



## Research Article

# Genetic Polymorphisms of Vascular Endothelial Growth Factor (VEGF) -2549 I/D and +405G/C in the susceptibility to Gastric Cancer

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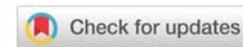
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## Abstract

**Objective:** Vascular Endothelial Growth Factor (VEGF) plays an important role in tumor angiogenesis. Although several studies revealed on association of VEGF polymorphisms with gastric cancer, still the results are inconclusive. The role of (VEGF) -2549 I/D and +405G/C polymorphisms in gastric cancer of Telangana Population is evaluated in the present study.

**Methods:** A case control study was carried out on 540 individuals which comprised of 180 Gastric Cancer patients and 360 healthy control subjects. The association of functional single nucleotide polymorphisms (SNPs) of the VEGF gene (-2549 I/D and +405G/C) were evaluated by polymerase chain reaction followed by restriction fragment length polymorphism (PCR-RFLP).

**Results:** VEGF -2549 polymorphism with I/D and I/I genotypes showed a threefold higher risk (95%CI= 1.75-4.63 and 95%CI= 1.72-5.78) to gastric cancer. A significant association was observed with respect to I allele (AOR= 1.67; 95%CI= 1.29-2.15; P= 7.641e-05) while genotypic and allelic frequencies of VEGF +405G/C polymorphism did not show any significant differences in both the groups. A significant increase in the frequency of I-G haplotype in Gastric cancer cases was observed compared to control with an AOR of 2.23 (95%CI= (1.51-3.27); P= 0.0001).

**Conclusion:** In conclusion VEGF -2549I/D polymorphism and I-G haplotype conferred significant susceptibility towards gastric cancer, whereas, no such association with respect to +405G/C polymorphism was observed.

## Introduction

Gastric Cancer (GC) of the digestive tract is the third leading cause of carcinoma related deaths worldwide [1]. Gastric cancer is a multifactorial disease associated with various risk factors like tobacco chewing, smoking, alcohol consumption, diet, Helicobacter pylori infection and gastric disorders [2]. Genetic factors play a role in the susceptibility to gastric cancer [3-6], where in Single Nucleotide Polymorphisms (SNPs) of various genes may be causal in the onset of gastric cancer. Angiogenesis is the prerequisite for the growth and progression of tumours with micro invasions. Vascular Endothelial

Growth Factor (VEGF) known to influence tumour-related angiogenesis [7,8]. The VEGF gene is located on chromosome 6p12-p21 with eight exons [9,10]. Earlier studies have reported an increase in the expression of VEGF to be associated with the grade of angiogenesis and prognosis of various human cancers [11-14]. However, studies investigating the role of VEGF gene polymorphisms in the outcome of gastric cancer are inconclusive. The present study is taken up to elucidate the role of -2549 Insertion/Deletion polymorphism in the promoter region and +405G/C polymorphism in 5' UTR of VEGF gene towards the susceptibility of gastric cancer.

## Materials and methods

### Study subjects

A case control study was carried out on 180 Gastric Cancers and 360 healthy control subjects with no family history of gastric cancer. Gastric Cancer cases were recruited from the Gastroenterology Department of Osmania General Hospital, Hyderabad. The study included primary Gastric cancer cases which were diagnosed by Upper Gastrointestinal Endoscopy (UGIE) and confirmed by histopathological examination. Lymphoma, other multiple organ malignancies, recurrent gastric tumor and patients with active treatment were excluded from the study. Informed consent was obtained from all the study subjects. The study was approved by Institutional Research Ethics Committee of Institute of Genetics and Hospital for Genetic Diseases. Information on epidemiology such as age, sex, smoking and alcohol consumption was collected using a structured questionnaire.

### Genotyping by PCR – RFLP and ARMS PCR

Total genomic DNA was isolated from peripheral blood leukocytes by the salting out method of Lahiri and Nuernberger [15]. The VEGF -2549I/D polymorphism was genotyped by Polymerase Chain Reaction (PCR) using allele specific primers. Forward primer 5'-GCTGAGAGTGGGGCTGACTAGGTA-3' and Reverse primer 5'-GTTTCTGACCTGGCTATTCCAGG-3' [16]. The PCR products were separated by agarose gel electrophoresis, wherein a 229 bp (I allele with the 18-bp insertion) and 211 bp (D allele with no insertion) fragments were obtained. Similarly, +405G/C polymorphism was genotyped by PCR-RFLP method using forward primer 5'-CAGGTCACCTACTTTGCCCGGTC-3' and reverse primer 5'-GCTTGCCATTCCCACTTGAATCG-3'. The obtained PCR product of 204 bp was digested by *Ava*II restriction enzyme which showed a 185 and 19bp fragment for G allele whereas, a 204bp fragment representing to C allele respectively.

### Statistical analysis

Statistical significance of the differences in the genotype frequencies between the gastric cancer cases and controls was determined by multiple logistic regression under different genetic models (i.e. co-dominant, recessive, dominant and log-additive) of inheritance using R version 3.3.1 and R package "SNPassoc." The Adjusted Odds Ratios (AORs) and corresponding 95% Confidence Intervals (CIs) were obtained after controlling confounding factors including age, gender, smoking, tobacco chewing and alcohol consumption. The Akaike Information Criterion (AIC) was adopted to determine the best-fit genetic model. The p-values obtained from MLR were adjusted for false discovery rate of BH method [17]. The observed genotype frequencies in the controls and cases were tested for Hardy-Weinberg Equilibrium (HWE) to ensure the independent distribution of the alleles in the sample and to rule out any genotyping errors. Haplotype analysis was performed using Haploview (version 4.2) software to understand the nature of the cosegregation of polymorphisms in gastric cancer. Most frequent haplotype was selected as reference

category and rare haplotype groups whose frequency <0.001 were eliminated from the study. The association analysis of haplotypes was shown as Odds Ratios (OR) and 95%CI. The adjusted odds ratio was calculated for each haplotype to know the true association by eliminating the effects of covariates (i.e. age, sex, and addictions). All 'p' values were two-tailed and the significance level at 5% was taken into consideration.

## Results

A total of 540 subjects comprising of 180 Gastric cancer patients and 360 controls were included in the study. Demographic data of gastric cancer patients and control subjects are given in Table 1. The patient group comprised of 128 (71.1%) males and 52 (28.9%) females while the control group constituted 222 (61.7 %) males and 138 (38.3 %) females. A 1.9-fold risk for gastric cancer in males was observed. The study group was subdivided into 3 age groups early ( $\leq 45$  years), middle (46-60 years) and late (>60 years). Increased risk of gastric cancer was observed in middle age group (AOR (95%CI) = 1.71 (1.09-2.68);  $p = 0.020$ ) followed by late onset (AOR (95%CI) = 2.11 (1.29-3.47);  $p = 0.003$ ) age groups. The percentage of smokers in gastric cancer was 51.1%, and 26.4% in control group revealing a 2.01-fold increased risk to gastric cancer compared to non-smokers (AOR (95%CI) = 2.01 (1.23-3.29);  $p = 0.005$ ). 36.1% of tobacco chewers were afflicted with gastric cancer compared to controls of 21.4%, showing a 2.12-fold increased risk (AOR (95%CI) = 2.12 (1.39-3.22);  $p < 0.000$ ). The percentage of alcohol consumers in gastric cancer group was 52.2% whereas in control subjects it was 28.9% showing 1.79-fold risk for alcoholics compared to non-alcoholics (AOR (95%CI) = 1.76 (1.08-2.86);  $p < 0.023$ ).

Distribution of genotypes and allele frequencies of VEGF -2549I/D polymorphism in gastric cancer patients and control group are depicted in Table 2. The genotype frequencies of D/D, I/D and I/I were 34.1%, 59.4% and 21.7% in patients while 36.7%, 49.2% and 14.2% in controls respectively. The frequencies of D and I alleles were 0.49 vs. 0.61 in gastric cancer and 0.51 vs. 0.39 in the control subjects. The distribution of genotypes and alleles differed significantly between the patients and controls. Further logistic regression analysis also corroborated that patients with I/D and I/I genotype had a 2.84-fold higher risk (95%CI= 1.75-4.63) and 3.15-fold (95%CI= 1.72-5.78) to gastric cancer compared with D/D genotype, with the risk being significant for I allele genotypes (AOR= 1.67; 95%CI= 1.29-2.15;  $P = 7.641e-05$ ). Based on the values of Akaike information criterion (AIC), a dominant model with least AIC value was found to be best genotypic model indicating about 2.92-fold (95%CI= 1.83-4.67,  $P = 3.76e-05$ ) increased risk of I allele carriers (I/D + I/I) to gastric cancer. The genotype distribution of VEGF -2549I/D polymorphism showed significant deviation from Hardy Weinberg equilibrium (HWE) in the patient group ( $P = 0.01663$ ) but not in controls ( $P = 0.578624$ ) which also supports the possible association and hence deviation from Hardy Weinberg equilibrium with gastric cancer. Genotype and allelic frequencies did not differ between the case and control groups with respect to +405G/C genotypes (Table 3).



**Table 1:** Distribution of Epidemiological variables in Gastric Cancer patients and controls.

Epidemiological characteristics		Control (N=360) n (%)	Gastric Cancer (N=180) n (%)	Crude OR (95%CI); P-value	AOR (95%CI); P-value
Sex	Female	138 (38.3)	52 (28.9)	1.00 (Refr.)	--
	Male	222 (61.7)	128 (71.1)	1.53 (1.04-2.25); 0.031*	1.04 (0.67-1.62); 0.866
Age (Mean ± SD)		49.37±12.08	53.23±11.78	--	----
Age Group	≤45 yrs.	144 (40.0)	50 (27.8)	1.00 (Refr.)	1.00 (Refr.)
	46-60 yrs.	130 (36.1)	76 (42.2)	1.68 (1.10-2.58); 0.017*	1.71 (1.09-2.68); 0.020*
	>60 yrs.	86 (23.9)	54 (30.0)	1.81 (1.13-2.89); 0.013*	2.11 (1.29-3.47); 0.003*
Smoking	Non smokers	265 (73.6)	88 (48.9)	1.00 (Refr.)	1.00 (Refr.)
	Smokers	95 (26.4)	92 (51.1)	2.92 (2.01-4.24); <0.0001*	2.01 (1.23-3.29); 0.005*
Tobacco chewing	No	283 (78.6)	115 (63.9)	1.00 (Refr.)	1.00 (Refr.)
	Yes	77 (21.4)	65 (36.1)	2.08 (1.40-3.08); <0.0001*	2.12 (1.39-3.22); <0.000*
Alcoholism	Non-alcoholics	256 (71.1)	86 (47.8)	1.00 (Refr.)	1.00 (Refr.)
	Alcoholics	104 (28.9)	94 (52.2)	2.69 (1.86-3.89); <0.0001*	1.76 (1.08-2.86); 0.023*

Adjusted for: age, sex and addictions; AOR: Adjusted odds ratio; Refr. : Reference

\*: P <0.05 at 5% level of significance

**Table 2:** Distribution of genotypes and allele frequencies of Vascular Endothelial Growth Factor (VEGF) -2549 Insertion Deletion polymorphism in Gastric Cancer patients and Control subjects.

Model	Genotype	Control n (%)	Gastric Cancer n (%)	AOR (95%CI)	P-value	Adjusted P-value	AIC
Co dominant	D/D	132 (36.7)	34 (18.9)	1.00 (Refr.)	1.431e-05*	0.000107*	619.8
	I/D	177 (49.2)	107 (59.4)	2.84 (1.75-4.63)			
	I/I	51 (14.2)	39 (21.7)	3.15 (1.72-5.78)			
Dominant	D/D	132 (36.7)	34 (18.9)	1.00 (Refr.)	2.509e-06*	3.76e-05*	618.0
	I/D-I/I	228 (63.3)	146 (81.1)	2.92 (1.83-4.67)			
Recessive	D/D-I/D	309 (85.8)	141 (78.3)	1.00 (Refr.)	0.0763	0.104049	637.0
	I/I	51 (14.2)	39 (21.7)	1.57 (0.96-2.57)			
Over-dominant	D/D-I/I	183 (50.8)	73 (40.6)	1.00 (Refr.)	0.003883*	0.0581984	631.8
	I/D	177 (49.2)	107 (59.4)	1.78 (1.20-2.64)			
Log-additive	--	--	--	1.83 (1.36-2.45)	3.825e-05*	0.000191*	623.2
Allelic	D	441(0.61)	175(0.49)	1.00 (Refr.)	7.641e-05*	----	----
	I	279(0.39)	185(0.51)	1.67(1.29-2.15)			

Adjusted for: age, sex and addictions; AOR: Adjusted Odds Ratio; Adjusted P-value: FDR adjusted P-value; AIC: Akaike Information Criterion; \*: P <0.05 at 5% level of significance.

Codominant AOR<sup>1</sup>:I/D vs. D/D; Codominant AOR<sup>2</sup>: I/I vs. D/D; Dominant AOR: I/D-I/I vs. D/D; Recessive AOR: I/I vs. D/D-I/D; Log-additive AOR: D/D-0, I/D-1, I/I- 2.

To evaluate the combined effect of VEGF polymorphisms (-2549I/D and +405G/C) in the susceptibility to GC, haplotype analysis was performed using SNPSTAT tool. Four haplotype groups were observed (Table 4). Haplotype D-G was the most frequently found among controls and cases thus considered as a reference group. A significant increase in the frequency of I-Ghaplotype in gastric cancer cases was observed compared to control (0.42 vs. 0.28) with an AOR of 2.23 (95%CI= (1.51-3.27); P= 0.0001). Global haplotype score test deviated significantly among controls and cases (Global haplotype P= 0.00012). As there are no previous reports on haplotype association of the VEGF (-2549I/D and +405G/C) polymorphisms with gastric cancer, a comparative analysis was not possible to strengthen the above associations.

## Discussion

Gastric cancer, a disease of heterogeneous origin involving several factors such as genetic, environmental, immune, diet, infections and inflammation may lead to disturbances in the signalling pathways related to growth and regulation of gastric

tumours due to the influence of gene/s variation [18,19]. Genetic variations and disease susceptibility play an important role in the pathogenesis of gastric cancer [20-22]. Tumour growth, relapse and metastasis turns on the “angiogenic switch” to induce tumour growth to a size greater than 1-2 mm which is regulated by angiogenic activators and inhibitors [23]. Hypoxia triggers tumour angiogenesis and which further activates the expression of Hypoxia-Inducible Factor-1 (HIF-1) in the expression of various other proangiogenic factors such as Vascular Endothelial Growth Factor (VEGF) and Vascular Endothelial Growth Factor Receptor (VEGFR) in micro angiogenesis and invasion [24,25].

Cancer cells in the growth phase encourage the new blood vessels formation by secreting VEGF and VEGFR into the Tumour Micro Environment (TME) surrounding and the secreted VEGF binds to VEGFR on the Endothelial Cells (ECs) outer surface. VEGF signalling pathway activates ECs and induces the growth, survival, vascular permeability and migration of ECs to encourage tumour angiogenesis [26]. The

**Table 3:** Distribution of genotypes and allele frequencies of Vascular Endothelial Growth Factor (VEGF) 405G/C polymorphism in Gastric Cancer patients and Control subjects.

Model	Genotype	Control n (%)	Gastric Cancer n (%)	AOR (95%CI)	P-value	Adjusted P-value	AIC
Co-dominant	G/G	172 (47.8)	100 (55.6)	1.00 (Refr.)	0.14261	0.152797	638.2
	G/C	160 (44.4)	64 (35.6)	0.68 (0.45-1.02)			
	C/C	28 (7.8)	16 (8.9)	1.05 (0.52-2.12)			
Dominant	G/G	172 (47.8)	100 (55.6)	1.00 (Refr.)	0.11453	0.171793	637.6
	G/C-C/C	188 (52.2)	80 (44.4)	0.73 (0.50-1.08)			
Recessive	G/G-G/C	332 (92.2)	164 (91.1)	1.00 (Refr.)	0.54073	0.540733	639.7
	C/C	28 (7.8)	16 (8.9)	1.24 (0.63-2.45)			
Over-dominant	G/G-C/C	200 (55.6)	116 (64.4)	1.00 (Refr.)	0.05112	0.06982	636.2
	G/C	160 (44.4)	64 (35.6)	0.67 (0.45-1.00)			
Log-additive	---	---	---	0.86 (0.64-1.17)	0.33501	0.364585	639.2
Allelic	G	504 (0.70)	264 (0.73)	1.00 (Refr.)	0.2546	---	---
	C	216 (0.30)	96 (0.27)	0.85(0.64-1.13)			

Adjusted for: age, sex and addictions; AOR: Adjusted odds ratio, Adjusted P-value: FDR adjusted P-value.

AIC: Akaike Information Criterion; \*: P <0.05 at 5% level of significance.

Codominant AOR<sup>1</sup>: G/C vs. G/G; Codominant AOR<sup>2</sup>: C/C vs. G/G; Dominant AOR: G/C-C/C vs. G/G; Recessive AOR: C/C vs. G/G-G/C; Log-additive AOR: G/G-0, G/C-1, C/C-2.

**Table 4:** Haplotype frequencies distribution and association of VEGF polymorphisms with Gastric Cancer.

VEGF -2549I/D	VEGF 405G/C	Total	Control	GC	OR (95%CI)	P-value
D	G	0.3773	0.412	0.3119	1.00	---
I	G	0.3338	0.288	0.4214	2.23 (1.51 - 3.27)	1e-04
D	C	0.1931	0.2005	0.1742	1.21 (0.76 - 1.92)	0.42
I	C	0.0958	0.0995	0.0924	1.29 (0.73 - 2.31)	0.38

Global haplotype association P-value: 0.00012\*

proangiogenic abilities of gastric cancer cells secrete angiogenic cytokines and stimulate ECs to support their own growth in an autocrine manner. VEGF acts as a key mediator of angiogenesis and micro invasion in cancers and is also involved in cellular processes which can be influenced by the functional polymorphic variants of the gene [27]. VEGF gene polymorphism may alter VEGF production and activity, thereby causing inter-individual differences in the angiogenesis, lymph and vascular and lymphatic tumor spread. According to Ohta, et al. peripheral blood plasma VEGF-A level was reported to be increased in patients with venous invasion and correlated with lymph node metastasis and reported as a sensitive marker for the progression of gastric cancer [28]. Similarly, VEGF +1612G > A gene polymorphism was found to be associated with gastric cancer in Chinese and Japanese population [29,30]. VEGF -2578C > A and -634G > C polymorphisms were associated with larger tumor size, poor differentiation, advanced stage of gastric cancer in Greek population [31]. The insertion/deletion (I/D) polymorphism in the promoter region of VEGF at the position - 2549 relative to the translation start site has been linked to an altered transcriptional activity [32].

This is the first study reporting an association of VEGF -2549I/D polymorphism with gastric cancer. The findings of the present study are in concordance with the earlier reports that I allele and I allele carrier genotypes (i.e. I/D, I/I) were associated with breast cancer of North Indian origin [33]. The I/D genotype was also being reported to be at greater risk to prostate cancer in a study from North India [34]. Further VEGF

+405G/C polymorphism in the 5' UTR has a significant effect on VEGF expression. Similarly, a study on association of +405C/C genotype with poor tumor differentiation and lymph node metastasis in gastric cancer was reported [21]. VEGF +405C allele reduces binding of the transcription factor myeloid zinc finger protein MZF1, which then subsequently reduces the gene expression [35-37]. According to a study 405C/C genotype was associated with larger tumor size, metastasis and advanced stages of gastric cancer [31]. However, in the present study no such association between +405G/C polymorphism and gastric cancer was observed.

Further haplotype analysis showed increased frequency of I-G haplotype in gastric cancer compared to controls. Study carried out by Chae, et al. on VEGF gene polymorphisms (-460T > C, +405G > C, and 936C > T) showed TCT haplotype was associated with decreased susceptibility to gastric cancer [38]. Kim, et al. reported association of CACC haplotype with worse survival compared to TGCC haplotype in patients with surgically resected gastric cancer [22]. Penelope, et al. showed CGC haplotype of combined 460T/C, 405G/C, and 936C/T VEGF polymorphisms associated with reduced overall survival and had a potential prognostic significance in oesophageal cancer [39].

## Conclusion

In conclusion VEGF -2549I/D polymorphism and I-G haplotype has shown a significant association and susceptibility towards gastric cancer which throws a light on the molecular mechanism of tumour angiogenesis in gastric cancer and helps in developing a novel antiangiogenic strategy. This is the first report of the VEGF polymorphism reflecting the synergistic action of two SNPs which seem to exert influence on the expression of VEGF.

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