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Full Length Research Paper

Refined mapping of loss of heterozygosity in Chinese sporadic gastric carcinoma

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The aim of this study is to explore precise deleted regions where the candidate tumor suppressor genes might be located in Chinese sporadic gastric carcinoma. By searching in Genothon, NCBI and GDB databases, 145 polymorphic microsatellite markers were chosen, at a mean density of approximately one marker every 2 - 4 cM, covering 15 chromosomes. These polymorphic microsatellite markers in gastric carcinoma and adjacent tissue were analyzed via PCR. PCR products were submitted to electrophoresis on an ABI 3730 DNA sequencer. Genemapper3.2 software was used for LOH (Loss of Heterozygosity) scanning and analysis. Comparison between LOH frequency and clinicopathological factors was performed by Fisher's exact test. 26 refined regions were mapped as candidate regions for TSGs (Tumor suppression genes) in Chinese sporadic gastric cancer. Associations between LOH and clinical information indicated that 6 loci was associated with pTNM stage, 5 with Lauren's type, 4 with lymph nodes metastasis and another 2 with distant metastasis. Through refined deletion mapping, 26 candidate regions, where TSGs may be located, were found and 17 loci were proposed to be used as clinical markers in Chinese sporadic gastric cancer.

Key words: Gastric carcinoma, refined mapping, loss of heterozygosity (LOH), tumor suppressor genes (TSGs), tumor markers.

INTRODUCTION

Gastric carcinoma is one of the leading causes of cancer death worldwide (Jemal et al., 2005). Gastric carcinoma develops through the accumulation of multiple genetic lesions that involve oncogenes, tumor suppressor genes and DNA mismatch repair genes (Fiocca et al., 2001). According to Knudson's hypothesis (Knudson, 1971), TSGs might lose its function when all the alleles are changed. LOH (loss of heterozygosity), the loss of one paternal or maternal allele at specific locus on tumor suppressor genes, is believed to be one of the key stepsto gastric carcinogenesis (Monpezat et al., 1988; Nishizuka et al., 1998). The LOH analysis on sporadic carcinoma by means of microsatellite markers has become an effective way to find allelic deletion regions (Semba et al., 1996), while genome-wide scan and refined mapping were seldom done in Chinese sporadic gastric carcinoma. So we explored the precise deleted regions where the candidate tumor suppressor genes might be located in 48 cases of Chinese gastric carcinoma using 145 polymorphic microsatellite markers, and found some candidate loci which were proposed to be used as clinical markers.

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Abbreviations: TSGs, Tumor suppression genes; **PCR,** polymerase chain reaction; **NCBI,** national centre for biotechnology information; **LOH,** loss of heterozygosity; **GDB,** genome database.

MATERIALS AND METHODS

Subjects

This study was based on 48 cases of Chinese sporadic gastric carcinoma, comprising 33 males and 15 females, treated at the Surgical Department of Shanghai Jiao Tong University Affiliated First People's Hospital, China, between 1998 and 1999. Ages ranged from 34 to 84 years with a median of 66 years. All patients were confirmed by pathological examination and were staged by pTNM criterion. The distribution according to their clinical stages was as follows: pTNM stage I, 6 cases; stage II, 13 cases; stage III, 15 cases; stage IV, 14 cases. There were 18 cases of intestinal type and 30 cases of diffuse type according to Lauren's type. None of them underwent preoperative chemotherapy and/or radiation therapy. All tissues were obtained with patients' consent, and the work involving human specimens was approved by the Institutional Review Board of Shanghai First People's Hospital.

DNA extraction

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

Microsatellite markers and PCR

By searching in Genothon, NCBI and GDB databases, 145 polymorphic microsatellite markers were chosen, at a mean density of approximately one marker every 2 - 4 cM, covering 15 chromosomas. 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 were as follows: 5 µL total volume with 1 µL (1.5 ng) DNA as a template, 0.5 µL 10 × standard buffer, 0.3 µL MgCl2, 0.8 µL deoxynucleotide triphosphates (dNTP), 0.3 unit of Hot-start Taq polymerase and 0.06 µL of each primer (100 nmol), with the forward primer fluorescence labeled with FAM (Shanghai Sheng Gong Biological Engineering and Technology and Service Co. Ltd, China), and filling ddH_2O up to 5 µL. Cycling conditions consisted of 4 stages: an initial denaturation at 96℃ for 10 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; 72℃ for 7 min, 4℃ for 10 min in stage IV.

LOH detection

A portion of each PCR product (0.5 µL) was combined with 0.1 µL of Genescan ROX400D size standard (PE Applied Biosystems, Foster city, CA, USA) and 6.90 µL of Hi-Di buffer. After denaturation at 96℃ for 5 min, products were submitted to electrophoresis on an ABI 3730 DNA sequencer (PE Applied Biosystems, Foster city, CA, USA) for 3 h. Genomapper3.2 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 LOH (Zhou et al., 2008; Grundei et al., 2000). 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 non-informative (Figure 1). The LOH frequency of a locus was equal to the ratio of the number between allelic loss and informative cases.

Statistical analysis

Comparison between LOH and clinicopathological data was performed by Fisher exact test. $P < 0.05$ was considered statistically significant.

RESULTS

Candidate regions on chromosomes

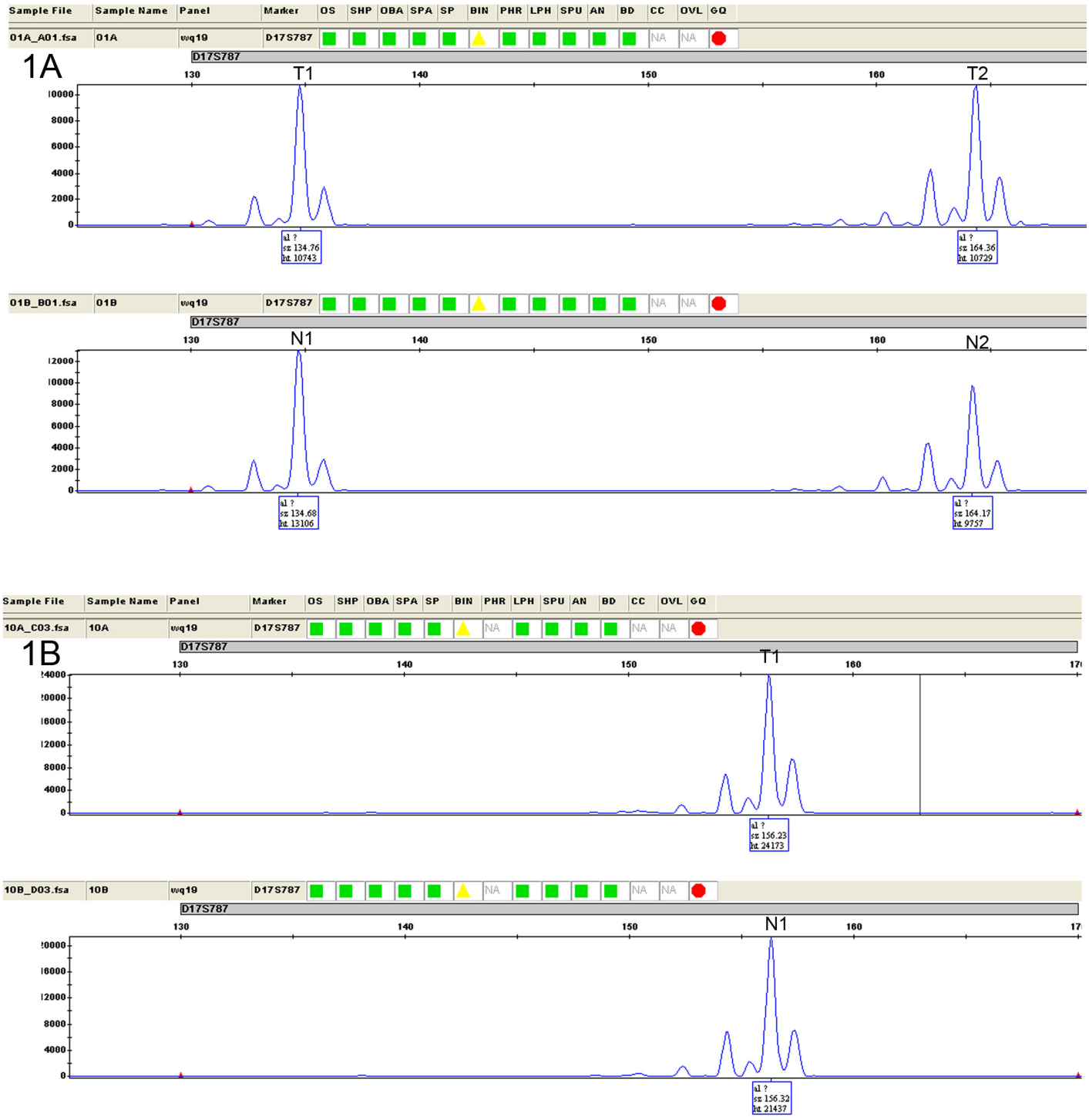
In this experiment, we analyzed the loss of heterozygosity (LOH) of chromosome 1,2,3,6,9,10,11,12,14, 15,16,17,18,20,22 by using 145 polymorphic microsatellite markers in 48 matched gastric normal and cancer tissues and defined the deletional mapping of the regions with putative tumor suppressor genes. Data of 105 (72.4%) polymorphic microsatellite markers were judged to be valid. High frequency of deletions were detected at the locations of microsatellite markers D1S196 (40%), D1S2785 (30%), D2S112 (34%), D2S117 (44%), D6S276 (36%), D9S175 (37%), D11S1338 (38%), D11S901 (33%), D12S368 (33%), D12S86 (43%), D14S283 (31%), D15S1007 (31%), D15S978 (30%), D17S831 (39%), D17S1857 (32%), D17S787 (31%), D18S59 (31%) and D20S173(35%) (Table 1). We also found 12 candidate regions such as D18S1140-D18S59, D14S985-D14S272, D12S1633-D12S368 with precise range of 0-2cM, 6 candidate regions such as D6S1597-D6S1660, D11S901-D11S4147, D15S1003-D15S998 with precise range of 2 - 4 cM and 8 candidate regions such as D17S1857 - D17S805, D9S237 - D9S1122, and D18S489-D18S70 with precise range more than 4 cM (Table 2).

Candidate markers for GC

We have characterized the 105 microsatellite markers in 48 patients with clinicopathological features and identified 17 microsatellite markers associated with GC clinicopathological features. D1S498 (19%), D2S311 (15%), D16S3102 (43%), D17S805 (45%), D17S956 (20%) and D18S1129 (17%) were associated with pTNM stage (Table 3). D9S1122 (32%), D9S175 (37%), D17S831 (39%), D17S921 (22%) and D22S1141 (39%) were involved in histological classification (Table 4). D3S3681 (19%), D9S1122 (32%), D11S4181 (22%), D14S990 (18%) were associated with lymphatic invasion (Table 5). D18S1129 (17%) and D20S171 (70%) were associated with distant invasion (Table 6).

DISCUSSION

During tumorigenesis, loss of the wild-type allele is the



Semba et al., 1998). Chromosomal aberrations in examples which have been mapped onto chromo-some 1p36.17 and 17q21.8, respectively (Bae et al., 1995; gastric cancer have been extensively studied and losses of many chromosomal loci have been discovered, including losses in 1p, 2p, 3p, 5q, 6q, 7q, 8q, 12q, 13p, 14q,17p, 17q and 18q (Sano et al., 1991; de Manzoni et al., 2001; Chae et al., 2002; Varis et al., 2002; Kaneda et al., 2004). While genome-wide scan and refined mapping were seldom done in Chinese gastric carcinoma, it was necessary to have such a test which might best figure out candidate regions for TSGs. In this study, 26 regions were mapped out as candidate region of TSGs in Chinese GC, and association

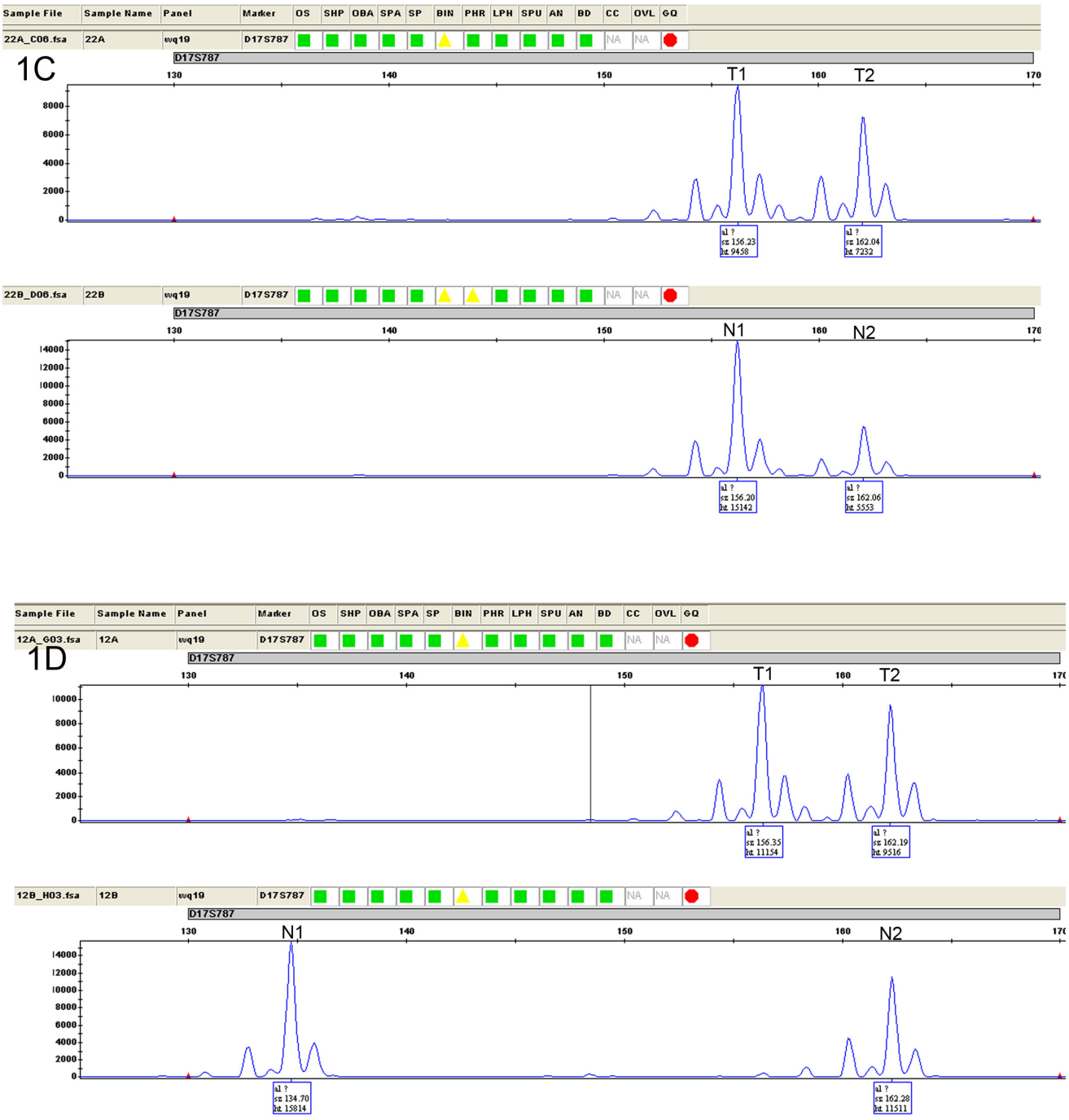


Figure 1. Examples of microsatellites figures determined by Genemapper 3.2 program. (A) Informative cases without LOH: Allele ratio = (T1 / T2) / (N1 / N2) =0.75 < 1.5 (> 0.67). (B) Non-informative cases: homozygote. (C), informative cases with LOH: Allele ratio = (T1 / T2) / (N1 / N2) = 0.47 < 0.67. (D) Non-informative cases: microsatellites instable (MSI). The numbers in the boxes (2 lines) in each panel were products length of a given PCR primer (upper line), and peak height (lower line), respectively. Values of peak heights were used for calculation to determine the presence of LOH.

between LOH and clinical information indicated that 6 loci were associated with pTNM stage, 5 with Lauren's type, 4 with lymph node metastasis and another 2 with distant invasion. Through comparing our data to articles published in NCBI, we found that high LOH frequency of 1q21, 1p36, 11q14, 12q13, 12q24, 14q32, 15q14, 16p13, 17p11, 17q21, 17q22, 18q21-22 and 22q13 areas were reported in GC (Koon et al., 2004; Vauhkonen et al., 2006;

Table 1. Primers and LOH data of key microsatellite loci in GC patients.

Microsatellite locus	Microsatellite position (NCBI)	Primer for loci	Rate of LOH
D1S196	1q22-23	**F:GGCTGTGGGTGTTTCTCCTA* *R:AGCTCTCATGACTTTACATTCT*	0.40
D1S2785	1q43	**F:CGTGAATATCCTCAGGGAAT* *R:ATTGTGGCACCGTACTCC*	0.30
D2S112	2q21	**F:GAGTGGCGGTGAGAAGGTAT* *R:AGCCATTGCTATCTTTGAGG*	0.34
D2S117	2q32-33	**F:GAGATCAGGTATATTCAATCCAC* *R:CAGAAAATGACAAACTTTAGAGAG*	0.44
D6S276	6p21.3	**F:TCAATCAAATCATCCCCAGAAG* *R:GGGTGCAACTTGTTCCTCCT*	0.36
D9S175	9q21.13	**F:GTAATGTGCTAAATACCAGAGTTG* *R:CCCTTACCTAGAATGCCC*	0.37
D11S1338	11p15.5	**F:TCAGAAATCTGATGGAAAAGTC* *R:TGCTACTTATTTGGAGTGTGAA*	0.38
D11S901	11q13-14	**F:TCAGAGGCACAAAAAATATTGGAAG* *R:CTGGGTGTTGAAGAAGTCAAAATG*	0.33
D12S368	12q13-14	**F:GCAACACCTTTGTGATGAAAAT* *R:AGTCTGCACAGCCTGTCC*	0.33
D12S86	12q24	**F:AGCTAGTCTGGCATGAGCAG* *R:CTATCCCCTGATGATCTCCC*	0.43
D14S283	14q11-12	**F:GGGACTATATCTCCCAGGC* *R:TGTTTTCCTAGTAACCGCA*	0.31
D15S1007	15q14	**F:GGGGAACCTACACTTCCG* *R:CCAGGATCTCAAATGGCTT*	0.31
D15S978	15q21	**F:AGCTTCATACACTGAAATTGTTG* *R:CACCGGGAAACCTTGAT*	0.30
D17S831	17p13	**F:CGCCTTTCCTCATACTCCAG* *R:GCCAGACGGGACTTGAATTA*	0.39
D17S1857	17p11-12	**F:TGCACAGGCCAATTCCTTAC* *R:TGCCTAAACTGCTTTCAGGTGAG*	0.32
D17S787	17q22	**F:TGGGCTCAACTATATGAACC* *R:TTGATACCTTTTTGAAGGGG*	0.31
D18S59	18p11.32	**F:GGGGCACAAGACAGATAGAT* *R:CCTACCAGAATGTGAACGAC*	0.31
D20S173	20q13	**F:ATCCAACCTGCCACTTA* *R:CCAAAGACTCGTGACTCAT*	0.35

*Marked with FAM dye.

Katoh, 2002; Wang et al., 2009; Takahata et al., 2009; Tokumaru et al., 2003; Wang et al., 2003; Katoh and Katoh 2003; Stephen et al., 2003; Dai et al., 2005; Nowacka-Zawisza et al., 2008; Yu et al., 2008; Jiao et al., 2006; Kang et al., 2006), 1q43, 2q21, 2q32, 6p22, 11p14, 14q11, 17q25, 18p11, and 18q22 - 23 were reported in other disease but not in GC (Dimova et al., 2009; Kobayashi et al., 2008; Prazeres et al., 2008; Friedrich et al., 2008; Chanudet et al., 2009; Xu et al., 2008; Papaemmanuil et al., 2009; Ariza et al., 2004), while LOH status of 9q21, 15q21, 18q12, and 20q13 was not reported before. Most areas in this research were confirmed in previous study by others, which somehow demonstrated the accuracy of our research. To find the candidate TSGs, more attention should be paid to the areas reported in other cancer. We pinpointed that 9q21, 15q21, 18q12, and 20q13 were associated with Chinese gastric cancer, and might find new tumor suppressor genes key to gastric carcinogenesis in these regions. Furthermore, the association between the LOH frequency of some loci and clinic pathologic data including pTNM stage, metastasis indicated that these loci might be used as clinical markers Further study should be explored to be sure of the possibility.

Table 2. Refined regions for tumor suppressor genes.

Locus and arrange	Genethon map (cM)	Microsatellite Position (NCBI)
D1S1458 - D1S1312	6*	1p36
D1S2343 - D1S1600	1*	1q21.3
D1S1594 - D1S2785	1*	1q43
D2S112 - D2S442	4*	2q21
D2S2387 - D2S2289	3.7	2q32.3-33.2
D6S1597 - D6S1660	2.2	6p22.3
D9S237 - D9S1122	5.2*	9q21.13-21.2
D11S4163 - D11S1324	3.4	11p14.1-14.3
D11S901 - D11S4147	2.7	11q14.1
D12S1633 - D12S368	0.5	12q13.13
D12S1720 - D12S86	1.2	12q24.23
D14S742 - D14S283	0.5*	14q11.2
D14S985 - D14S272	0.2 *	14q32.2－32.32
D15S1040 - D15S971	1.2	15q14
D15S1003 - D15S998	3.1	15q21.3
D16S446 - D16S3102	5	16p13.13
D17S1857 - D17S805	4.3	17p11.2
D17S930 - D17S1877	8.4	17q21.31-21.33
D17S956－D17S787	1.2	17q21.33-22
D17S836－D17S784	0.6	17q25.3
D18S1140－D18S59	0.1	18p11.32
D18S475－D18S1157	1.1	18q12.2-12.3
D18S479－D18S1129	10	18q21.1-21.32
D18S489－D18S70	5.3*	18q22.3 - 23
D20S164－D20S173	1.9	20q13.32-13.33
D22S1171 - D22S1169	12	22q13.31-13.32

* Not shown in Genethon map

Table 3. LOH status associated with PTNM stage.

Microsatellite locus	PTNM stage								P	Microsatellite position (NCBI)
	Ⅰ		Ⅱ		Ⅲ		Ⅳ			
	L*	N*	L	N	L	N	L	N		
D1S498	1	2	4	6	0	8	0	9	0.024	1q21.3
D2S311	0	3	0	7	0	7	4	5	0.030	2q33.1
D16S3102	3	0	1	7	6	4	3	5	0.042	16p13.13
D17S805	3	2	4	4	8	3	0	9	0.010	17p11.2
D17S956	1	2	4	3	1	10	0	8	0.030	17q21.33
D18S1129	0	3	0	8	1	10	4	4	0.029	18q21.32

*L: Number of cases with LOH. *N: Number of cases without LOH.

Conclusion

In summary, through this study, the critical and precise deleted regions in Chinese gastric cancer where TSGs might be located were shown. It was a precise genome-wide scan for LOH and our study provided the significant data to reveal the mechanism of gastric carcinogenesis and further microarray-based high-throughput gene screening

Table 4. LOH status associated with histological classification.

Microsatellite locus	Lauren's type				P	Microsatellite position (NCBI)
	Intestinal type		Diffuse type			
	L*	N*	L	N		
D9S1122	6	4	4	17	0.040	9q21.2
D9S175	1	9	9	8	0.042	9q21.13
D17S831	8	4	6	18	0.029	17p13.3
D17S921	0	12	7	13	0.029	17p12
D22S1141	1	8	8	6	0.040	22q13.31

*L: Number of cases with LOH.
*N: Number of cases without LOH.

Table 5. LOH status associated with lymphatic invasion.

Microsatellite locus	Lymphatic invasion				P	Microsatellite position (NCBI)
	Positive		Negative			
	L*	N*	L	N		
D3S3681	1	20	5	6	0.011	3p12
D9S1122	5	19	5	2	0.022	9q21.2
D11S4181	3	21	4	4	0.047	11p14
D14S990	2	26	5	6	0.012	14q11.2

*L: Number of cases with LOH.
*N: Number of cases without LOH.

Table 6. LOH status associated with distant invasion.

Microsatellite locus	Distant invasion				*P*	Microsatellite position (NCBI)
	Positive		Negative			
	L*	N*	L	N		
D18S1129	3	2	2	23	0.022	18q21.32
D20S171	4	6	24	6	0.041	20q13.32

*L: Number of cases with LOH.

in the finite regions and functional research might provide much more genetic information and find the potential tumor suppressor genes and biomarkers in gastric cancer.

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