcinomas. *Int J Oncol* 1998; **13**: 319-323

29 **Kapiteijn E**, Liefers GJ, Los LC, Kranenbarg EK, Hermans J, Tollenaar RA, Moriya Y, van de Velde CJ, van Krieken JH. Mechanisms of oncogenesis in colon versus rectal cancer. *J Pathol* 2001; **195**: 171-178

Edited by Ren SY and Wang XL **Proofread by** Xu FM