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OBSERVATIONAL STUDY

TT genotype of *GNAS1 T393C* polymorphism predicts better outcome of advanced non-small cell lung cancer patients

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Abstract

AIM: To evaluate the potential prognostic value of *GNAS1 T393C* polymorphism in advanced non-small cell lung cancer.

METHODS: We extracted genomic DNA from the peripheral blood leucocytes of 94 patients with advanced non-small cell lung cancer. Quantitative real-time polymerase chain reaction was used to determine the allelic discrimination. The correlation between genotype and overall survival was evaluated using the multivariate analysis and Kaplan-Meier approach.

RESULTS: Thirty-eight out of 94 (40%) patients displayed a TT genotype, 29 out of 94 (31%) a CT genotype and 27 out of 94 (29%) a CC genotype. The median survival of TT (25 mo) genotype carriers was longer than CT (12 mo) or CC (8 mo) genotype carriers. The favorable TT genotype predicted better overall survival (OS) (2-year OS: 48%; P =0.01) compared with CT (2-year OS: 18%) or CC (2-year OS: 15%) genotype. However, dichotomization between C-genotypes (CC + CT) and T-genotypes (TT) revealed significantly lower survival rates (2-year OS: 16%; P = 0.01) for C allele carriers.

CONCLUSION: Our data provided strong evidence that the *GNAS1 T393C* genetic polymorphism influenced the prognosis in advanced non-small lung cancer with a worse outcome for C allele carriers.

Key words: *GNAS1*; Polymorphism; Advanced non-small cell lung cancer; Prognosis

Core tip: We genotyped *GNAS1 T393C* single nucleotide polymorphism in a homogenous (Han) study population of patients to evaluate the effect of this polymorphism on survival in non-small cell lung cancer (NSCLC). Our study indicated that the *GNAS1 T393C* polymorphism affected the overall survival in advanced NSCLC with a worse outcome for C allele carriers.

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INTRODUCTION

The incidence of lung cancer has increased substantially over the past ten years[1]. Non-small cell lung cancer (NSCLC) constitutes about 85% of all lung cancer cases[2] with only 16.6% being able to live 5 years or more

after diagnosis[3]. To date, the most feasible treatment for advanced NSCLC patients is the platinum-based combination chemotherapy and it turns out to be associated with better overall survival rates[4]. Tumor-node-metastasis stage normally correlates with the clinical outcome of a large population of patients, but patients with similar clinical characteristics have different outcomes, which may be affected by their individual genes. The identification of patients with high-risk lung cancer could thus help to set up novel treatment strategies and could theoretically improve the outcome of anti-cancer therapy. Therefore, it is desirable to characterize more reliable and accurate molecular markers to identify more aggressive lung cancer phenotypes in order to individually tailor the therapy.

Actually, previous studies have implied that biomarkers could help define the subgroups of patients. However, there is no standard way to immunohistochemically detect these biomarkers, which prevents their application as prognostic factors. Nowadays, people choose to study single nucleotide polymorphisms (SNPs) as prognostic markers because these SNPs can be easily evaluated using patients' blood samples, which can avoid issues such as the availability and the quality of materials. One typical example is the *GNAS1 T393C* polymorphism.

The *GNAS1* gene has been mapped to chromosome 20q13 and contains 13 exons. The *GNAS1 T393C* polymorphism is located in exon 5, which encodes the α-subunit of the stimulatory G protein, namely Gαs. Somatic mutations of *GNAS1* have been reported to be involved in the etiology of McCune-Albright syndrome and sporadic, isolated endocrine tumors[5-7], suggesting that *GNAS1* could participate in cancer initiation and progression. What's more, previous studies have demonstrated that the *T393C* polymorphism was significantly correlated with the prognosis of patients with various cancers, such as breast carcinoma, squamous cell carcinoma of the larynx, bladder cancer, cholangiocarcinoma, colorectal cancer, clear cell renal carcinoma, and cancers of the oropharynx and hypopharynx[8-20].

In this study, we genotyped the *T393C SNP* in a Han population to evaluate the effect of this polymorphism on lung cancer prognosis. Our purpose was to determine whether the common *GNAS1 T393C* polymorphism can be used as a predictive factor for survival in NSCLC patients.

MATERIALS AND METHODS

Patients and clinical samples

Two milliliters of peripheral blood samples were collected from patients diagnosed with advanced NSCLC pathologically before any antineoplastic treatment at Renmin Hospital of Wuhan University (China) between March 2010 and March 2012. Patients were chosen based on the following criteria: (1) histologically confirmed UICC (2009) stage ⅢB or Ⅳ NSCLC; (2) Eastern Cooperative Oncology Group performance status (PS) score of 2 or less; and (3) life expectancy of more than 3 mo. Patients were not included if they had received any anti-tumor therapy previously. All patients were asked to sign the informed consent before they were included in the database. The study cohort (94 patients; for clinicopathological data, Table 1) composed exclusively of patients with a meticulously complete follow-up record. This study was performed following the guidelines of the local research ethics committee.

DNA extraction and genotyping

Genomic DNA was isolated from whole blood samples using the QIAamp kit (Qiagen, Germany). *T393C* SNP (dbSNP rs7121) was amplified by polymerase chain reaction (PCR) with the following primers: 5'-CAGCCCACATTAGGGAGCATAT-3' (forward) and 5'-TAATCCCTGCCTATGCTCACGA-3' (reverse). After denaturation at 95 ℃, 50 cycles of DNA amplification was done using $(NH4)_2SO_4$ containing buffer (Bioron, Germany) at 95 ℃ for 60 s, 60 ℃ for 30 s, and 70 ℃ for 60 s. The 807-bp PCR product was genotyped according to their sequences.

Statistical analysis

The software SPSS 17.0 was used for statistical analyses in this study. Descriptive statistics were applied to describe patients' baseline characteristics. The correlation between *T393C* genotypes and the clinical outcome was evaluated by Kaplan-Meier plots and the log-rank test. The survival time was calculated from the date of the primary diagnosis to the end of follow-up or date of death, whichever occurred first. The independent influence of *T393C* SNP and other covariates on survival rates was assessed in multivariate analysis using the Cox regression hazard model. *P* values < 0.05 were considered statistically significant. The compatibility with the Hardy-Weinberg equilibrium was calculated with HWE program (http://linkage.rockefeller.edu/ott/linkutil.htm).

RESULTS

Analysis of GNAS1 T393C genotypes and associated clinicopathological features

The clinicopathological characteristics of patients with genotype distribution are shown in Table 1. There were 94 advanced NSCLC patients participating in this study, including 23 women and 71 men. The average age of participants was 58.6 years (range, 31 to 80 years).

Among 94 patients, 38 (40%) displayed a TT genotype, 29 (31%) with a CT genotype and 27 (29%) with a CC genotype. In the entire patient group, the frequency of the C allele (fC) was 0.55. The distribution was compatible with the Hardy-Weinberg equilibrium. There was no significant correlation between the *GNAS1 T393C* genotypes and clinicopathological parameters, such as age ($P = 0.48$), gender ($P = 0.42$), PS ($P = 0.30$), smoking status ($P = 0.44$) or pathology ($P = 0.59$) (Table 2). Further analysis showed that there was no significant correlation of overall survival (OS) with age ($P = 0.135$), gender ($P = 0.0580$), PS ($P = 0.658$), smoking ($P = 0.473$), pathology ($P = 0.559$), or treatment mode ($P = 0.116$).

Table 1 Clinicopathological characteristics of 94 patients with non-small cell lung cancer

	Subgroup	*n*	MST	1-yr OS (%)	2-yr OS (%)	*P*
Gender	Male	71	14	59	36	0.058
	Female	23	13	53	28	
Age	⩾ 60 yr	51	13	61	26	0.135
	< 60 yr	43	16	52	36	
PS	⩾ 2	25	13	51	25	0.658
	< 2	69	17	64	32	
Smoking	Yes	23	13	55	29	0.473
	No	71	14	58	32	
Pathology	Adenocarcinoma	48	13	54	36	0.559
	Squamous cell carcinoma	46	14	63	29	
Treatment	Supportive treatment only	12	10	49	25	0.116
	Chemotherapy	14	13	56	32	
	Radiotherapy	11	13	60	30	
	Chemoradiotherapy	57	16	64	35	
GNAS1 T393C	TT	38	25	76	48	0.01
	TC	29	12	54	18	
	CC	27	8	23	15	
	TC + CC	56	11.5	25	16	0.01

OS: Overall survival; PS: Performance status.

Table 2 Association between *GNAS1 T393C* single nucleotide polymorphism and clinical parameters

	Subgroup	All (*n* = 94)	TT (*n* = 38; 40%)	TC (*n* = 29; 31%)	CC (*n* = 27; 29%)	*P*
Gender	Male	71	31 (43.6)	22 (30.9)	18 (25.5)	0.42
	Female	23	7 (30.4)	7 (30.4)	9 (39.2)	
Age	⩾ 60 yr	51	22 (43.1)	13 (25.5)	16 (31.4)	0.48
	< 60 yr	43	16 (37.2)	16 (37.2)	11 (25.6)	
Performance status	⩾ 2	25	13 (52.0)	5 (20.0)	7 (28.0)	0.30
	< 2	69	25 (36.2)	24 (34.8)	20 (29.0)	
Smoking	Yes	23	12 (52.2)	6 (26.1)	5 (21.7)	0.44
	No	71	26 (36.6)	23 (32.4)	22 (31.0)	
Pathology	Adenocarcinoma	48	19 (39.6)	17 (35.4)	12 (25.0)	0.59
	Squamous cell carcinoma	46	19 (41.3)	12 (26.1)	15 (32.6)	

GNAS1 T393C TT genotype predicts favorable survival

The median survival of carriers of TT, CT and CC genotypes was 25, 12, and 8 mo, respectively. We analyzed the relationship between overall survival rate and *T393C* genotypes using Kaplan-Meier survival curves. Our data showed that the favorable *TT* genotype was significantly associated with better OS (2-year OS: 48%; $P = 0.01$) when compared with the other genotypes. For example, the 2-year OS for CT genotype was 18% and 15% for CC genotype (Figure 1). By applying the multivariate Cox proportional hazards model, we found that *GNAS1 T393C* polymorphism was independently associated with OS after adjusting the clinicopathological factors ($P < 0.05$). However, the dichotomization between C-genotypes (CC + CT) and T-genotypes (TT) indicated significant lower survival rates for C-allele carriers ($P = 0.01$), which had a 2-year OS rate of 16% (Figure 2).

DISCUSSION

Lung cancer is the major cause of cancer death in the world and there is an urgent need to accurately and individually treat patients with lung cancer. Although clinicopathological parameters such as UICC stage may serve as prognostic markers in lung cancer, it is still desirable to develop more reliable and accurate biomarkers to more precisely predict the clinical outcome of individual patients. Most prognostic biomarkers are developed according to the features of the tumor tissue itself. The *GNAS1* gene encodes the Gαs subunit of G protein and it has been shown that the *GNAS1 T393C* polymorphism correlates with lung cancer[20]. Hence, we investigated whether *GNAS1 T393C* polymorphism can be used to predict the clinical outcome in patients with NSCLC. Our study clearly indicated that the homozygous TT genotype patients had a much higher survival rate than patients with either homozygous CC or heterozygous CT genotype. If we could identify patients with poor clinical outcome, we might develop novel treatment strategies accordingly at the initial stage of management, which could lead to improved individual therapy strategies with higher survival rates. Meanwhile, our results also indicated the potential role of the *GNAS1 T393C* polymorphism as a possible general genetic marker for tumor progression and survival since T-allele carriers demonstrated better clinical outcome than C-allele carriers (TC and CC genotypes). However, it should be noted that the connection between *GNAS1 T393C* polymorphism and survival was

Table 3 The effect of *GNAS1 T393C* on distinct carcinomas

Author	Year	Cancer type	All	Genotype	*n*	OS (%)	Benefit	*P*
Alakus	2009	Gastric cancer	122	TT	26	56.9	TT	0.043
				TC	57	32.7		
				CC	39	42.6		
Schmitz	2007	Cholangiocarcinoma	87	TT	15	10	C+	0.04
				TC	41	17		
				CC	31	18		
Lehnerdt	2008	Laryngocarcinoma	157	TT	40	76	TT	0.037
				TC	75	49		
				CC	42	43.5		
Frey	2006	Chronic lymphocytic leukemia	144	TT	27	73	T+	0.013
				TC	72	63.3		
				CC	45	33.2		
Vashist	2011	Esophageal cancer	190	TT	38	19	CC	0.001
				TC	96	15		
				CC	56	51		
Frey	2005	Bladder cancer	254	TT	49	82	TT	0.015
				TC	121	60		
				CC	84	58		
Frey	2006	Renal cancer	150	TT	34	91	TT	0.01
				TC	79	81		
				CC	37	69		
Frey	2005	Colorectal cancer	151	TT	36	87.8	TT	0.009
				TC	72	71		
				CC	43	50		
Otterbach	2007	Breast cancer	279	TT	64	23	CC	0.01
				TC	162	40		
				CC	53	63		
Lehnerdt	2008	Oral carcinoma	202	TT	48	51.3	TT	0.015
				TC	89	44.7		
				CC	65	36.8		
Kaderi	2008	Chronic lymphocytic leukemia	279	TT	80	65	NS	0.802
				TC	115	70		
				CC	84	64		
Frey	2010	Malignant melanoma	328	TT	69	87.1	TT	0.017
				TC	149	NS		
				CC	110	66		
Xie	2013	Non-small cell lung cancer	131	TT	33	NS	TT	0.02
				TC	63	NS		
				CC	35	NS		

OS: Overall survival.

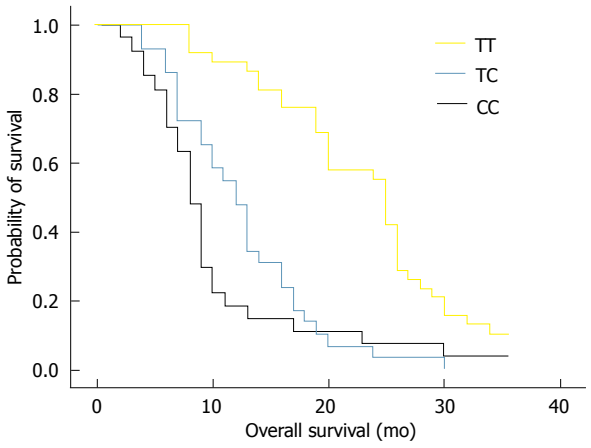

Figure 1 The overall survival of 94 lung cancer patients according to *GNAS1 T393C* genotypes. The data were analyzed by Kaplan-Meier analysis, $P < 0.01$, TT genotype *vs* other genotypes.

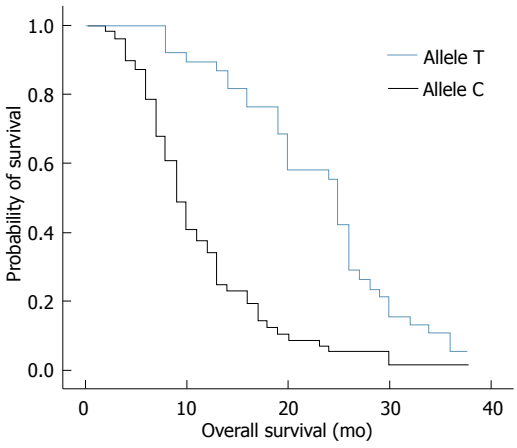

Figure 2 The overall survival of 94 lung cancer patients according to *GNAS1 T393C* genotype with dichotomization between C+ and C- genotypes, $P < 0.01$.

different in different types of tumors. For some tumors, TT genotype was significantly correlated with better OS compared with CT or CC genotype. For example, in advanced squamous cell carcinoma of the larynx, the five-

year survival rate for TT genotype patients was 76%, 49% for TC genotype, and 43.5% for CC genotype[10]. Also, it had been reported that the five-year survival rate of sporadic colorectal cancer patients with a TT genotype (87.8%) was much higher than that of patients with a TC (71.0%) or CC genotype (50.0%)[15]. On the other hand, in intrahepatic cholangio-carcinoma[9], esophageal cancer[12] and breast cancer[16], the patients with a CC genotype had a more favorable clinical outcome (Table 3). Thus, it was conceivable that the *GNAS1 T393C* polymorphism in various tumor types had different biological effects. In order to understand the significance of the T393C genotypes in different tumor types, further more studies are needed to clarify the molecular mechanisms.

In vitro studies demonstrated that increased Gαs expression promotes apoptosis[21]. Therefore, it is highly likely that increased Gαs expression and the subsequently increased apoptosis could be associated with better survival rate in patients with a GANS1 *TT* genotype. *In vitro* experiments also suggest that the product of Gαs, cyclic AMP, could play a crucial role in the proapoptotic process. It has been reported that increasing the intracellular concentration of cyclic AMP leads to enhanced apoptosis in several cell lines including lymphoma cells[5], leukemic[22] and ovarian cancer cells[23]. Gαs was also found to be differentially expressed between various *GNAS1 T393C* genotypes. Previous studies have suggested that Gαs transcription level is increased in individuals with a *GNAS1 393 TT* genotype[13]. Intriguingly, the mRNA stability has been shown to be determined by the coding region of some genes[24-26]. Using the MFOLD (the software for the prediction of the secondary structure of single stranded nucleic acids), Alakus *et al*[8] have reported that the substitution of T393 to C affects the structure of mRNA, most likely the mRNA folding.

Several biomarkers have been used as predictive and prognostic markers for NSCLC patients. A prognostic biomarker is a molecule that can be used to indicate the patient survival independent of the treatment received. In other words, it is an indicator of the innate tumor aggressiveness. For example, KRAS mutations can serve as a good prognostic biomarker indicating the poor survival for NSCLC patients when compared with the patients without KRAS mutations, independent of therapy. Xie *et al*[20] has reported that the *GNAS1 T393C* polymorphism can somehow predict the chemotherapy sensitivity and overall survival rate in advanced NSCLC patients treated with gemcitabine and platinum[20]. Here, our data clearly showed that the *GNAS1 T393C* TT genotype was prognostic of better overall survival for NSCLC patients, independent of therapy.

Nevertheless, it should be emphasized that in this study, we only investigated a small population of patients. Although our study indicated that genetic host factors play a role in tumor progression, which was consistent with the previously published data[20], further independent studies of large cohorts are necessary to confirm the reliability of our findings. Furthermore, the molecular mechanisms underlying the significance of the *GNAS1 T393C* genotype associated with potentially surrogate SNPs remain to be explored.

COMMENTS

Background

Lung cancer is major cause of cancer death around the world. Although some clinicopathological parameters like UICC stage may be used as prognostic biomarkers in lung cancer, other reliable markers that can help precisely predict the clinical outcome of individual patients are still desirable. Most prognostic biomarkers are based on features of the tumor tissue itself.

Research frontiers

Characterization of single nucleotide polymorphisms (SNPs) as a prognostic biomarker in cancer has become the hotspot of recent research. The *T393C* polymorphism of the *GNAS1* gene is one such polymorphism.

Innovations and breakthroughs

Several molecular markers have been used as predictive and prognostic markers for non-small cell lung cancer (NSCLC). A prognostic biomarker is a biomolecule that can be used to indicate the patient survival independent of the treatment received. It can also indicate for the innate tumor aggressiveness. For example, the KRAS mutations are prognostic of poor survival for NSCLC patients when compared to the absence of KRAS mutations, independent of therapy. Xie *et al* reported that the *GNAS1 T393C* polymorphism can be used to predict the chemotherapy sensitivity as well as the survival rates in advanced NSCLC patients treated with gemcitabine and platinum. Here, the data clearly indicate that the *GNAS1 T393C* TT genotype was prognostic of better survival rates for NSCLC patients, independent of therapy.

Applications

The identification of patients with high-risk lung cancer could help develop novel and individual treatment strategies and could improve the clinical outcome. This data clearly indicate that genetic polymorphism in the *GNAS1 T393C* influenced survival in advanced non-small lung cancer with a worse clinical outcome for C allele patients.

Terminology

SNPs refer to a DNA sequence variation occurring commonly within a population (*e.g.*, 1%) in which a single nucleotide -A, T, C or G - in the genome (or other shared sequence) differs between members of a biological species or paired chromosomes.

Peer review

The manuscript is comprehensive and important.

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