Association between genetic polymorphisms in cortactin and susceptibility to gastric cancer

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INTRODUCTION

Gastric cancer is the most prevalent cancer in Korea and it ranks as one of the leading causes of cancer death, followed by lung cancer [1,2]. Helicobacter pylori infection, diet, bile reflux, excessive cell proliferation, and DNA damage are known to be risk factors for gastric adenocarcinoma [3,4]. Numerous other factors, such as histological features and clinical stage, have also been shown to play important roles in tumor development [5,6].

Cortactin (CTTN) regulates the actin cytoskeleton through its involvement in several processes, including cell motility, adhesion, polarization, contraction, and others [7-9]. The amplification of chromosome 11q13 has been reported in several human carcinomas along with increased expression of CTTN [9]. Overexpression of CTTN induces cell motility and migration, inhibits cell-cell adhesion, and accelerates tumor

Purpose: Overexpression of cortactin (CTTN) in human tumors has been proposed to result in increased cell migration and metastatic potential. Here, we determined the frequencies of CTTN g.-9101C>T, g.-8748C>T, and g.72C>T polymorphisms in apparently healthy subjects and gastric cancer patients, respectively, and the influence of the CTTN polymorphisms on gastric cancer susceptibility.

Methods: Blood samples were collected from 267 patients and 533 controls. CTTN g.-8748C>T and g.-9101C>T polymorphisms were determined using polymerase chain reaction-restriction fragment length polymorphism; the g.72C>T polymorphism was determined using the TaqMan method.

Results: Genotype frequencies of the CTTN g.-9101C>T polymorphism were 97.5% [TT], 2.5% [TC], and 0% [CC] in the patient group, and 98.6% [TT], 1.4% [TC], and 0% [CC] in the control group. Genotype frequencies of the CTTN g.-8748C>T polymorphism were 93.3% [TT], 6.8% [TC], and 0% [CC] in the patient group, and 94.2% [TT], 5.8% [TC], and 0% [CC] in the control group. Genotype frequencies of the CTTN g.72C>T polymorphism were 82.4% [CC], 17.2% [CT], and 0.4% [TT] in the patient group, and 78.0% [CC], 20.1% [CT], and 1.9% [TT] in the control group. Genotype and allele frequencies of the CTTN g.-9101C>T polymorphism differed significantly between the advanced gastric cancer and control groups. Patients with advanced gastric cancer, possessing the TC genotype, had a significantly poorer prognosis than the group with the TT genotype.

Conclusion: The CTTN g.-9101C>T polymorphism might influence advanced gastric cancer susceptibility. However, the role of the CTTN g.-9101C>T, g.-8748C>T, and g.72C>T polymorphisms requires careful interpretation and confirmation through larger studies.

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Key Words: Human CTTN protein, Genetic polymorphism, Stomach neoplasms
spreading [10]. CTTN is overexpressed in many types of human cancers, including esophageal squamous cell carcinoma, head and neck squamous cell carcinomas (HNSCC), colorectal, gastric, hepatocellular, breast, and ovarian cancers [11-14].

In some studies, overexpression of CTTN correlated with histological differentiation, T and N stage in gastric cancer, depth of invasion in colorectal cancer, as well as poor prognosis for patients with lymph node metastasis [15,16]. However, direct evidence is still lacking to establish a relationship between CTTN overexpression and tumor progression and metastasis in gastric adenocarcinoma. The relationship between CTTN polymorphisms and susceptibility to gastric cancer is also unclear. Therefore, this study was aimed at investigating the association between the CTTN g.-9101C>T, g.-8748C>T, and g.72C>T polymorphisms and susceptibility to gastric cancer to identify specific polymorphisms as potential risk factors.

METHODS

Peripheral blood samples were collected from 267 consecutive patients who were diagnosed with gastric cancer at Wonkwang University Hospital between June 2001 and August 2007. We collected blood samples from 533 healthy volunteers, which served as controls. Retrospectively, three single nucleotide polymorphisms (SNPs), CTTN g.-9101C>T, g.-8748C>T, and g.72C>T polymorphisms, and clinicopathologic data in the corresponding patients and controls, were analyzed to investigate the association of CTTN genetic polymorphisms with susceptibility to gastric cancer.

The stages of gastric cancer were sorted using the American Joint Committee on Cancer manual, seventh edition. Patients were divided by tumor depth into an early gastric cancer (EGC) group and an advanced gastric cancer (AGC) group, respectively. Patients were also divided based on the presence or absence of lymph node metastasis, into an LN (+) group and an LN (–) group, respectively. Clinicopathologic characteristics of gastric cancer patients are listed in Table 1.

Analysis of CTTN polymorphisms

Genomic DNA extracted from the peripheral blood of members of each group was analyzed using the polymerase chain reaction-restriction fragment length polymorphism method for the CTTN g.-9101C>T, g.-8748C>T, and g.72C>T polymorphisms, and using the TaqMan method for the g.72C>T polymorphism. In gastric cancer patients, CTTN SNPs were analyzed using their peripheral blood collected before surgery.

The DNA samples used in the current study were provided by the Biobank of Wonkwang University Hospital, a member of the National Biobank of Korea: this Biobank is supported by the Ministry of Health and Welfare. The current study was approved by the Institutional Review Board of Wonkwang University Hospital (WKUH-1157). and written informed consent was obtained from all participants.

Polymerase chain reaction-restriction fragment length polymorphism

Each of the CTTN sequences containing the -9101C>T or -8748C>T polymorphic sites was partially amplified using the corresponding primer set (CTTN-PF1: 5’-TCCAGGTGAG TACCATGTTG-3’ and CTTN-PR1: 5’-TCGCGGCCAGGCGACGCC ACA-3’). An initial polymerase chain reaction (PCR) denaturation step was performed at 95°C for 5 minutes, followed by 30 cycles of denaturation at 98°C for 10 seconds, then annealing at the melting temperature of each primer pair for 15 seconds, and then extension at 72°C for 30 seconds, with a final 10-minute extension step at 72°C. The PCR products of the sequences containing -9101C>T and -8748C>T were digested with 2U of Eco52I for 12 hours at 37°C, and with 1U of NarI for 12 hours.

Table 1. Clinicopathologic characteristics of 267 patients with gastric adenocarcinoma

| Variable                   | Value   |
|----------------------------|---------|
| Age (yr)                   | 60.2 ± 10.8 |
| Gender                     |         |
| Male                       | 177 (66.3) |
| Female                     | 90 (33.7)  |
| Histological type          |         |
| Well-differentiated        | 70 (26.2) |
| Moderately differentiated   | 75 (28.1) |
| Poorly differentiated      | 63 (23.6) |
| Poorly cohesive carcinoma  | 42 (15.7) |
| Mixed type                 | 17 (6.4)  |
| Others                     | 0 (0)    |
| Pathologic T stage<sup>a</sup> |        |
| T1                         | 157 (58.8) |
| T2                         | 60 (22.5)  |
| T3                         | 43 (16.1)  |
| T4                         | 7 (2.6)   |
| Pathologic N stage<sup>a</sup> |       |
| N0                         | 131 (49.1) |
| N1                         | 45 (16.9)  |
| N2                         | 54 (20.2)  |
| N3                         | 37 (13.8)  |
| Tumor stage<sup>a</sup>    |         |
| I                          | 165 (61.8) |
| II                         | 31 (11.6)  |
| III                        | 63 (23.6)  |
| IV                         | 8 (3.0)   |
| Lymphovascular invasion    |         |
| Absent                     | 204 (76.4) |
| Present                    | 63 (23.6)  |

Values are presented as mean ± standard deviation or number (%).<sup>a</sup>TNM classification as per guidelines in American Joint Committee on Cancer 7th edition.
at 37°C, respectively, and then separated on a 1.5% agarose gel and visualized under UV light with ethidium bromide. After restriction enzyme digestion, the PCR products of the sequences containing -9101C>T (630bp) and -8748C>T (630bp) took the form of two fragments, of 490 bp and 140 bp in length, respectively.

**Taq-Man analysis**

The assay reagents used for analysis of the g.72C>T (rs2298397) polymorphic site in the CTTN gene were designed by Applied Biosystems (Applied Biosystems, Foster City, CA, USA). The reagents consist of a 40× mix of unlabeled PCR primer and TaqMan MGB probes (FAM and VIC dye-labeled). The 10-μL reaction mix was optimized to work with 0.125 μL of 40× reagents, 5 μL of 2× TaqMan Genotyping Master mix (Applied Biosystems) and 2 μL of 50-ng genomic DNA. PCR conditions were as follows: one cycle at 95°C for 15 minutes; 50 cycles, each at 95°C for 10 seconds and 60°C for 45 seconds. The PCR was performed in the Rotor-Gene thermal cycler RG6000 (Corbett Research, Sydney, Australia). The samples were read and analyzed using the Rotor-Gene 1.7.40 software (Corbett Research). The reference sequence for the CTTN gene was based on sequence 11q13 of human chromosome 11.

**Statistical analysis**

We determined whether the allelic distribution of the SNPs was consistent with the Hardy-Weinberg equilibrium using the chi-square test. The allele and genotype frequencies of these SNPs were compared between the patients and controls using the chi-square test or the Fisher exact test. Survival rates were calculated using the Kaplan-Meier method. P-values less than 0.05 were considered to indicate statistical significance.

**RESULTS**

**Genotype and allele frequencies of the CTTN polymorphisms**

The genotype frequencies of the CTTN g.-9101C>T polymorphism were 97.5% (TT), 2.5% (TC), and 0% (CC) in the patient group, and were 98.6% (TT), 1.4% (TC), and 0% (CC) in the control group. The genotype frequencies of the CTTN g.-8748C>T polymorphism were 93.2% (TT), 6.8% (TC), and 0% (CC) in the patient group, and were 94.2% (TT), 5.8% (TC), and 0% (CC) in the control group. The genotype frequencies of the CTTN g.72C>T polymorphism were 82.4% (CC), 17.2% (CT), and 0.4% (TT) in the patient group, and were 78.0% (CC), 20.1% (CT), and 1.9% (TT) in the control group. The genotype and allele frequencies of the CTTN polymorphisms in gastric cancer patients and controls with susceptibility to gastric cancer are presented in Table 2.

**Table 2. Genotype and allele frequencies of the CTTN polymorphisms in gastric cancer patients and controls with susceptibility to gastric cancer**

| Position | Genotype/allele | Control | Gastric cancer | P-value \(^b\) |
|----------|-----------------|---------|---------------|----------------|
|          | Total           |         |               |                |
|          | TT 430 (98.6)   | 153 (97.5) |               | 0.618          |
|          | TC 6 (1.4)      | 4 (2.5)   |               |                |
|          | CC 0 (0)        | 0 (0)    |               |                |
|          | TT vs. TC vs. CC|         |               |                |
|          | T 866 (99.3)    | 310 (98.7) |               |                |
|          | C 6 (0.7)       | 4 (1.3)   |               |                |
|          | T vs. C         |         |               | 0.141          |
| g.-9101C>T (rs12576561) | TT 404 (94.2) | 124 (93.2)  |               |                |
|          | TC 25 (5.8)     | 9 (6.8)   |               |                |
|          | CC 0 (0)        | 0 (0)    |               |                |
|          | TT vs. TC vs. CC|         |               |                |
|          | T 833 (97.1)    | 257 (96.6) |               | 0.923          |
|          | C 25 (2.9)      | 9 (3.4)   |               |                |
|          | T vs. C         |         |               | 0.684          |
| g.-8748C>T (rs11825736) | CC 416 (78.0) | 220 (82.4)  |               |                |
|          | CT 107 (20.1)   | 46 (17.2)  |               |                |
|          | TT 10 (1.9)     | 1 (0.4)   |               |                |
|          | CC vs. CT vs. TT|         |               |                |
|          | C 939 (88.1)    | 486 (91.0) |               | 0.129          |
|          | T 127 (11.9)    | 48 (9.0)  |               | 0.089          |
|          | C vs. T         |         |               |                |

Values are presented as number (%).
CTTN, cortactin.
\(^a\)Calculated from the translation start site. \(^b\)Fisher exact test or chi-square test from a \(2 \times 3\) contingency table.
### Table 3. Comparison of genotype and allele frequencies of the CTTN polymorphisms among patients in the EGC group, the AGC group, and controls susceptible to gastric cancer

| Position  | Genotype/allele | Control (Tumor depth, n (%)) | T1 | T2 | T3 | T4 | vs. EGC | vs. AGC |
|-----------|----------------|-----------------------------|----|----|----|----|---------|---------|
| g.-9101C>T (rs12576561) | TT | 430 (98.6) | 97 (61.8) | 26 (16.5) | 22 (14.0) | 2 (1.3) |
|           | TC | 6 (1.4) | 0 (0) | 4 (2.6) | 3 (2.0) | 1 (0.6) |
|           | CC | 0 (0) | 0 (0) | 0 (0) | 1 (0.6) | 1 (0.6) |
|           | TT vs. TC vs. CC | 0.677 | 0.036 |
|           | T | 866 (99.3) | 194 (61.8) | 56 (17.8) | 47 (15.0) | 5 (1.6) |
|           | C | 6 (0.70) | 0 (0.0) | 4 (1.3) | 5 (1.6) | 3 (0.9) |
| g.-8748C>T (rs11825736) | TT | 404 (94.2) | 73 (55.0) | 32 (24.1) | 22 (16.5) | 4 (3.0) |
|           | TC | 25 (5.8) | 0 (0) | 1 (0.7) | 1 (0.7) | 0 (0) |
|           | CC | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
|           | TT vs. TC vs. CC | 0.208 | 0.970 |
|           | T | 833 (97.1) | 146 (54.9) | 65 (24.4) | 45 (16.9) | 8 (3.0) |
|           | C | 25 (2.9) | 0 (0) | 1 (0.4) | 1 (0.4) | 0 (0) |
| g.72C>T (rs2298397) | CC | 416 (78.0) | 127 (47.6) | 54 (20.2) | 29 (10.7) | 4 (1.5) |
|            | CT | 107 (20.1) | 30 (11.2) | 5 (1.9) | 14 (5.2) | 3 (1.1) |
|            | TT | 10 (1.9) | 0 (0.4) | 1 (0.3) | 0 (0) | 0 (0) |
|            | CC vs. CT vs. TT | 0.304 | 0.835 |
|            | T | 939 (88.1) | 284 (53.2) | 113 (21.2) | 72 (13.4) | 11 (2.1) |
|            | C | 127 (11.9) | 30 (5.6) | 7 (1.3) | 14 (2.6) | 3 (0.6) |

CTTN, cortactin; EGC, early gastric cancer; AGC, advanced gastric cancer.

*Calculated from the translation start site. *Calculated from the translation start site.

### Table 4. Comparison of genotype and allele frequencies of the CTTN polymorphisms among the LN (–) and LN (+) gastric cancer groups, and controls susceptible to gastric cancer

| Position  | Genotype/allele | LN (–) vs. LN (+), n (%) | P-value* |
|-----------|----------------|------------------------|----------|
| g.-9101C>T (rs12576561) | TT | 430 (98.6) | 53 (100) | 94 (97.0) |
|           | TC | 6 (1.4) | 0 (0) | 3 (3.0) |
|           | CC | 0 (0) | 0 (0) | 0 (0) |
|           | TT vs. TC vs. CC | 0.852 | 0.300 |
|           | T | 866 (99.3) | 106 (100) | 191 (98.5) |
|           | C | 6 (0.7) | 0 (0) | 3 (1.5) |
| g.-8748C>T (rs11825736) | TT | 404 (94.2) | 40 (100) | 91 (97.8) |
|           | TC | 25 (5.8) | 0 (0) | 2 (2.2) |
|           | CC | 0 (0) | 0 (0) | 0 (0) |
|           | TT vs. TC vs. CC | 0.541 | 0.557 |
|           | T | 833 (97.1) | 80 (100) | 184 (98.9) |
|           | C | 25 (2.9) | 0 (0) | 2 (1.1) |
| g.72C>T (rs2298397) | CC | 416 (78.0) | 117 (89.3) | 124 (91.1) |
|            | CT | 107 (20.1) | 14 (11.7) | 11 (8.1) |
|            | TT | 10 (1.9) | 0 (0) | 1 (0.8) |
|            | CC vs. CT vs. TT | 0.622 | 0.410 |
|            | C | 939 (88.1) | 248 (94.7) | 259 (92.2) |
|            | T | 127 (11.9) | 14 (5.3) | 13 (7.8) |

CTTN, cortactin; LN (–), lymph node-negative gastric cancer; LN (+), lymph node-positive gastric cancer.

*Calculated from the translation start site. *Fisher exact test or chi-square test from a 2 × 3 contingency table.
frequencies of the CTTN g.-9101C>T, g.-8748C>T, and g.72C>T polymorphisms were not significantly different between the patient group and the control group (Table 2).

**Genotype and allele frequencies of the CTTN polymorphisms, compared among the EGC group, AGC group, and controls susceptible to gastric cancer**

The genotype and allele frequencies of the CTTN g.-8748C>T and g.72C>T polymorphisms were not different among the EGC, AGC, and control groups. However, the genotype and allele frequencies of the CTTN g.-9101C>T polymorphism were significantly different between the AGC group and the control group (P = 0.036 and P = 0.040, respectively) (Table 3).

**Genotype and allele frequencies of the CTTN polymorphisms among the LN (–) and LN (+) gastric cancer groups, and controls susceptible to gastric cancer**

The genotype and allele frequencies of the CTTN g.-9101C>T, g.-8748C>T, and g.72C>T polymorphisms were not different among lymph node-negative, lymph node-positive, and control groups (Table 4).

**Relationship between the genotypes in the CTTN g.-9101C>T polymorphism and the survival time in patients with AGC**

Clinicopathologic characteristics of 60 patients with advanced gastric adenocarcinoma based on the genotypes of CTTN g.-9101C>T polymorphism are listed in Table 5 and there was no different between the genotypes (Table 5).

The 60 patients with AGC in the CTTN g.-9101C>T polymorphism were followed up for 5 years, and were divided into 3 groups based on the CTTN genotype. The group with a TC genotype had a significantly poorer prognosis than the group with the TT genotype (P = 0.020) (Fig. 1).

**DISCUSSION**

The development of gastric cancer appears to be the result of a complex interaction between environmental and genetic factors. In particular, the frequency and the variety of genetic polymorphisms in gastric cancer patients seem to vary according to contributing factors, including genetic background and personal factors, which usually go together [3-7,17-19].

Various associations of polymorphisms with disease have been shown in many studies, enabled by the sequencing of the entire human genome and by recent developments in genetics. There has also been an explosion of information concerning natural genetic variations in the human genome, and their functional and clinical significance. This scientific progress allows us to delineate the complex role that genetic factors play in the onset and progression of common multifactorial diseases [20,21].
CTTN was initially identified as a tyrosine-phosphorylated protein in v-Src-infected chicken embryofibroblasts [22]. Subsequent cloning of the cDNA encoding CTTN revealed a novel protein with a unique domain structure. Structural predictions based on the amino acid sequence indicated that CTTN is comprised of several domains. At that time, little was known about its function, except that it binds to actin filaments, has an Src homology (SH) 3 domain, and is phosphorylated in its C-terminus by an Src kinase [7-9,23].

CTTN contains a proline-rich region with c-Src tyrosine phosphorylation sites and a SH3 domain at the COOH terminus. It also contains an N-terminal acidic region that binds to the Arp2/3 complex. Phosphorylation binding sites and the SH3 domain are necessary for both the activation and the regulation of Arp2/3-complex-mediated branched actin assembly [7-9,24].

Recent research suggests that CTTN may regulate endocytosis of integrins and growth factor receptors, or secretion of proteases and extracellular matrix. These regulations have effects on cell motility, which is dependent on the cell context [25,26].

The CTTN gene was found to be identical to EmsI, a gene that is frequently overexpressed in breast and head and neck cancers, due to its presence in the 11q13 amplicon. 11q13 amplification has been frequently tied to a poor prognosis, with outcomes including associations with a higher pathological stage, lymph node and distant metastases, and a decreased survival rate [9-16].

Although many other genes are present within this amplicon, the consistent overexpression of CTTN in 11q13-amplified tumors, along with its ubiquitous presence in structures involved in cell motility, such as lamellipodia and invadopodia, have generated a great deal of interest in the role of CTTN in tumor invasion [9-16].

In HNSCC patients, 30%–40% of tumors contain the 11q13 amplicon, and its presence clearly correlates with poor patient prognosis, including decreased survival [13].

Of the many interesting genes, which are present in this amplicon, cyclinD1 and CTTN have been considered the best candidates for promoting tumor aggressiveness since, unlike many of the other genes in the amplicon, they are consistently overexpressed upon amplification [28].

Chuma et al. [14] reported that overexpression of CTTN may play a role in the metastasis of hepatocellular carcinomas (HCC) by influencing cell motility, and that CTTN could be a sensitive marker for HCC with intrahepatic metastasis. Recent research has also shown that overexpression of CTTN is closely associated with a poor prognosis in patients affected by HCC caused by cancer embolus and metastasis [29].

In colorectal cancer, Lee et al. [30] reported that the genotype and allele frequencies of the CTTN g.-8748C>T and g. 72C>T polymorphisms were not different between the colorectal cancer patient group and the control group, but that the genotype and allele frequencies of the CTTN g.-9101C>T polymorphism were significantly different between the lymph node-positive colorectal cancer group and the control group. These results show that the CTTN g.-9101C>T polymorphism may have an influence on lymph node-positive colorectal cancer.

At present, direct evidence is still lacking to establish a relationship among CTTN overexpression, tumor progression, and metastasis in gastric adenocarcinoma, and the relationship between CTTN polymorphisms and susceptibility to gastric cancer is unclear.

In our study, we successfully demonstrated that the genotype and allele frequencies of the CTTN g.-9101C>T polymorphism were significantly different between the AGC group and the control group, and that advanced gastric patients in the group with the TC genotype in the CTTN g.-9101C>T polymorphism had a significantly poorer prognosis than those in the group with the TT genotype.

These results show that there is an association between the specific CTTN polymorphism and the depth of invasion of the tumor in gastric cancer. Moreover, there is the possibility that the specific CTTN g.-9101C>T polymorphism present influences the susceptibility to AGC.

To our knowledge, this is the first report to evaluate the association between CTTN polymorphisms and the susceptibility to gastric cancer.

However, additional studies with large populations and many ethnic groups are needed to clarify the associations between the respective CTTN g.-9101C>T, g.-8748C>T, and g.72C>T polymorphisms and susceptibility to gastric cancer.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. The Information Committee of the Korean Gastric Cancer Association. 2004 Nationwide Gastric Cancer Report in Korea. J Korean Gastric Cancer Assoc 2007;7:47-54.
2. Hartgrink HH, Jansen EP, van Grieken NC, van de Velde CJ. Gastric cancer. Lancet 2009;374:477-90.
3. de Martel C, Forman D, Plummer M. Gastric cancer: epidemiology and risk factors. Gastroenterol Clin North Am 2013;42:219-40.
4. Wang XQ, Yan H, Terry PD, Wang JS, Cheng L, Wu WA, et al. Interaction between dietary factors and Helicobacter pylori infection in noncardia gastric cancer: a population-based case-control study in China. J Am Coll Nutr 2012;31:375-84.
5. Songun I, van de Velde CJ, Arends JW, Blok P, Grond AJ, Offerhaus GJ, et al. Classification of gastric carcinoma using the Goseki system provides prognostic information additional to TNM staging. Cancer 1999;85:214-8.
6. Shiraiishi N, Sato K, Yasuda K, Inomata M, Kitano S. Multivariate prognostic study on large gastric cancer. J Surg Oncol 2007;96:14-8.
7. Bougnères L, Girardin SE, Weed SA, Karginov AV, Olivo-Marín JC, Parsons JT, et al. Cortactin and Crk cooperate to trigger actin polymerization during Shigella invasion of epithelial cells. J Cell Biol 2004;166:225-35.
8. Daly RJ. Cortactin signalling and dynamic actin networks. Biochem J 2004;382(Pt 1):13-25.
9. van Rossouw AG, Moolenaar WH, Schuuring E. Cortactin affects cell migration by regulating intercellular adhesion and cell spreading. Exp Cell Res 2006;312:1658-70.
10. van Rossouw AG, Gibcus J, van der Wal J, Schuuring E. Cortactin overexpression results in sustained epidermal growth factor receptor signaling by preventing ligand-induced receptor degradation in human carcinoma cells. Breast Cancer Res 2005;7:235-7.
11. Luo ML, Shen XM, Zhang Y, Wei F, Xu X, Cai Y, et al. Amplification and overexpression of CTTN (EMS1) contribute to the metastasis of esophageal squamous cell carcinoma by promoting cell migration and anoikis resistance. Cancer Res 2006;66:11690-9.
12. Rothschild BL, Shim AH, Ammer AG, Kelley LC, Iby KB, Head JA, et al. Cortactin overexpression regulates actin-related protein 2/3 complex activity, motility, and invasion in carcinomas with chromosome 11q13 amplification. Cancer Res 2006;66:8017-25.
13. Akervall JA, Jin Y, Wennerberg JP, Zatterstrom UK, Kjellen E, Mertens F, et al. Chromosomal abnormalities involving 11q13 are associated with poor prognosis in patients with squamous cell carcinoma of the head and neck. Cancer 1995;76:853-9.
14. Chuma M, Sakamoto M, Yasuda J, Fujii G, Nakanishi K, Tsuchiya A, et al. Overexpression of cortactin is involved in motility and metastasis of hepatocellular carcinoma. J Hepatol 2004;41:629-36.
15. Tsai WC, Jin JS, Chang WK, Chan DC, Yeh MK, Chering SC, et al. Association of cortactin and fascin-1 expression in gastric adenocarcinoma: correlation with clinicopathological parameters. J Histochem Cytochem 2007;55:955-62.
16. Lee YY, Yu CP, Lin CK, Nieh S, Hsu KF, Chiang H, et al. Expression of survivin and cortactin in colorectal adenocarcinoma: association with clinicopathological parameters. Dis Markers 2009;26:9-18.
17. Zhang K, Zhou B, Wang Y, Rao L, Zhang L. The TLR4 gene polymorphisms and susceptibility to cancer: a systematic review and meta-analysis. Eur J Cancer 2013;49:946-54.
18. Saeki N, Ono H, Sakamoto H, Yoshida T, Ito Y, Takahashi K, et al. Expression of survivin and cortactin in colorectal adenocarcinoma: association with clinicopathological parameters. Dis Markers 2009;26:9-18.
19. Lynch HT, Grady W, Suriano G, Huntsman D. Gastric cancer: new genetic developments. J Surg Oncol 2005;90:114-33.
20. Salisbury BA, Pungliya M, Choi JY, Jiang R, Sun XJ, Stephens JC. SNP and haplotype variation in the human genome. Mutat Res 2003;526:53-61.
21. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471-4.
22. Balasubramanian SP, Cox A, Brown NJ, Reed MW. Candidate gene polymorphisms in solid cancers. Eur J Surg Oncol 2004;30:593-601.
23. Yu H, Parsons JT. Cortactin, an 80/85-kilodalton pp60src substrate, is a filamentous actin-binding protein enriched in the cell cortex. J Cell Biol 1993;120:1417-20.
24. Uruno T, Liu J, Zhang P, Fan Yx, Egile C, Li R, et al. Activation of Arp2/3 complex-mediated actin polymerization by cortactin. Nat Cell Biol 2001;3:259-66.
25. Timpson P, Lynch DK, Schramek D, Walker F, Daly RJ. Cortactin overexpression inhibits ligand-induced down-regulation of the epidermal growth factor receptor. Cancer Res 2005;65:3273-80.
26. Clark ES, Whigham AS, Yarbrough WG, Weaver AM. Cortactin is an essential regulator of matrix metalloproteinase secretion and extracellular matrix degradation in invadopodia. Cancer Res 2007;67:4227-35.
27. Ormandy CJ, Musgrove EA, Hui R, Daly RJ, Sutherland RL. Cyclin D1, EMS1 and 11q13 amplification in breast cancer. Breast Cancer Res Treat 2003;78:323-35.
28. Schuuring E. The involvement of the chromosome 11q13 region in human malignancies: cyclin D1 and EMS1 are two new candidate oncogenes: a review. Gene 1995;159:83-96.
29. Zhao G, Huang ZM, Kong YL, Wen DQ, Li Y, Ren L, et al. Cortactin is a sensitive biomarker relative to the poor prognosis of human hepatocellular carcinoma. World J Surg Oncol 2013;11:74.
30. Lee SY, Kang DB, Park WC, Lee JK, Chae SC. Association of CTTN polymorphisms with the risk of colorectal cancer. J Korean Surg Soc 2012;82:156-64.