Received: 21 July 2020 | Revised: 11 October 2020 | Accepted: 13 October 2020

DOI: 10.1002/mgg3.1541

Molecular Genetics & Genomic Medicine Open Access WILEY

ORIGINAL ARTICLE

Association of long noncoding RNA *MALAT1* polymorphisms with gastric cancer risk in Korean individuals

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Funding information
This work was supported by the research fund of Chungnam National University, by the National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIP) (NRF-2016R1D1A3B03936067), and by the Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education (NRF-2017R1D1A1B04033515, NRF-2018R1D1A1B07050285, and NRF-2019R1F1A1063469).

Abstract

Background: Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) drives tumorigenesis of various human cancers. However, the association between *MALAT1* variants and gastric cancer (GC) risk is unknown. We performed a case-control study to evaluate the possible association between rs619586 and rs3200401 SNPs in *MALAT* and GC risk.

Methods: Samples from 458 patients with GC and 381 controls were genotyped using the TaqMan genotyping assay.

Results: In stratified analyses, we observed that rs3200401 CT in the codominant model and CT+TT in the dominant model were associated with increased GC risk in male patients (CT: odds ratio [OR] = 1.81, 95% confidence interval [CI] = 1.09–3.01, $p = 0.022$; CT+TT: OR = 1.74, 95% CI = 1.07–2.83, $p = 0.026$), and the differentiated (CT: OR =1.79, 95% CI = 1.18–2.73, $p = 0.007$; CT+TT: OR = 1.76, 95% CI = 1.17–2.64, $p = 0.007$), and intestinal (CT: OR = 1.67, 95% CI = 1.11–2.49, $p = 0.013$; CT+TT: OR = 1.68, 95% CI = 1.14–2.47, $p = 0.009$) GC subgroups.

Conclusion: *MALAT1* rs3200401 increases GC susceptibility and might affect GC development. Further studies are needed to validate our results in large populations and different ethnic groups.

KEYWORDS

case-control study, gastric cancer, long noncoding RNA, metastasis-associated lung adenocarcinoma transcript 1, single-nucleotide polymorphism

Jang Hee Hong and Eun-Heui Jin contributed equally to this work.

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1 | INTRODUCTION

Gastric cancer (GC) was the fifth most common cancer and the third leading cause of cancer-related deaths worldwide in 2018. Although GC incidence and mortality rates have decreased in recent decades, the rates remain high in Asia. In Korea, GC is the third most common cancer, with 30,504 new cases and 8264 deaths recorded in 2016 (Bray et al., 2018; Jung et al., 2019). Long noncoding RNAs (lncRNAs) are non-translated RNAs longer than 200 nucleotides. They play pivotal roles in tumorigenesis as proto-oncogenes (Li et al., 2009, 2014) and tumor suppressors (Zhao et al., 2015, 2016) that regulate cell proliferation, invasion, and metastasis (Cruickshanks et al., 2013; Gupta et al., 2010; Liu et al., 2015; Qiu et al., 2015; Zhao et al., 2015, 2016). Recently, genome-wide association studies have demonstrated that a number of single-nucleotide polymorphisms (SNPs) in lncRNAs are related to cancer susceptibility (Cheetham et al., 2013; Chen et al., 2013). According to recent genome-wide association studies, disease-related SNPs are located in noncoding regions consisting of intronic, intergenic, and regulatory regions (Freedman et al., 2011; Hindorff et al., 2009). SNPs in the regulatory regions of lncRNAs affect lncRNA expression by enhancing or disrupting the binding of transcription factors to DNA (Guo et al., 2016; Huang et al., 2014).

Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) is an intergenic lncRNA >800 nucleotides in length located on chromosome 11q13. *MALAT1* was first identified as a prognostic marker for non-small-cell lung cancer (NSCLC), and is associated with NSCLC metastasis (Ji et al., 2003). Multiple studies have demonstrated that aberrant expression of *MALAT1* is involved in the proliferation, migration, invasion, and metastasis of several human cancers, such as breast cancer (BC), hepatocellular carcinoma (HCC), GC, and esophageal squamous cell carcinoma (ESCC) (Ellis et al., 2012; Hu et al., 2015; Lai et al., 2012; Okugawa et al., 2014). Moreover, recent studies have shown that genetic variations in *MALAT1* are associated with the risk of various cancers, including colorectal cancer (CRC), NSCLC, BC, papillary thyroid cancer (PTC), ESCC, and HCC (Li et al., 2017; Peng et al., 2018; Qu et al., 2019; Wang et al., 2017; Wen et al., 2019; Yuan et al., 2019). Recent evidence in the context of GC has shown that plasma levels of *MALAT1* are higher in patients with GC with distant metastases than in those with no metastases and healthy controls; that upregulated *MALAT1* expression enhances the proliferation, migration, and invasion of GC cells through the phosphoinositide 3-kinase/protein kinase B pathway (PI3K/AKT); and that *MALAT1* promotes metastasis by suppressing tumor suppressor protocadherin 10 (*PCDH10*) via targeting by the *MALAT1–EZH2* complex (Xia et al., 2016; Zhu et al., 2019). Although a number of control-case studies have evaluated possible associations between lncRNA SNPs and GC risk, no studies have reported an association between an SNP in *MALAT1* and GC risk.

We hypothesized that *MALAT1* SNPs might affect genetic susceptibility to GC. Therefore, we performed a case-control study to explore the association between SNPs in *MALAT1* and GC risk in a Korean population. We further evaluated the impact of *MALAT1* SNPs on GC risk in combination with various characteristics and clinical features, including age, sex, tumor differentiation, histologic type, T classification, lymph node metastasis (LNM), and tumor stage.

2 | MATERIALS AND METHODS

2.1 | Study subjects

This case-control study population consisted of 458 GC patients and 381 controls. GC patients were recruited from the outpatient clinic at the Chungnam National University Hospital and classified according to Lauren's classification (Lauren, 1965). The control group was randomly selected among healthy volunteers visiting the Chungnam National University Hospital; only individuals who had no history of cancer were included. The blood samples used in this study were provided by the Chungnam National Hospital Biobank, a member of the National Biobank of Korea, which is supported and audited by the Ministry of Health and Welfare of Korea. All individuals enrolled in this study provided written informed consent before blood collection. This study was approved and reviewed by the Ethics Committee of the institutional review board of Chungnam National University Hospital (IRB#201707023).

2.2 | SNP selection and genotyping

Two SNPs (rs619586 and rs3200401) in *MALAT1* were selected based on previously reported to be associated with cancer risk (Peng et al., 2018; Qu et al., 2019; Wang et al., 2017; Wen et al., 2019; Yuan et al., 2019). Genomic DNA was isolated from peripheral blood samples of all subjects using the QIAamp DNA Blood Mini Kit (Qiagen GmbH), according to the manufacturer's instructions. *MALAT1* rs619586 and rs3200401 SNPs were genotyped by the Applied Biosystems TaqMan SNP Genotyping Assay using predesigned primer/probe sets (assay ID C_1060479_10 and C_3246069_10, respectively). PCR was performed using the StepOnePlus Real-time PCR System (Applied Biosystems) according to the following conditions: one cycle at 95°C for 10 min; 45 cycles at 92°C for 15 s and 60°C for 90 s.

2.3 | Statistical analysis

Hardy Weinberg equilibrium (HWE) for each SNP in the control groups was assessed using the Chi-square *t*-test. Linkage disequilibrium (LD) between SNPa pair was analyzed by calculating D′ and r^2 values obtained using Haploview software version 4.0 (the Broad Institute). Differences in age and gender between the GC and control groups were calculated using the two-sided Pearson chi-square test and the Mann–Whitney *U*-test. The association was analyzed with three genetic models, including codominant (ht or mt vs. wt), dominant (ht + mt vs. wt), and recessive (mt vs. wt + ht) models. A binary logistic regression was used to estimate the GC risk according to odds ratios (ORs) and 95% confidence intervals (CIs). The association analysis was adjusted by age and sex, which were included in the model as covariates. Stratified analyses by age, gender, and clinical features (Tumor differentiation, histological type, LNM, T classification, and tumor stage) were performed. All statistical analyses were performed using the SPSS (SPSS Inc.), version 20.0 for Windows. $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the study subjects

The characteristics and clinical features of the 458 patients with GC and the 381 controls are shown in Table 1. There were significant differences in the age and sex distributions of the GC group and control group ($p < 0.001$ and $p < 0.001$, respectively). The mean age was 65.2 ± 10.1 years for the patients and 55.6 ± 10.9 years for the controls. The proportion of male subjects (70.1%) was higher than that of female

TABLE 1 Characteristics and clinical features of the GC and control groups

	Gastric cancers	Controls	
Variables	***N*** **(%)**	***N*** **(%)**	***p***
Age (years) (mean ± SD)	458 (65.2 ± 10.1)	381 (55.6 ± 10.9)	<0.001[a]
<60	198 (43.2)	197 (51.7)	0.014[b]
≥60	260 (56.8)	184 (48.3)	
Gender (%)			
Male	321 (70.1)	122 (32.0)	<0.001[b]
Female	137 (29.9)	259 (68.0)	
Tumor differentiation			
Differentiated	222 (48.5)		
Undifferentiated	195 (42.6)		
Missing	41 (8.9)		
Histological type (%)			
Intestinal	259 (56.6)		
Diffuse	145 (31.7)		
Mixed	54 (11.7)		
T classification (%)			
T1	233 (50.9)		
T2	66 (14.4)		
T3	16 (3.5)		
T4	143 (31.2)		
Lymph node metastasis (%)			
Negative	283 (61.8)		
Positive	175 (38.2)		
Tumor stage (%)			
I (A + B)	273 (59.6)		
II (A + B)	54 (11.8)		
III (A + B + C)	131 (28.6)		

Abbreviation: SD, standard deviation.

[a]Mann–Whitney *U*-test.

[b]Two-sided Pearson χ^2 test.

subjects (29.9%) in the GC group, whereas the percentage of female subjects (68.0%) was higher than that of male subjects (32.0%) in the control group (67.2%). The majority of the GC patients was classified into differentiated tumor (48.5%), intestinal type (56.6%), T1 (50.9%), LNM-negative (61.8%), and tumor stage I (59.6%).

3.2 | Association of SNPs with GC risk

To evaluate associations between *MALAT1* SNPs and GC risk, we genotyped rs619586 and rs3200401 SNPs in *MALAT1*, which have previously reported association with cancers. The distributions of the rs619586 and rs3200401 genotypes in the control group were in HWE ($p = 0.906$ and $p = 0.908$, respectively). LD coefficients (|D′|) were estimated for two SNPs, and an absolute LD (|D′| =1 and r^2) was not found for any pair-wise combination of the two SNPs using Haploview 4.0 software. We used three genetic models to determine if the rs619586 and rs3200401 SNPs were associated with GC risk. However, there was no significant association between rs619586 and rs3200401 in *MALAT1* and GC risk (Table 2).

3.3 | Stratification analysis for rs619586 and rs3200401 SNPs

As shown in Tables 3 and 4, we performed stratified analyses based on various clinical features, including age, gender, LNM, T classification, and tumor stage, to further evaluate possible associations between the rs619586 and rs3200401 SNPs and GC risk in the GC subgroups. After adjusting for age and gender, in a stratified analysis by gender, rs3200401 showed significant associations with increased GC risk in the GC male subgroup in the codominant (CT) and dominant (CT + TT) models when compared with the CC genotype (OR = 1.81, 95% CI = 1.09–3.01, $p = 0.022$ and OR = 1.74, 95% CI = 1.07–2.83, $p = 0.026$, respectively). In a stratified

TABLE 2 Genotype and allele frequencies of *MALAT1* polymorphisms in subjects and their associations with GC risk

	CON	GC	GC vs. CON	
Genotype	***N* (%)**	***N* (%)**	**AOR (95% CI)[a]**	***p*[a]**
rs619586				
Codominant				
AA	334 (87.7)	396 (86.5)	1	
AG	46 (12.1)	59 (12.8)	0.95 (0.61-1.49)	0.836
GG	1 (0.3)	3 (0.7)	2.82 (0.26-31.07)	0396
Dominant				
AA	334 (87.7)	396 (86.5)	1	
AG + GG	47 (12.3)	62 (13.5)	1.05 (0.66-1.66)	0.848
Recessive				
AA + AG	380 (99.7)	455 (99.3)	1	
GG	1 (0.3)	3 (0.7)	3.84 (0.35-42.21)	0.272
HWE	0.906	0.886		
rs3200401				
Codominant				
CC	280 (73.5)	312 (68.1)	1	
CT	92 (24.1)	133 (29.0)	1.32 (0.94-1.85)	0.104
TT	9 (2.4)	13 (2.9)	1.38 (0.53-3.54)	0.496
Dominant				
CC	280 (73.5)	312 (68.1)	1	
CT + TT	101 (26.5)	146 (31.9)	1.33 (0.96-1.84)	0.088
Recessive				
CC + CT	372 (97.6)	445 (97.1)	1	
TT	9 (2.4)	13 (2.9)	1.28 (0.51-3.26)	0.600
HWE	0.908	0.967		

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; CON, control; GC, gastric cancer; HWE, Hardy-Weinberg equilibrium.

[a]Adjusted for age and gender. The significant results are in bold.

TABLE 3 Stratified analysis of the *MALAT1* SNPs rs619586 and rs3200401 by age and gender in GC patients and controls

	GC vs. CON							
	Codominant (ht/wt)				Dominant (ht+mt/wt)			
Variables	GC	CON	OR (95% CI)[a]	p^a	GC	CON	OR (95% CI)[a]	p^a
rs619586								
Age (years)								
<60	29/169	20/176	1.30 (0.65-2.61)	0.460	29/169	21/176	1.25 (0.62-2.48)	0.534
≥60	30/227	26/158	0.91 (0.49-1.70)	0.771	33/227	26/158	1.01 (0.55-1.86)	0.966
Gender								
Male	48/271	15/107	1.26 (0.68-2.34)	0.470	50/271	15/107	1.31 (0.71-2.44)	0.391
Female	11/125	31/227	0.65 (0.31-1.35)	0.246	12/125	32/227	0.68 (0.34-1.38)	0.288
rs3200401								
Age (years)								
<60	58/134	51/144	1.39 (0.83-2.33)	0.214	64/134	53/144	1.51 (0.91-2.51)	0.108
≥60	75/178	41/136	1.42 (0.88-2.29)	0.155	82/178	48/136	1.30 (0.83-2.05)	0.257
Gender								
Male	98/215	24/95	1.81 (1.09-3.01)	**0.022**	106/215	27/95	1.74 (1.07-2.83)	**0.026**
Female	35/97	68/185	1.03 (0.63-1.67)	0.913	38/97	74/185	1.07 (0.68-1.71)	0.765

Abbreviations: CI, confidence interval; CON, controls; GC, gastric cancer; ht, heterozygous; mt, mutant; OR, odds ratio; wt, wild-type.

[a]Adjusted by age and gender. The significant results are in bold.

analysis by tumor differentiation, rs3200401 was significantly associated with enhanced GC risk in the GC subgroup with differentiated tumors in the codominant (CT) and dominant (CT + TT) models compared with the CC genotype (OR = 1.79, 95% CI = 1.18–2.73, $p = 0.007$ and OR = 1.76, 95% CI = 1.17–2.26, $p = 0.007$, respectively). In addition, according to a stratified analysis by histological type, rs3200401 was significantly associated with increased GC risk in the subgroup with intestinal-type GC in the codominant model (CT) and dominant model (CT + TT) compared with the CC genotype (OR = 1.67, 95% CI = 1.11–2.49, $p = 0.013$ and OR = 1.68, 95% CI = 1.14–2.47, $p = 0.009$, respectively). However, rs619586 showed no significant associations with GC risk in any of the analyses stratified by age, gender, and clinical features.

4 | DISCUSSION

MALAT1 is one of the first lncRNAs identified as a proto-oncogene in early stage NSCLC (Ji et al., 2003), and it promotes cancer proliferation, migration, and metastasis (Bi et al., 2017; Li et al., 2009; Wu et al., 2014). We performed the first investigation of the association between the rs619586 and rs3200401 SNPs in *MALAT1* and GC susceptibility in a Korean population. Although we did not observe statistically significant associations between *MALAT1* rs619586 or rs3200401 and overall GC risk, we found significant associations between rs3200401 and GC risk in stratified analyses by gender, tumor differentiation, and histological type. In our stratified analyses, we found that the rs3200401 CT genotype in the codominant model and the CT + TT genotype in the dominant model were significantly associated with 1.81- and 1.74-times higher GC risk in the male subgroup, 1.79- and 1.76-times higher GC risk in the differentiated GC subgroup, and 1.67- and 1.68-times higher GC risk in the intestinal-type GC subgroup than the wild-type genotype. Furthermore, the rs3200401 CT genotype was associated with the highest GC risk (1.81 times greater than the wild-type genotype) in the male subgroup. Consistent with our results, Qu et al. (2019) showed, through stratified analysis, that the rs3200401 CT, TT, and CT + TT genotypes in the dominant model were associated with increased ESCC risk in the group that never smoked compared with the CC genotype. In contrast to our results, Wang et al. (2017) found that the rs3200401 CT and CT + TT genotypes were associated with decreased risk of death by NSCLC, and Peng at al. (2018) also showed that the CT genotype was associated with decreased BC risk in the subgroup >50 years old compared with the CC + TT genotype. *MALAT1* interacts with serine/argine-rich (SR) proteins thus regulates the alternative splicing of pre-miRNAs (Tripathi et al., 2010). The rs3200401 SNP locates in the region M of *MALAT1* (6008-7011 nts), one of the binding sites to SRSF2 (Miyagawa et al., 2012). The rs3200401 variation may regulate the expression of cancer-related genes thus influence cancer development. Further studies are needed to elucidate the different roles of rs3200401 SNP in different cancers. Wen et al. (2019) and Yuan et al. (2019) evaluated

TABLE 4 Associations of the clinical features of GC with the *MALAT1* rs619586 and rs3200401 SNPs in GC patients and controls

	GC vs. CON							
	Codominant (ht/wt)				Dominant (ht + mt/wt)			
Variables	**GC**	**CON**	**OR (95% CI)[a]**	***p*[a]**	**GC**	**CON**	**OR (95% CI)[a]**	***p*[a]**
rs619586								
Tumor differentiation								
Differentiated	27/193	46/334	0.96 (0.54-1.69)	0.878	28/193	47/334	0.98 (0.56-1.72)	0.937
Undifferentiated	25/169	46/334	1.00 (0.58-1.73)	0.999	27/169	47/334	1.07 (0.63-1.83)	0.799
Histological type								
Intestinal	31/226	46/334	0.91 (0.53-1.57)	0.741	32/226	47/334	0.93 (0.54-1.59)	0.784
Diffuse	19/125	46/334	1.01 (0.56-1.83)	0.971	21/125	47/334	1.12 (0.63-1.98)	0.708
Lymph node metastasis								
Negative	38/243	46/334	1.06 (0.64-1.75)	0.822	40/243	47/334	1.11 (0.68-1.83)	0.671
Positive	21/153	46/334	0.87 (0.48-1.57)	0.640	22/153	47/334	0.89 (0.50-1.59)	0.695
T classification								
T1/T2	37/260	46/334	0.97 (0.58-1.61)	0.902	39/260	47/334	1.04 (0.58-1.87)	0.902
T3/T4	22/136	46/334	1.02 (0.62-1.68)	0.939	23/136	47/334	1.06 (0.60-1.89)	0.842
Tumor stage								
I (A + B)/II (A + B + C)	41/284	46/334	0.98 (0.60-1.61)	0.948	43/284	47/334	1.03 (0.63-1.67)	0.910
III (A + B + C)	18/112	46/334	1.03 (0.55-1.93)	0.925	19/112	47/334	1.06 (0.58-1.97)	0.845
rs3200401								
Tumor differentiation								
Differentiated	73/142	92/280	1.79 (1.18-2.73)	**0.007**	80/142	101/280	1.76 (1.17-2.64)	**0.007**
Undifferentiated	53/138	92/280	1.18 (0.78-1.78)	1.175	57/138	101/280	1.16 (0.77-1.73)	0.481
Histological type								
Intestinal	82/168	92/280	1.67 (1.11-2.49)	**0.013**	91/168	101/280	1.68 (1.14-2.47)	**0.009**
Diffuse	38/104	92/280	1.20 (0.76-1.89)	0.436	41/104	101/280	1.19 (0.76-1.85)	0.349
Lymph node metastasis								
Negative	85/192	92/280	1.43 (0.98-2.09)	0.066	91/192	101/280	1.38 (0.95-1.99)	0.090
Positive	48/120	92/280	1.27 (0.82-1.97)	0.286	55/120	101/280	1.34 (0.88-2.04)	0.172
T classification								
T1/T2	89/204	92/280	1.37 (0.94-1.99)	0.101	95/204	101/280	1.33 (0.93-1.92)	0.123
T3/T4	44/108	92/280	1.33 (0.84-2.10)	0.219	51/108	101/280	1.39 (0.90-2.14)	0.140
Tumor stage								
I (A + B)/II (A + B + C)	99/220	92/280	1.41 (0.98-2.03)	0.067	107/220	101/280	1.38 (0.97-1.96)	0.077
III (A + B + C)	34/92	92/280	1.20 (0.73-1.97)	0.465	39/92	101/280	1.26 (0.78-2.01)	0.345

Abbreviations: CI, confidence interval; CON, controls; GC, gastric cancer; ht, heterozygous; mt, mutant; OR, odds ratio; wt, wild-type.

[a]Adjusted by age and gender. The significant results are in bold.

possible associations between rs3200401 and PTC and HCC risks, respectively, but found no associations. Moreover, we found no association between rs619586 and GC risk, even in stratified analyses. However, in contrast to our results, four studies observed an association between rs619586 and cancer risk. Peng et al. (2018) found that the rs619586 AG and AG + GG genotypes were associated with decreased BC risk, Wen et al. (2019) found that the rs619586 GG genotype was associated with decreased PTC risk, Qu et al. (2019) observed that the rs619586 GG genotype was associated with decreased risk of ESCC in the subgroup that never drank alcohol, and Yuan et al. (2019) showed that the rs619586 AG and AG + GG genotypes were associated with decreased risk of HCC in the subgroup of patients <55 years old.

There were a few limitations to our study. First, the sample size was too small to have statistical power for the stratification analysis. Second, cases and controls were not matched on age and gender. Therefore, binary logistic regression models with adjustment for age and gender were used to reduce the effect of covariate. Third, we failed to explore the association between the SNPs and other clinical features, such as *Helicobacter pylori* infection, smoking, and drinking, due to a lack of data from both the GC and control groups. Finally, our findings cover only a specific ethnic group.

In conclusion, we suggest that the *MALAT1* rs3200401 SNP is associated with increased GC risk in male patients, and those in the differentiated and intestinal tumor subgroups. The SNP may contribute to GC development as a proto-oncogene by altering *MALAT1* expression, as has been observed in other cancers. Further studies are required to validate our findings in large populations and different ethnic groups.

ACKNOWLEDGMENTS

This work was supported by the research fund of the Chungnam National University, by the National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIP) (NRF-2016R1D1A3B03936067), and by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2017R1D1A1B04033515, NRF-2018R1D1A1B07050285, and NRF-2019R1F1A1063469).

CONFLICT OF INTEREST

The authors have declared that no competing interest exists.

AUTHOR'S CONTRIBUTIONS

Sung JK, Hong JH, and Jin EH concepted and designed the research; Chang IA and Kang H performed the experiments; Lee SI contributed the selection of subjects and clinical data acquisition; Jin EH and Chang IA performed the data and statistical analysis; Sung JK, Lee SI, Hong JH, and Jin EH contributed to writing and revision of the manuscript.

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How to cite this article: Hong JH, Jin EH, Chang IA, Kang H, Lee SI, Sung JK. Association of long noncoding RNA *MALAT1* polymorphisms with gastric cancer risk in Korean individuals. *Mol Genet Genomic Med*. 2020;8:e1541. https://doi.org/10.1002/mgg3.1541