Association of the GNAS1 T393C polymorphism with tumor stage and survival in gastric cancer

Hakan Alakus, Stefan P Mönig, Ute Warnecke-Eberz, Gül Alakus, Günther Winde, Uta Drebber, Klaus J Schmitz, Kurt W Schmid, Kathrin Riemann, Winfried Siffert, Elfriede Bollschweiler, Arnulf H Hölscher, Ralf Metzger

Hakan Alakus, Stefan P Mönig, Ute Warnecke-Eberz, Elfriede Bollschweiler, Arnulf H Hölscher, Ralf Metzger, Department of General, Visceral and Cancer Surgery, Center for Integrated Oncology, University of Cologne, D-50937 Cologne, Germany Gül Alakus, Günther Winde, Department of Gastrointestinal Surgery, Klinikum Herford, D-32049 Herford, Germany Uta Drebber, Institute of Pathology, University of Cologne, D-50937 Cologne, Germany Klaus J Schmitz, Kurt W Schmid, Institute of Pathology and Neuropathology, University Hospital of Essen, University of Duisburg-Essen, D-45122 Essen, Germany Kathrin Riemann, Winfried Siffert, Institute of Pharmacogenetics, University Hospital of Essen, University of Duisburg-Essen, D-45122 Essen, Germany

Author contributions: Alakus H was involved in the majority of experiments, in statistical analysis, in writing the manuscript and in providing financial support; Mönig SP contributed to the acquisition of surgical and routine histopathologic data; Warnecke-Eberz U performed the majority of experiments; Bollschweiler E performed statistical analysis and contributed to the conception and design of the manuscript; Metzger R and Hölscher AH performed the study, edited the manuscript and coordinated the study; Winde G was the main initiator for the study together with Alakus G who performed data and human material collection; Drebber U, Schmitz KJ and Schmid KW were responsible for pathological assessment of the resected tumor samples and for editing the manuscript; Riemann K and Siffert W built up the database of the healthy reference group, performed genotyping of this group and edited the manuscript.

Supported by The Köln Fortune Program, the CIO/Faculty of Medicine, University of Cologne and the Hoff’sche Stiftung Correspondence to: Ralf Metzger, MD, Department of General, Visceral and Cancer Surgery, Center for Integrated Oncology, University Hospital of Cologne, Kerpener Str. 62, D-50937 Cologne, Germany. ralf.metzger@uk-koeln.de Telephone: +49-221-4785453 Fax: +49-221-4786258 Received: September 16, 2009 Revised: October 14, 2009 Accepted: October 21, 2009 Published online: December 28, 2009

Abstract

AIM: To analyze the impact of the GNAS1 T393C polymorphism on prognosis and histopathology of gastric cancer.

METHODS: Genomic DNA was extracted from paraffin-embedded tissues of 122 patients with primary gastric carcinoma and from the blood of 820 healthy white individuals. Allelic discrimination was performed by quantitative real-time polymerase chain reaction. Genotyping was correlated with histopathologic parameters and with overall survival according to the Kaplan-Meier approach and with multivariate analysis by multiple stepwise regression.

RESULTS: Thirty-nine (32%) patients displayed a CC genotype, 57 (46.7%) a CT genotype and 26 (21.3%) a TT genotype. The frequency of the C allele (fC) in the patient group was 0.55, which was not significantly different from that of healthy donors. The distribution was compatible with the Hardy-Weinberg equilibrium. Analysis of clinicopathological parameters did not show any significant correlation of the T393C genotype with gender (P = 0.50), differentiation (P = 0.29), pT-category (P = 0.19), pN-category (P = 0.30), pM-category (P = 0.25), R-category (P = 0.95), the classifications according to WHO (P = 0.34), Laurén (P = 0.16), Goseki (P = 1.00) and Ming (P = 0.74). Dichotomization between C+ (CC+CT) and C-genotypes (TT), however, revealed significantly more advanced tumor stages (P = 0.023) and lower survival rates (P = 0.043) for C allele carriers.

CONCLUSION: The present study provides strong evidence to suggest that the GNAS1 T393C allele carrier status influences tumor progression and survival in gastric cancer with higher tumor stages and a worse outcome for C allele carriers.

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Key words: Gastric cancer; G Protein; Polymorphism; Prognosis; Tumor stage

Peer reviewer: You-Yong Lu, Professor, Beijing Molecular Oncology Laboratory, Peking University School of Oncology and Beijing Institute for Cancer Research, #52, Fucheng Road, Haidian District, Beijing 100036, China

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INTRODUCTION

Gastric cancer has substantially decreased in incidence over the past decades, but it still remains one of the most common cancers in the world and the second most frequent cause of cancer-related death after lung cancer[4,5]. Most patients are diagnosed with advanced gastric cancer, and overall survival remains poor[2,3]. The 5-year survival rate for gastric cancer is still only at 40%[4,8].

Of particular interest are prognostic factors, as they give the basis to identify gastric cancer patients with high-risk and poor prognosis. The identification of patients with poor outcome can help to set up novel treatment strategies at the beginning of treatment and may lead to better and more individualized therapy strategies with better survival[8]. Current efforts in research are therefore focused on the detection and validation of biomarkers and genetic markers that give additional information about prognosis to classical prognostic factors such as the TNM classification. The majority of new detected markers are related to properties of the tumor itself, e.g. somatic mutations or differential expression of genes or proteins. However, difficulties in standardization of such markers often prevent their routine application in clinical practice[8].

In recent years, studies have focused on the detection of single nucleotide polymorphisms (SNPs) that have a prognostic impact in cancer. One major advantage of SNPs as prognostic markers is that they can be determined independently from the availability and quality of tumor material as they can be easily evaluated from a blood sample from individual patients.

The T393C polymorphism of the gene GNAS1 is one such polymorphism. This SNP is located in exon 5 of the gene GNAS1, which encodes the ubiquitously expressed Gαs subunit of heterotrimeric G proteins. Previous studies indicate that increased expression of Gαs enhances apoptosis[7,8] and that Gαs mRNA expression is different between T393C genotypes[9,10]. For various solid tumors, previous studies demonstrated that patient survival and tumor progression depended on T393C genotype[10-17].

Until now, nothing has been published about the impact of the GNAS1 T393C polymorphism on gastric cancer. Thus, the aim of the present study was to determine the influence of this polymorphism on prognosis in gastric cancer. Furthermore, we looked for possible correlations between the GNAS1 T393C polymorphism and clinicopathological parameters.

MATERIALS AND METHODS

Patients

Of 159 patients, who were treated surgically between May 1996 and January 2005 for primary gastric carcinoma at the Department of General, Visceral and Cancer Surgery of the University of Cologne, 13 (8.2%) patients with a second tumor, a previous operation of the upper digestive tract or missing paraffin-embedded tissue from normal cells, and 24 (15.1%) patients with neoadjuvant treatment received before surgery were excluded. Excluded patients did not differ in age and gender from the remaining patients.

All of the included 122 patients [median age 67.6 years, range 33-87 years; 78 (63.9%) male, 44 (36.1%) female] were initially treated by operation with curative intention. Gastroscopic examination, endoscopic ultrasound and computed tomography (CT) of the chest and abdomen were performed before surgery on all patients for clinical staging.

One hundred and six (86.9%) of the 122 patients underwent a gastrectomy with D2-lymphadenectomy (compartment I and II) and in 16 (13.1%) cases, a subtotal gastrectomy with D2-lymphadenectomy was performed. The median number of resected lymph nodes was 36.0 (range 15-80).

The present study was performed according to the guidelines of the local Research Ethics Commission.

Histopathology

The specimens were removed en bloc and the lymph nodes of the specimens were dissected with the cooperation of surgeons and pathologists according to a standardized protocol. The resected specimens were routinely fixed in 5% phosphate-buffered formalin and embedded in paraffin. Histopathologic examination of all resected specimens consisted of a thorough and standardized evaluation of the tumor stage, residual tumor (R) category, grading and the number of resected and infiltrated lymph nodes. The gastric lymph nodes were documented according to the classification of the Japanese Research Society of Gastric Cancer (JRGCS) with lymph node groups 1 to 13[18]. The tumor localization was defined according to the International Classification of Diseases for Oncology. The lesions were further classified and graded in accordance with WHO recommendations, the Laurén-classification and tumor differentiation. Postoperative staging was performed according to the 6th edition of the TNM-classification of malignant tumors[19].

Genotyping

DNA was extracted from paraffin-embedded tissues from resection boundaries containing exclusively normal cells using a DNA extraction kit (QIAamp, Qiagen, Hilden, Germany) according to the manufacturer's instructions. Genotyping was performed in 96-well plates by 5’nuclease assay (TaqMan) using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Darmstadt, Germany). The pre-developed TaqMan assay ID C_9901536_10 (Applied Biosystems, Darmstadt, Germany) was used for genotyping of GNAS1 T393C polymorphism (dbSNP rs7121). Polymerase chain reaction (PCR) reactions contained 10 ng DNA, 200 μmol/L dNTPs and 900 nmol/L primers (Figure 1).

PCR conditions were: 95°C for 10 min followed by 40 cycles of 15 s at 92°C and 60 s at 60°C.

Reference group

The Caucasian control sample consisted of 820 healthy
Table 1  Allele frequencies and genotype distribution of GNAS1 T393C polymorphism in 122 gastric cancer patients and in the reference group (n = 820) n (%)  

| T393C        | Patients (n = 122) | Reference group (n = 820) | χ² | P | Odds ratio 95% CI |
|--------------|--------------------|---------------------------|----|---|-------------------|
| Allele       |                    |                           |    |   |                   |
| C            | 135 (55.3)         | T 109 (44.7)              |    |   |                   |
| Genotype     | CC 39 (32.0)       | CT 57 (46.7)              |    |   |                   |
|              | TT 182 (22.2)      | CC 235 (28.7)             |    |   |                   |
| Reference    |                    |                           |    |   |                   |
| C            | 135 (55.3)         | T 109 (44.7)              |    |   |                   |
| Genotype     | CC 39 (32.0)       | CT 57 (46.7)              |    |   |                   |
|              | TT 182 (22.2)      | CC 235 (28.7)             |    |   |                   |

Figure 1 Amplification plot of one heterozygous GNAS1 T393C (CT) by two allele specific TaqMan probes.

white individuals who were recruited at the local Department for Transfusion Medicine, University Hospital, Essen. All samples were collected at random from subjects donating blood. The details of this sample have been published previously.\[12\]

Statistical analysis
Associations between T393C genotype and clinicopathological parameters were evaluated using the χ² test. Pearson’s χ² was used for Hardy-Weinberg analysis and to examine differences in allele frequencies between our patient group and the reference group. Relations to overall survival were evaluated with univariate analysis according to the Kaplan-Meier approach using the log-rank test to assess statistical differences between groups. Prognostic factors were determined by multiple stepwise regression analysis using the Cox model. Only potential prognostic factors were included in the multivariate analysis. The level of significance was set at P < 0.05 and P values were for 2-sided testing. All statistical tests were performed using the Software Package SPSS for Windows, Version 17.0 (Chicago, IL, USA).

RESULTS
Genotype distribution and reference group
Thirty-nine (32.0%) patients displayed a CC genotype, 57 (46.7%) a CT genotype and 26 (21.3%) a TT genotype. The frequency of the C allele (fC) in the entire patient group was 0.55, which is not significantly different from that of healthy blood donors (Table 1). The distribution was compatible with the Hardy-Weinberg equilibrium.

Clinicopathological characteristics
Clinicopathological characteristics of the whole patient group with genotype distribution are displayed in Table 2. Thirty (24.6%) patients showed an early gastric carcinoma (pT1). In 73 (59.8%) cases, lymph node metastasis (pN+) was detected. An M1 category was found in 23 (18.9%) patients with localized peritoneal carcinosis, distant lymph node metastasis (M1 lymph) or single liver metastasis (M1 Hep). Patients with diffuse peritoneal or multiple liver metastasis had been treated non-surgically and were excluded from the study.

Analysis of clinicopathological parameters did not show any significant correlation of the T393C genotype with gender (P = 0.50), differentiation (P = 0.29), pT-category (P = 0.19), pN-category (P = 0.30), pM-category (P = 0.25), R-category (P = 0.95), or the classifications according to WHO (P = 0.34), Laurén (P = 0.16), Goseki (P = 1.0, M1 Hep). Patients with diffuse peritoneal or multiple liver metastasis had been treated non-surgically and were excluded from the study.

Univariate survival analysis
Overall survival dependent on T393C genotypes is displayed in Figure 2. The 5-year survival rate for patients with a TT genotype was 56.9% (SE ± 10.4%), followed by patients with CC genotype with a 5-year survival rate of 42.6% (SE ± 8.3%). Heterozygous CT patients showed a 5-year survival rate of 32.7% (SE ± 6.3%). Survival was not significantly associated with the T393C genotype when the three genotypes were compared (P = 0.082). However, dichotomization between C+ (CC+CT) and TT demonstrated a significantly (P = 0.043) lower survival rate for C allele carriers (Figure 3) with a 5-year survival rate of 56.9% (SE ± 10.4%) for the TT group.

Multivariate survival analysis
In the multivariate Cox regression analysis, known prognostic factors for gastric cancer (pT, pN, pM and R-category) and T393C genotype with dichotomization between C+ (CC+CT) and TT were included. pT-category (P < 0.001), R-category (P = 0.022) and pM-category (P = 0.027) maintained their prognostic independence (Table 3). pN-category (P = 0.55), and the T393C genotype (P = 0.33) lost their prognostic independence.

DISCUSSION
Gastric cancer is the fourth most common cancer with
|                     | All (n=122) | T393C genotypes | P     |
|---------------------|-------------|-----------------|-------|
|                     |             | CC   | CT   | TT   |       |
| n (%)               | 122 (100)  | 39 (32) | 57 (46.7) | 26 (21.3) |       |
| Gender              |             |       |       |       |       |
| Male                | 78 (63.9)  | 25 (32.1) | 34 (43.6) | 19 (24.4) | 0.274 |
| Female              | 44 (36.1)  | 14 (31.8) | 23 (52.3) | 7 (15.9)  |       |
| WHO                 |             |       |       |       |       |
| Papillary/Tubular/Mucinous | 76 (62.3) | 23 (30.3) | 34 (44.7) | 19 (25)  |       |
| Signet-ring cancer  | 38 (31.1)  | 12 (31.6) | 19 (50)  | 7 (18.4)  |       |
| Other               | 8 (6.6)    | 4 (50)  | 4 (50)  | 0        | 0.340 |
| Differentiation     |             |       |       |       |       |
| Well/Moderate (G1-G2) | 42 (34.4) | 12 (28.6) | 22 (52.4) | 8 (19)   |       |
| Poor (G3-G4)        | 80 (65.6)  | 27 (33.8) | 35 (43.8) | 18 (22.5) | 0.805 |
| Laurén              |             |       |       |       |       |
| Intestinal          | 52 (42.6)  | 16 (30.8) | 25 (48.1) | 11 (21.2) |       |
| Diffuse             | 55 (45.1)  | 17 (30.9) | 29 (52.7) | 9 (16.4)  |       |
| Mixed               | 15 (12.5)  | 6 (40)   | 3 (20)   | 6 (40)    | 0.171 |
| Ming                |             |       |       |       |       |
| Expanding           | 47 (38.5)  | 14 (29.8) | 24 (51.1) | 9 (19.1)  |       |
| Infiltrative        | 75 (61.5)  | 25 (33.3) | 33 (44)  | 17 (22.7) | 0.620 |
| pT-category         |             |       |       |       |       |
| T1                  | 30 (24.6)  | 7 (23.3)  | 13 (43.3) | 10 (33.3) |       |
| T2                  | 44 (36.1)  | 12 (27.3) | 22 (50)  | 10 (22.7) |       |
| T3                  | 38 (31.1)  | 14 (36.8) | 18 (47.4) | 6 (15.8)  |       |
| T4                  | 10 (8.2)   | 6 (60)   | 4 (40)   | 0        | 0.110 |
| pN-category         |             |       |       |       |       |
| N0                  | 49 (40.2)  | 11 (22.4) | 24 (49)  | 14 (28.6) |       |
| N1                  | 34 (27.9)  | 13 (38.2) | 13 (38.2) | 8 (23.5)  |       |
| N2                  | 14 (11.5)  | 6 (42.9)  | 6 (42.9)  | 2 (14.3)  |       |
| N3                  | 25 (20.5)  | 9 (36)    | 14 (56)  | 2 (8)     | 0.196 |
| pM-category         |             |       |       |       |       |
| M0                  | 99 (81.1)  | 30 (30.3) | 45 (45.5) | 24 (24.2) |       |
| M1                  | 23 (18.9)  | 9 (39.1)  | 12 (52.2) | 2 (8.7)   | 0.101 |
| R-category          |             |       |       |       |       |
| R0                  | 118 (96.7) | 38 (32.5) | 54 (46.2) | 25 (21.4) |       |
| R1/R2               | 4 (3.3)    | 1 (25)   | 2 (50)   | 1 (25)    | 0.950 |
| UICC stage          |             |       |       |       |       |
| I a                 | 26 (21.3)  | 5 (19.2)  | 11 (42.3) | 10 (38.5) |       |
| I b                 | 22 (18)    | 7 (31.8)  | 12 (54.5) | 3 (13.6)  |       |
| II                  | 18 (14.8)  | 4 (22.2)  | 7 (38.9)  | 7 (38.9)  |       |
| III a               | 11 (9)     | 4 (36.4)  | 5 (45.5)  | 2 (18.2)  |       |
| III b               | 4 (3.3)    | 2 (50)    | 2 (50)    | 0        |       |
| N                  | 41 (33.6)  | 17 (41.5) | 20 (48.8) | 4 (9.8)   | 0.023 |

P values are given for dichotomization between C+ (CC+CT) and C- (TT) genotypes.

Figure 2 Overall survival of 122 resected gastric cancer patients based on GNAS1 T393C genotype (Kaplan-Meier analysis), P = 0.082 (Mantel-Cox log-rank test).

Figure 3 Overall survival of 122 resected gastric cancer patients based on GNAS1 T393C genotype with dichotomization between C+ and C- genotypes, P = 0.043.
### Table 3 Univariate and multivariate survival analysis of 122 gastric cancer patients

| Covariate        | n   | Univariate analysis | Multivariate analysis |
|------------------|-----|---------------------|-----------------------|
|                  |     | P value | 5-yr-SR (%) | SE (%) | P value | HR | 95% CI |
| pT-category      |     | < 0.001 |            |        | < 0.001 |    |       |
| pT1              | 30  |         | 85.4      | 6.8    |          |    |       |
| pT2              | 44  |         | 44.5      | 7.8    | < 0.001  | 6.212 | 2.31-16.70  |
| pT3              | 38  |         | 5.4       | 3.7    | < 0.001  | 13.026 | 4.44-38.23  |
| pT4              | 10  |         | 33.3      | 15.7   | 0.001    | 7.838  | 2.24-27.46  |
| pN-category      |     | < 0.001 |            |        |          |    |       |
| pN0              | 49  |         | 61.6      | 7.4    |          |    |       |
| pN1              | 34  |         | 47.1      | 8.6    | 0.226    | 0.663  | 0.34-1.29   |
| pN2              | 14  |         | 16.9      | 10.9   | 0.986    | 0.993  | 0.43-2.27   |
| pN3              | 25  |         | 8.0       | 5.4    | 0.814    | 0.905  | 0.40-2.07   |
| T393C SNP        |     | 0.043   |            |        | 0.333    |    |       |
| CC/CT            | 96  |         | 36.7      | 5.1    |          |    |       |
| TT               | 26  |         | 56.9      | 10.4   | 0.027    | 0.712  | 0.36-1.42   |
| pM-category      |     | < 0.001 |            |        |          |    |       |
| M0               | 99  |         | 48.1      | 5.2    |          |    |       |
| M1               | 23  |         | 9.2       | 6.2    | 2.087    | 1.094  | 0.01-4.01   |
| R-category       |     | < 0.001 |            |        | 0.022    |    |       |
| R0               | 118 |         | 42.3      | 4.7    |          |    |       |
| R+               | 4   |         | 0         | 0      | 3.128    | 1.188  | 1.18-8.27   |

SNP: Single nucleotide polymorphism; 5-yr-SR: 5-yr-survival; HR: Hazard ratio.

### Table 4 Summary of the effect of the GNAS1 T393C polymorphism on various carcinomas

| Cancer type                  | Yr | n   | Effect                                                                 | Benefit (survival) |
|------------------------------|----|-----|------------------------------------------------------------------------|-------------------|
| Gastric cancer               | 2009 | 122 | The present study demonstrates a significant survival benefit for the TT genotype with a 5-yr-survival rate of 56.9% vs the CC/CT group with a 5-yr-survival rate of only 36.7% (P = 0.043) | TT-genotype       |
| Squamous cell cancer of larynx[14] | 2008 | 157 | Survival was significantly dependent on the T393C genotype in advanced American Joint Committee on Cancer (AJCC) stages (III-IV) with higher 5-yr survival rates for TT, followed by TC and CC (P = 0.0437) | TT-genotype       |
| Oro- and hypopharyngeal squamous cell carcinom[38] | 2008 | 202 | C homozygous patients displayed a higher risk for disease progression than T homozygous patients (P = 0.019) and a higher risk for death (P = 0.015). In multivariate analysis, besides cancer stage and tumor localization, the T393C polymorphism was an independent prognostic factor for disease progression and death | TT-genotype       |
| Clear cell renal cell carcinoma[39] | 2006 | 150 | Tumor progression, development of metastasis and tumor-related death was significantly associated with the T393C polymorphism. In multivariate analysis CC patients were at highest risk for progression or tumor-related death compared with T-allele carriers (P = 0.018) | TT-genotype       |
| Chronic lymphocytic leukemia[22] | 2006 | 144 | Median progression-free survival was significantly higher for T-allele carriers (P = 0.007). In multivariate analysis, the T393C polymorphism kept its prognostic independence (P = 0.01) besides of ZAP-70 (P = 0.005) and Binet stage (P < 0.001). Regarding overall survival, CC genotypes were significantly at highest risk for death compared to T-alleles both in univariate (P < 0.001) and multivariate analysis (P = 0.002) | TT-genotype       |
| Bladder cancer[20] | 2005 | 254 | Progression-free survival (P = 0.011), metastasis-free survival (P = 0.001) and cancer-specific survival (P = 0.014) were significantly increased in TT genotypes compared with CC genotypes. In multivariate analysis, the T393C polymorphism kept its prognostic independence | TT-genotype       |
| Sporadic colorectal cancer[23] | 2005 | 151 | In UICC stages I to II, the 5-yr survival rate was significantly (P = 0.009) higher in TT genotypes (88%) compared with TC (71%) and CC genotypes (50%). In multivariate analysis, the T393C polymorphism was also an independent prognostic factor. No significant effect could be seen for UICC stages III to IV | TT-genotype       |
| Cholangiocarcinoma[46] | 2007 | 87  | Disease-specific overall survival was significantly dependent on the T393C genotype (P = 0.02), with TT genotypes showing reduced survival compared to patients carrying at least one C allele. In multivariate analysis (TT/C+) the T393C genotype kept its prognostic independence (P = 0.04) | CC-genotype       |
| Breast carcinoma[33] | 2007 | 279 | Overall survival was significantly (P = 0.033) associated with the T393C polymorphism with lowest survival rates for the TT-genotype and highest survival rate for the CC-genotype. In multivariate analysis, the TT-genotype still had a significant survival benefit compared to the CC genotype (P = 0.045) | CC-genotype       |
| Esophageal cancer[28] | 2009 | 51  | T393C polymorphism was significantly associated with tumor response to Cisplatin/5-FU-based radiochemotherapy. 63% of the T allele carriers had a minor histopathologic response (MiHR) with more than 10% residual vital tumor cells in resection specimens. For the CC genotype MiHR was seen only in 20%. In binary logistic regression analysis, the T393C genotype kept its independence (P < 0.05) | CC-genotype       |

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have been implicated in the etiology of ...molecular marker for tumor response to cisplatin/5-FU...[25]. In a recent study, we demonstrated that besides the T393C polymorphism as a risk factor for gastric cancer could not be established in the present study.

In conclusion, this study demonstrated for the first time that in primary gastric cancer, homozygous GNAS1 393T patients have less advanced tumor stages and higher survival rates than C allele carriers. These findings further support the concept of a general role for the GNAS1 T393C polymorphism in tumor progression.

COMMENTS

Background

Identification of gastric cancer patients with poor outcome can help to set up novel treatment strategies at the beginning of treatment and may lead to better and more individualized therapy strategies with better survival. In recent years, studies have focused on the detection of single nucleotide polymorphisms (SNPs) as prognostic molecular markers in cancer.

Research frontiers

The GNAS1 T393C polymorphism is located in exon 5 of the gene GNAS1. In this study the authors describe, for the first time, the impact of this SNP in gastric cancer. The study demonstrates that the GNAS1 T393C polymorphism affects tumor stage and progression in gastric cancer.

Innovations and breakthroughs

For various solid tumors, previous studies have demonstrated that patient survival and tumor progression depend on the GNAS1 T393C genotype. In the present study, the authors have described for the first time that the GNAS1 T393C polymorphism affects tumor stage and progression in gastric cancer.

Applications

The GNAS1 T393C polymorphism will contribute to identifying high-risk patients with gastric cancer and might help to establish a more individualized treatment strategy for gastric cancer.

Terminology

A single-nucleotide polymorphism (SNP) is a DNA sequence variation occurring when a single nucleotide - A, T, C, or G - in the genome differs between members of a species. The GNAS1 T393C is located in exon 5 of the gene GNAS1. For several cancer types, studies have demonstrated that patient survival is affected by this SNP.

Peer review

Overall, this paper provides information on GNAS1 T393C allele carrier status which influences tumor progression and survival in gastric cancer, with higher tumor stages and worse outcome for C allele carriers.

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