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RAPID COMMUNICATION

Refined mapping of loss of heterozygosity on 1q31.1-32.1 in sporadic colorectal carcinoma

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Abstract

AIM: To explore precise deleted regions and screen the candidate tumor suppressor genes related to sporadic colorectal carcinoma.

METHODS: Six markers on 1q31.1-32.1 were chosen. These polymorphic microsatellite markers in 83 colorectal cancer patients tumor and normal DNA were analyzed *via* PCR. PCR products were electrophoresed on an ABI 377 DNA sequencer. Genescan 3.1 and Genotype 2.1 software were used for Loss of heterozygosity (LOH) scanning and analysis. Comparison between LOH frequency and clinicopathological factors was performed by χ^2 test.

RESULTS: 1q31.1-32.1 exhibited higher LOH frequency in colorectal carcinoma. The average LOH frequency of 1q31.1-32.1 was 23.0%, with the highest frequency of 36.7% (18/49) at D1S2622, and the lowest of 16.4% (11/67) at D1S412, respectively. A minimal region of frequent deletion was located within a 2 cM genomic segment at D1S413-D1S2622 (1q31.3-32.1). There was no significant association between LOH of each marker on 1q31.1-32.1 and the clinicopathological data (patient sex, age, tumor size, growth pattern or Dukes stage), which indicated that on 1q31.1-32.1, LOH was a common phenomenon in all kinds of sporadic colorectal carcinoma.

CONCLUSION: Through our refined deletion mapping, the critical and precise deleted region was located within 2 cM chromosomal segment encompassing 2 loci (D1S413, D1S2622). No significant association was found between LOH and clinicopathologic features in 1q31.1-32.1.

Key words: Sporadic colorectal carcinoma; Loss of heterozygosity; Tumor suppressor genes; 1q31.1-32.1

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INTRODUCTION

The progression of the colorectal carcinoma is thought to result from an accumulation of genetic alteration at numerous loci controlling growth and proliferation[1-3]. 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), the loss of one paternal or maternal allele at specific locus, on tumor suppressor genes is believed to be one of the key steps to colorectal carcinogenesis[3,4]. When this occurs at a tumor suppressor gene locus where one of the alleles is already abnormal, it can result in neoplastic transformation[5]. According to the previous study, in colorectal carcinomas, frequent allelic loss was identified in chromosome 5q (30%)[3,6], 8p (40%)[3,7], 17p (75%-80%)[3,8], 18q (80%)[3,9], and 22q (20%-30%)[3,10,11]. Moreover tumor suppressor genes APC, p53, and DCC were found, which were located on chromosome 5q, 17p, and 18q, respectively[12-14]. The LOH analysis on sporadic carcinoma by means of microsatellite markers has become an effective way to find allelic deletion regions and then to find candidate

tumor suppressor genes[3,15,16]. In a previous study we used microsatellite markers to analyze the LOH at 21 loci on chromosome 1 in sporadic colorectal carcinoma. We found that D1S468 (1p36.33-36.31, 9.4 cM) and D1S413 (1q31.1-32.1, 9.8 cM) exhibited higher LOH frequencies, which indicated that the two regions might harbor putative tumor suppressor gene(s)[17,18]. However, the allelic deletion region found in our previous studies contained about 50 genes, which was inconvenient for further gene screening and functional studies. Therefore, further LOH scanning with high-density microsatellite markers in the two regions was necessary to narrow the research scope and select fewer candidate genes in the finite regions to functional research. In this study, other six markers from 1q31.1-32.1, at a density of approximately one marker every 1.67 cM, were chosen to analyze refined LOH mapping of the region.

MATERIALS AND METHODS

Subjects

This study was based on 83 cases of sporadic colorectal carcinoma, comprising 40 males and 43 females, treated at the surgical department in Shanghai Jiaotong University Affiliated First People's Hospital, China, between 1998 and 1999. Ages ranged from 31 to 84 years with a median of 66 years. All patients were confirmed by pathology and were staged by Dukes criterion. Their distribution according to their clinical stages was as follows: Dukes stage A, 8 cases; stage B, 21 cases; stage C, 40 cases; stage D, 14 cases. Their distribution, according to cancer location, was as follows: proximal colon cancer, thirty-three cases; distal colon, 21 cases; and rectal, 29 cases. The carcinomas were confirmed, *via* pathological examination, as being well differentiated adenocarcinoma in 23 patient cases, moderate differentiated adenocarcinoma in 39 cases, poorly differentiated adenocarcinoma in 6 cases, mucinous adenocarcinoma in 15 cases. HNPCC patients were ruled out by the Amsterdam criteria[19,20]. Each patient gave his or her informed consent for the use of his or her tissue in this study.

DNA extraction

The cancerous and adjacent normal tissues were frozen within 30 min after removal. The tissues were then cut into cubes of approximately 2 mm^3 and immediately frozen in liquid nitrogen. DNA was extracted by standard methods with proteinase K digestion and phenol/chloroform purification[21].

Microsatellite markers and PCR

By searching in Genothon, NCBI and GDB databases, 6 polymorphic microsatellite markers were chosen, at a density of approximately one marker every 1.67 cM, covering the chromosomal region 1q31.1-32.1 and spanned the D1S413 locus. Based on the databases described previously, the order of these markers was centromere-D1S2877-D1S412-D1S2757-D1S413-D1S2622-D1S2683-D1S2668-qter. The primer sequences are shown in Table 1. Polymorphic microsatellite markers were analyzed in each patients' tumor and normal DNAs by PCR

Table 1 The primer sequences of seven microsatellite markers

Primer	3'-5'	5'-3'
D1S2877	AGACATTNCATTGAAGTCTATTTAT	CAAGCCACTAGCGTAAGAGC
D1S412	TAGGACTTTTCAACTTCCACAG	ATAGGCACAGAATCAATGAATG
D1S2757	TTTTTTAATGACTGACCAGTG	TGCCTTCTGCTATGTTTG
D1S413	GCCAAGCCTGAGATCAAAAT	ACTTGAACAGATTGGGATTG
D1S2622	CTGCAACATAAGAACCTAGTGTAAC	AAACTGGTAGGCCATTGATAGA
D1S2683	TGCCTTGTCTTCAAGAGC	GCAGTGACAGGAATCTGG
D1S2668	AATCACTTGAACCTGGGAG	ACTGACTGGCTGTTTCTGAG

(GeneAmp PCR System 9700, PE Applied Biosystems Foster city CA, USA). PCR conditions were as follows: 5 μL total volume with 1 μL (1.4 ng) DNA as a template with 10 × standard buffer, 0.3 μL $MgCl_2$, 0.8 μL deoxynucleotide triphosphates, 0.3 unit of Hot-start Taq polymerase and 0.06 μL of each primer, with the forward primer fluorescence labeled with FAM (Shanghai Shenggong Biological Engineering & Technology and Service Co. Ltd, China), and fill ddH_2O up to 5 μL. 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, 63-56℃ for 1 min (0.5℃ decreased per cycle), 72℃ for 1 min, in Stage Ⅱ: 35 cycles each at 94℃ for 20 s, 56℃ for 1 min, 72℃ for 1 min in stage Ⅲ[17,18, 22-24].

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℃ for 5 min, products were electrophoresed on a 5% polyacrylamide gels on an ABI 377 DNA sequencer (PE Applied Biosystems Foster city CA, USA) for 3 h. Genotype 2.1 software displayed individual gel lanes as electrophoretograms 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 LOH (Figure 1). Most amplification of normal DNA produced two PCR products indicating heterozygosity. A single fragment amplified from normal DNA (homozygote) and 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 was the average value of each locus LOH frequency[17,18, 22-24].

Statistical analysis

Comparison between LOH and clinicopathological data was performed by χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

LOH analysis on 1q31.1-32.1

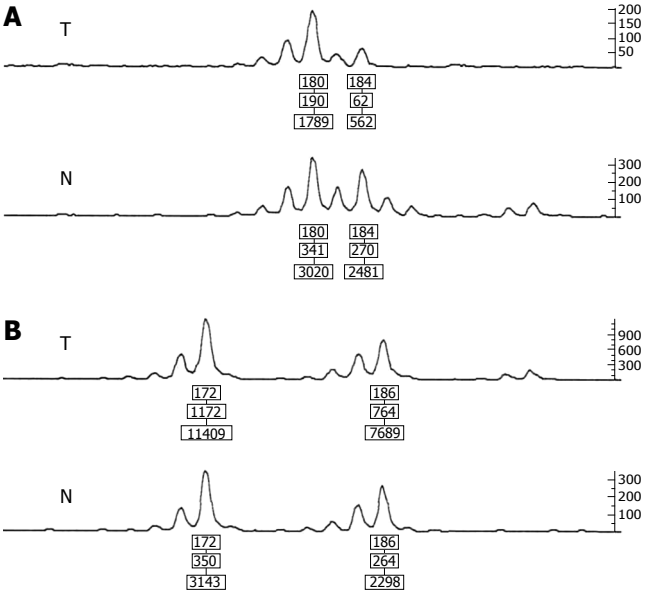

Figure 1 The LOH and normal peak. **A**: The typical peak of LOH: Allele ratio = (T1/T2)/(N1/N2) = (190/62)/(341/270) = 2.43 > 1.5; **B**: The peak of normal (no LOH): Allele ratio = (T1/T2)/(N1/N2) = (1172/764)/(350/264) = 1.15; T: Tumor; N: Normal.

The average LOH frequency of 1q31.1-32.1 was 23.0%, with the highest frequency of 36.7% (18/49) at D1S2622, and the lowest of 16.4% (11/67) at D1S412, respectively. According to this study, a minimal region of frequent deletion was located within a 2 cM genomic segment at D1S413-D1S2622 on 1q31.3-32.1 (Table 2).

Relationship between clinicopathological features and LOH frequency

There was no significant association between LOH of each marker on 1q31.1-32.1 and the clinicopathological data (patient sex, age, tumor size, growth pattern or Dukes stage). It indicated that on 1q31.1-32.1, LOH was a common phenomenon in all kinds of sporadic colorectal carcinoma (Table 3).

DISCUSSION

During tumorigenesis, loss of the wild-type allele is frequently observed at the appropriate locus. It has been admitted that LOH on tumor suppressor genes plays a key role in colorectal carcinoma transformation. LOH is common to all human solid tumors and allows expressivity of recessive loss of function mutations of tumor suppressor genes. Therefore, detection of recurrent LOH in a chromosome region is now considered critical evidence of localization of tumor suppressor genes[3,25-28]. In the previous study, initial LOH scanning was carried out in 83 sporadic colorectal carcinoma samples with 21 highly polymorphic markers on chromosome 1. We found that D1S468 (1p36.33-36.31) and D1S413 (1q31.1-32.1) exhibited higher LOH frequencies[17,18]. However, the average genetic distance of the loci in our previous study was 9.6 cM, which contained so many genes that was inconvenient for further gene screening. Further LOH scanning with high-density microsatellite markers in the two regions was necessary to narrow the research scope and select fewer candidate genes in the finite regions to functional research. In another study of ours, we carried out the refined LOH mapping on 1p36.33-36.31 and found two critical and precise deleted regions, D1S243 (1 cM) and D1S468-D1S2660 (3 cM)[29]. In this study, six high-density polymorphic microsatellite markers were chosen for refined LOH mapping of LOH on 1q31.1-32.1 in order to get much more genetic information and to screen the potential tumor suppressor genes.

Table 2 LOH frequencies of microsatellite loci on 1q31.1-32.1 in colorectal cancer

Locus	Location	LOH case	Normal case	LOH rate (%)	Informative rate (%)
D1S2877	1q31.1	7	29	19.44	43.37
D1S412	1q31.3	11	56	16.42	80.72
D1S2757	1q31.3	18	43	29.51	73.49
D1S413	1q31.3	13	27	32.50	48.19
D1S2622	1q32.1	18	31	36.73	59.04
D1S2683	1q32.1	10	41	19.61	61.45
D1S2668	1q32.1	4	20	16.67	28.92

The results showed that the average LOH frequency of 1q31.1-32.1 was 23.0%, with the highest frequency of 36.7% (18/49) at D1S2622, and the lowest of 16.4% (11/67) at D1S412, respectively. According to this study, a minimal region of frequent deletion was located within a 2 cM genomic segment at D1S413-D1S2622 on 1q31.3-32.1. There are few reports in past years about the relationship between the long arm of chromosome 1 and colorectal carcinoma. Moreover, some previous studies showed that 1q frequently presents allelic loss in other tumors, such as breast cancer, medulloblastoma, thyroid cancer, sporadic insulinoma and esophageal carcinoma. Benitez's[30] study showed more than 60% of the breast tumors exhibited allelic loss in the 1q31-32 region. Pietsch *et al*[31] found that 36% of the medulloblastomas showed LOH on 1q31-32.1. Moreover accordingly to the study of Kitamura[32], frequent allelic loss was identified on 1q31-42 (40%) in anaplastic thyroid carcinomas. Yang *et al*[33] found that thirty-five out of forty (88%) insulinomas had 1q LOH of the 35 insulinomas with 1q LOH, 14 (40%) had 1q21.3-23.2 LOH over a 7.5 cM region, whereas in 21 tumors (60%) LOH occurred at 1q31.3 over an 11.4 cM area. Li *et al*[34] analyzed LOH in 61 esophageal squamous cell carcinomas using 18 microsatellite markers on chromosome 1q. Forty-six of 61 tumors (75.4%) presented LOH at one or more loci. These results suggested that putative tumor suppressor genes might locate on the 1q. Our study firstly demonstrated that 1q31-32 exhibited higher LOH frequency in colorectal carcinoma, which suggesting the presence of a tumor suppressor gene in this region. This gene might be involved in the tumorigenesis of colorectal carcinoma and other tumors. Based on our study, allelic deletion was located within 2 cM chromosomal segment encompassing 2 loci (D1S413, D1S2622). Searching the databases, no known tumor suppressor genes have been found in this region. However, we presumed CSRP1 might

Table 3 The relationship between clinicopathological features and LOH of the loci on 1q31.1-32.1

		D1S2877		D1S412		D1S2757		D1S413		D1S2622		D1S2683		D1S2668	
		T[1]	N[2]	T	N	T	N	T	N	T	N	T	N	T	N
Gender	Male	4	13	3	27	10	18	7	14	11	15	5	20	2	5
	Female	3	16	8	29	8	25	6	13	7	16	5	21	2	15
Age(yr)	> 60	5	24	9	39	13	32	10	18	16	22	10	29	2	16
	⩽ 60	2	5	2	17	5	11	3	9	2	9	0	12	2	4
Location	Proximal colon	2	10	6	22	5	18	6	10	9	13	6	13	0	9
	Distal colon	2	8	4	15	5	11	3	7	5	8	0	14	1	7
	Rectum	3	11	1	19	8	14	4	10	4	10	4	14	3	4
Gross pattern	Massive	2	15	5	25	7	22	5	14	6	16	3	22	1	9
	Ulcerative	4	13	5	23	9	18	5	9	9	14	6	17	1	7
	Encroaching	1	1	1	8	2	3	3	4	3	1	1	2	2	4
Size (cm)	⩾ 5	4	12	7	22	6	18	6	11	8	15	5	17	2	9
	< 5	3	17	4	34	12	25	7	16	10	16	5	24	2	11
LN metastasis	(+)	4	20	6	39	12	29	6	16	15	20	5	26	1	16
	(-)	3	9	5	17	6	14	7	11	3	11	5	15	3	4
Differentiation	Well	3	4	1	14	5	7	3	7	4	5	1	10	3	5
	Moderately	2	21	8	26	8	27	6	12	10	18	5	25	0	12
	Poorly	1	1	2	2	2	2	1	2	1	2	2	1	0	1
	Mucinous	1	3	0	14	3	7	3	6	3	6	2	5	1	2
Dukes stage	A	2	5	2	3	3	3	2	3	1	3	2	5	0	1
	B	1	4	3	14	3	11	5	8	2	8	3	10	3	3
	C	3	16	4	29	11	19	4	12	10	17	3	19	0	13
	D	1	4	2	10	1	10	2	4	5	3	2	7	1	3

T: Tumor; N: Normal.

be the candidate colorectal carcinoma related gene in this region. At the mRNA level, the highest concentrations of CSRP1 were found in the prostate and the colon followed by the brain and the testis[35]. CSRP1 was a member of the CSRP family of genes encoding a group of LIM domain proteins, which might be involved in regulatory processes important for development and cellular differentiation[36]. We supposed that the inactivation of this genes could lead to the abnormality of cell differentiation and then result in neoplastic transformation. Recently, Hirasawa *et al*[37] found that CSRP1 were inactivated in HCC by aberrant methylation and they may serve as important biomarkers of malignancy, indicating that CSRP1 was a the tumor related gene. Further functional research will provide additional proof. In order to find the colorectal carcinoma related gene in 1q31.1-32.1, we are performing a microarray-based high-throughput gene screening approach in this region to identify unknown candidate related genes, and this may provide much more genetic information and find the potential tumor suppressor gene(s). In our study, there was no significant association between LOH of all loci on 1q31.1-32.1 and the clinicopathological data, indicating that in this region, LOH was a common phenomenon in all kinds of sporadic colorectal cancer.

In summary, through our detailed deletion mapping studies, the critical and precise deleted region was located within 2 cM chromosomal segment encompassing 2 loci (D1S413, D1S2622). No significant association was found between LOH and clinicopathologic features. The region identified in the present study might harbor one or more tumor suppressor genes, which might be involved in several types of human cancer. Our study provided the significant data to reveal the mechanism of colorectal carcinogenesis. And further microarray-based high-throughput gene screening and functional research may provide much more genetic information and find the potential tumor suppressor genes.

COMMENTS

Background

The loss of heterozygosity (LOH) analysis on sporadic carcinoma by means of microsatellite markers has become an effective way to find allelic deletion regions and then to find candidate tumor suppressor genes. In a previous study Zhou *et al* found that D1S413 (1q31.1-32.1, 9.8 cM) exhibited higher LOH frequencies and this indicated that this region might harbor the putative tumor-suppressor-gene(s). However, the allelic deletion region the previous studies found contained so many genes that it was inconvenience to further gene screening and functional study. Therefore, in this study, another six markers with high-density microsatellite markers in 1q31.1-32.1 were chosen to analyze refined LOH mapping to narrow the research scope and select fewer candidate genes in the finite regions to functional research.

Research frontiers

LOH on tumor suppressor genes is believed to be one of the key steps to colorectal carcinogenesis. According to the previous study, in colorectal carcinomas, frequent allelic loss was identified in chromosome 5q (30%), 8p (40%), 17p (75%-80%), 18q (80%), and 22q (20%-30%). Subsequently, tumor suppressor genes APC, p53, and DCC were found, which were located on chromosome 5q, 17p, and 18q, respectively. The LOH analysis on sporadic carcinoma by means of microsatellite markers has become an effective way to find allelic deletion regions and then to find candidate tumor suppressor genes.

Innovations and breakthroughs

This study found that the precise deleted region was located within 2 cM chromosomal segment encompassing 2 loci (D1S413, D1S2622), in which might harbor one or more tumor suppressor genes related to the colorectal carcinogenesis.

Terminology

LOH: The loss of one allele at a specific locus, caused by a deletion mutation; or loss of a chromosome from a chromosome pair, resulting in abnormal hemizygosity. It is detected when heterozygous markers for a locus appear monomorphic because one of the alleles was deleted. When this occurs at a tumor suppressor gene locus where one of the alleles is already abnormal, it can result in neoplastic transformation.

Peer review

It is possible that 1q will be an informative site in colorectal carcinogenesis. But, it may also simply reflect the chromosomal instability (CIN) pathway of genomic instability that was selected for in the selection of predominantly distal, non-mucinous cancers. CIN causes wide spread aneuploidy, and thus LOH in the 1q31.1-32.1 region may be an epiphenomenon, rather than a sentinel event in carcinogenesis. Nevertheless, this study provides some important information about this region. It would be interesting to know whether they have looked at gene expression of CSRP1 in any of their samples, or in any CRC cell lines, to support their assertion that this is a likely candidate in this region.

REFERENCES

1 **Kinzler KW**, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell* 1996; **87**: 159-170
2 **Fearon ER**, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759-767
3 **Vogelstein B**, Fearon ER, Kern SE, Hamilton SR, Preisinger AC, Nakamura Y, White R. Allelotype of colorectal carcinomas. *Science* 1989; **244**: 207-211
4 **Fearon ER**. Molecular genetics of colorectal cancer. *Ann N Y Acad Sci* 1995; **768**: 101-110
5 **Lasko D**, Cavenee W, Nordenskjold M. Loss of constitutional heterozygosity in human cancer. *Annu Rev Genet* 1991; **25**: 281-314
6 **Solomon E**, Voss R, Hall V, Bodmer WF, Jass JR, Jeffreys AJ, Lucibello FC, Patel I, Rider SH. Chromosome 5 allele loss in human colorectal carcinomas. *Nature* 1987; **328**: 616-619
7 **van der Bosch K**, Becker I, Savelyeva L, Bruderlein S, Schlag P, Schwab M. Deletions in the short arm of chromosome 8 are present in up to 90% of human colorectal cancer cell lines. *Genes Chromosomes Cancer* 1992; **5**: 91-95
8 **Monpezat JP**, Delattre O, Bernard A, Grunwald D, Remvikos Y, Muleris M, Salmon RJ, Frelat G, Dutrillaux B, Thomas G. Loss of alleles on chromosome 18 and on the short arm of chromosome 17 in polyploid colorectal carcinomas. *Int J Cancer* 1988; **41**: 404-408
9 **Lanza G**, Matteuzzi M, Gafa R, Orvieto E, Maestri I, Santini A, del Senno L. Chromosome 18q allelic loss and prognosis in stage II and III colon cancer. *Int J Cancer* 1998; **79**: 390-395
10 **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
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 **Stella A**, Resta N, Gentile M, Susca F, Mareni C, Montera MP, Guanti G. Exclusion of the APC gene as the cause of a variant form of familial adenomatous polyposis (FAP). *Am J Hum Genet* 1993; **53**: 1031-1037
13 **Isobe M**, Emanuel BS, Givol D, Oren M, Croce CM. Localization of gene for human p53 tumour antigen to band 17p13. *Nature* 1986; **320**: 84-85
14 **Cho KR**, Oliner JD, Simons JW, Hedrick L, Fearon ER, Preisinger AC, Hedge P, Silverman GA, Vogelstein B. The DCC gene: structural analysis and mutations in colorectal carcinomas. *Genomics* 1994; **19**: 525-531
15 **Sieben NL**, ter Haar NT, Cornelisse CJ, Fleuren GJ, Cleton-Jansen AM. PCR artifacts in LOH and MSI analysis of microdissected tumor cells. *Hum Pathol* 2000; **31**: 1414-1419
16 **Fromont G**, Vallancien G, Validire P, Levillain P, Cussenot O. BCAR1 expression in prostate cancer: association with 16q23 LOH status, tumor progression and EGFR/KAI1 staining. *Prostate* 2007; **67**: 268-273
17 **Peng Z**, Zhang F, Zhou C, Ling Y, Bai S, Liu W, Qiu G, He L, Wang L, Wei D, Lin E, Xie K. Genome-wide search for loss of heterozygosity in Chinese patients with sporadic colorectal cancer. *Int J Gastrointest Cancer* 2003; **34**: 39-48
18 **Zhou CZ**, Qiu GQ, Zhang F, He L, Peng ZH. Loss of heterozygosity on chromosome 1 in sporadic colorectal carcinoma. *World J Gastroenterol* 2004; **10**: 1431-1435
19 **Vasen HF**, Griffioen G, Offerhaus GJ, Den Hartog Jager FC, Van Leeuwen-Cornelisse IS, Meera Khan P, Lamers CB, Van Slooten EA. The value of screening and central registration of families with familial adenomatous polyposis. A study of 82 families in The Netherlands. *Dis Colon Rectum* 1990; **33**: 227-230
20 **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
21 **Blin N**, Stafford DW. A general method for isolation of high molecular weight DNA from eukaryotes. *Nucleic Acids Res* 1976; **3**: 2303-2308
22 **Zheng HT**, Peng ZH, Zhou CZ, Li DP, Wang ZW, Qiu GQ, He L. Detailed deletion mapping of loss of heterozygosity on 22q13 in sporadic colorectal cancer. *World J Gastroenterol* 2005; **11**: 1668-1672
23 **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
24 **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* (Engl) 2002; **115**: 1529-1532
25 **Kyndi M**, Alsner J, Hansen LL, Sorensen FB, Overgaard J. LOH rather than genotypes of TP53 codon 72 is associated with disease-free survival in primary breast cancer. *Acta Oncol* 2006; **45**: 602-609
26 **Huang Z**, Wen Y, Shandilya R, Marks JR, Berchuck A, Murphy SK. High throughput detection of M6P/IGF2R intronic hypermethylation and LOH in ovarian cancer. *Nucleic Acids Res* 2006; **34**: 555-563
27 **Sanchez de Abajo A**, de la Hoya M, van Puijenbroek M, Godino J, Diaz-Rubio E, Morreau H, Caldes T. Dual role of LOH at MMR loci in hereditary non-polyposis colorectal cancer? *Oncogene* 2006; **25**: 2124-2130
28 **Woenckhaus M**, Grepmeier U, Wild PJ, Merk J, Pfeifer M, Woenckhaus U, Stoelcker B, Blaszyk H, Hofstaedter F, Dietmaier W, Hartmann A. Multitarget FISH and LOH analyses at chromosome 3p in non-small cell lung cancer and adjacent bronchial epithelium. *Am J Clin Pathol* 2005; **123**: 752-761
29 **Zhou CZ**, Zheng HT, Qiu GQ, Zhang F, He L, Peng ZH. Refined mapping of loss of heterozygosity of 1p36.33-36.31 in sporadic colorectal carcinoma. *Zhonghua Yixue Zazhi* 2006; **86**: 1804-1807
30 **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
31 **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
32 **Kitamura Y**, Shimizu K, Tanaka S, Ito K, Emi M. Allelotyping of anaplastic thyroid carcinoma: frequent allelic losses on 1q, 9p, 11, 17, 19p, and 22q. *Genes Chromosomes Cancer* 2000; **27**: 244-251
33 **Yang YM**, Liu TH, Chen YJ, Jiang WJ, Qian JM, Lu X, Gao J, Wu SF, Sang XT, Chen J. Chromosome 1q loss of heterozygosity frequently occurs in sporadic insulinomas and is associated with tumor malignancy. *Int J Cancer* 2005; **117**:

234-240
34 **Li J**, Liu Z, Wang Y, Yu Z, Wang M, Zhan Q, Liu Z. Allelic imbalance of chromosome 1q in esophageal squamous cell carcinomas from China: a novel region of allelic loss and significant association with differentiation. *Cancer Lett* 2005; **220**: 221-230
35 **Dube JY**, Chapdelaine P, Trahan PL, Deperthes D, Frenette G, Tremblay RR. Abundant cysteine-rich protein-1 is localized in the stromal compartment of the human prostate. *Arch Androl* 1998; **40**: 109-115
36 **Wang X**, Ray K, Szpirer J, Levan G, Liebhaber SA, Cooke NE. Analysis of the human cysteine-rich protein gene (CSRP), assignment to chromosome 1q24-1q32, and identification of an associated MspI polymorphism. *Genomics* 1992; **14**: 391-397
37 **Hirasawa Y**, Arai M, Imazeki F, Tada M, Mikata R, Fukai K, Miyazaki M, Ochiai T, Saisho H, Yokosuka O. Methylation status of genes upregulated by demethylating agent 5-aza-2'-deoxycytidine in hepatocellular carcinoma. *Oncology* 2006; **71**: 77-85

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