CDH1 Promoter Variants rs16260 and rs5030625 and Gastric Cancer Susceptibility: A Hospital-Based Case-Control Study in South India

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Abstract

Background: Common regulatory variants in CDH1 may influence E-cadherin expression and gastric cancer susceptibility, but published associations are heterogeneous across populations. Population-specific evaluation of these variants is therefore important, particularly in South Indian populations where genetic association data remain limited.

Methods: The study included 110 histopathologically confirmed gastric adenocarcinoma cases and 110 unrelated controls. CDH1 rs16260 (−160 C>A) and rs5030625 (−347 G>GA) were genotyped by PCR-RFLP. Genotype and allele distributions, control-group Hardy–Weinberg equilibrium (HWE), and odds ratios (ORs) with 95% confidence intervals (CIs) were evaluated under codominant, dominant, recessive, overdominant and allelic models.

Results: For rs16260, the overall three-genotype distribution was not statistically significant (P=0.077), whereas significant associations were observed under the dominant model (AC+AA vs CC: OR=1.80, 95% CI=1.05–3.07; P=0.032) and allelic model (A vs C: OR=1.61, 95% CI=1.07–2.42; P=0.023). No significant association was observed for rs5030625 under any of the genetic models examined. Control genotype distributions for both variants were in HWE (rs16260, P=0.661; rs5030625, P=0.208). Exploratory case-only analyses showed differences in rs16260 genotype distribution according to smoking status (P=0.040) and lymph-node status (P=0.038).

Conclusion: CDH1 rs16260 was associated with gastric cancer susceptibility under the dominant and allelic models in this South Indian population, whereas rs5030625 showed no significant association. These findings suggest a possible role of rs16260 in gastric cancer susceptibility and warrant confirmation in larger, independent populations.

Keywords: Gastric cancer; CDH1; E-cadherin; rs16260; rs5030625; Genetic susceptibility; South India

I. Introduction

Gastric cancer remains a major global health burden. GLOBOCAN 2022 estimated 968,784 new stomach-cancer cases and 660,175 deaths worldwide, ranking it fifth for both incidence and cancer mortality [1]. Although age-standardized rates have declined in many settings, population growth and ageing sustain a substantial absolute burden [2,3]. Gastric carcinogenesis is multifactorial, involving infectious, environmental, behavioural and inherited determinants. Helicobacter pylori is the principal established infectious cause, while tobacco smoking, high-salt and salt-preserved foods, heavy alcohol consumption in some settings, and familial susceptibility also contribute to risk [4–6]. Chronic H. pylori infection promotes persistent gastric inflammation and progressive mucosal damage [7]. Particularly in intestinal-type gastric carcinogenesis, this process may follow the Correa cascade, progressing from chronic gastritis through atrophic gastritis, intestinal metaplasia and dysplasia to invasive adenocarcinoma [8]. However, infection alone is insufficient, as bacterial virulence, host inflammatory responses, genetic susceptibility and environmental exposures collectively modify individual risk [9].

India has considerable geographical, dietary, ethnic and socioeconomic diversity, and susceptibility patterns may therefore vary across populations. Lifestyle exposures such as smoking, alcohol consumption and smokeless tobacco use also vary across regions. These differences support population-specific investigation of gastric cancer susceptibility, particularly in South Indian populations where genetic association data remain limited. Gastric adenocarcinoma is clinicopathologically heterogeneous. Anatomical site, histological subtype, TNM stage and metastatic status are important characteristics of the disease. Lauren's classification categorizes gastric adenocarcinomas into intestinal, diffuse and mixed types [10], while the tumour-node-metastasis system provides a standardized framework for assessing primary tumour extent, regional lymph-node involvement and distant metastasis [11].

Genetic susceptibility to gastric cancer includes both rare high-penetrance pathogenic variants and common variants with smaller potential effects. CDH1 encodes E-cadherin, a calcium-dependent transmembrane protein essential for epithelial cell-cell adhesion, polarity and tissue architecture. Pathogenic germline CDH1 variants are an established cause of hereditary diffuse gastric cancer; however, these rare variants are distinct from common promoter polymorphisms investigated as potential low-penetrance modifiers of sporadic disease [12].

Two common CDH1 promoter variants, rs16260 (−160 C>A) and rs5030625 (−347 G>GA), have been investigated in relation to gastric cancer susceptibility. Functional studies have shown that the rs16260

A allele can reduce promoter transcriptional efficiency relative to the C allele, providing biological plausibility for a potential association [13]. Epidemiological findings, however, have been inconsistent. A 2024 meta-analysis found no significant overall association for rs16260, although increased risk was observed in the Caucasian subgroup, whereas rs5030625 showed evidence of increased susceptibility, particularly in Asian populations [14]. A more recent 2026 meta-analysis reported significant associations for rs16260 under the recessive and homozygous models and for rs5030625 under the heterozygous model [15]. These findings indicate variation across genetic models and populations and support further evaluation in different populations.

Evidence from South Indian populations remains limited. Therefore, the present study evaluated the association of CDH1 rs16260 and rs5030625 with gastric cancer susceptibility in a hospital-based South Indian case-control population. Secondary objectives were to describe demographic, lifestyle and clinicopathological characteristics and to explore rs16260 genotype distributions across selected characteristics among gastric cancer cases.

II. Materials and Methods

A. Study design and setting

A hospital-based case-control genetic association study was conducted in Visakhapatnam, India. The study included 110 patients with histopathologically confirmed gastric adenocarcinoma and 110 apparently healthy, unrelated controls from the same geographic region. Cases were recruited from King George Hospital, Mahatma Gandhi Cancer Hospital and Research Institute, and Pinnacle Cancer Hospital. Most participants originated from Visakhapatnam, Vizianagaram and Srikakulam districts. Controls were recruited among individuals attending routine health check-ups or accompanying patients.

B. Participants and Ethical considerations

Eligible cases were adults with newly diagnosed or untreated, histopathologically confirmed gastric adenocarcinoma who provided written informed consent. Patients were excluded if they had recurrent gastric cancer, had received chemotherapy or radiotherapy before sample collection, had another primary malignancy or severe autoimmune disease, or declined consent. Controls had no previous malignancy or first-degree family history of gastric cancer and were excluded for chronic inflammatory gastrointestinal disease, severe systemic illness, biological relationship to an enrolled case or refusal of consent. The study protocol was approved by the Institutional Ethics Committee of Andhra University and the participating hospitals (IEC53, dated 1-04-2022). Written informed consent was obtained from

all participants before enrolment, and participant confidentiality was maintained in accordance with the Declaration of Helsinki.

C. Data collection and clinical classification

Demographic, lifestyle and clinical information was recorded using a structured case-record proforma and supplemented by hospital records, pathology reports, imaging findings, operative records and information from treating clinicians. Age was recorded in completed years and categorized as ≤40, 41–50, 51–60 or >60 years. Sex and permanent rural or urban residence were recorded. Smoking, alcohol consumption and tobacco chewing were analyzed as dichotomous variables. Family history was considered positive when at least one first-degree relative had any cancer. Tumor site was categorized as cardia, body, antrum or whole-stomach involvement. Histological type was classified as intestinal, diffuse or mixed according to Lauren's classification [10]. TNM stage and regional lymph-node and distant-metastasis status were determined from pathological, imaging, operative and clinical findings using the American Joint Committee on Cancer framework [11].

D. Blood collection and DNA extraction

Approximately 5 mL of peripheral venous blood was collected into EDTA-coated tubes. Genomic DNA was isolated using a modified non-enzymatic salting-out procedure based on Nasiri et al. [16]. DNA concentration and purity were assessed spectrophotometrically, and DNA integrity was evaluated by agarose-gel electrophoresis.

E. CDH1 genotyping

CDH1 rs16260 (−160 C>A) and rs5030625 (−347 G>GA) were genotyped by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP). A 447-bp promoter segment was amplified using the forward primer 5′-GCCCCGACTTGTCTCTCTAC-3′ and reverse primer 5′-TACCGCTGATTGGCTGAGGG-3′. For rs16260, amplification products were digested with HincII: CC produced 367- and 80-bp fragments, AC produced 447-, 367- and 80-bp fragments, and AA remained undigested at 447 bp. For rs5030625, products were digested with BanII: GG produced 293-, 115- and 39-bp fragments; GGA produced 293-, 154-, 115- and 39-bp fragments; and GAGA produced 293- and 154-bp fragments. Digested products were resolved by 3% agarose-gel electrophoresis.

F. Statistical analysis

Continuous variables were summarized as mean±standard deviation, and categorical variables as frequencies and percentages. Mean age was compared between cases and controls, while categorical variables were compared using Pearson's chi-square test. Hardy–Weinberg equilibrium was assessed

among controls. Associations between CDH1 variants and gastric cancer susceptibility were evaluated using odds ratios (ORs) with 95% confidence intervals (CIs) under codominant, dominant, recessive, over dominant and allelic genetic models. Case-only analyses were performed to compare rs16260 genotype distributions across demographic, lifestyle and clinicopathological characteristics. All tests were two-sided, and P<0.05 was considered statistically significant.

III. Results

A. Participant characteristics

Table 1: Demographic and lifestyle characteristics of gastric cancer cases and controls

Characteristics	Category	Cases n (%)	Controls n (%)	Chi-square	P value
Age group	<=40 years	8 (7.3)	22 (20.0)	13.479	**0.004**
	41-50 years	20 (18.2)	28 (25.5)		
	51-60 years	36 (32.7)	34 (30.9)		
	>60 years	46 (41.8)	26 (23.6)		
Mean age, years	Mean ± SD	56.8 ± 10.9	56.2 ± 11.3	-	0.68
Sex	Male	78 (70.9)	75 (68.2)	0.193	0.660
	Female	32 (29.1)	35 (31.8)		
Residence	Rural	78 (70.9)	48 (43.6)	16.717	**<0.001**
	Urban	32 (29.1)	62 (56.4)		
Smoking	Smoker	52 (47.3)	28 (25.5)	11.314	**<0.001**
	Non-smoker	58 (52.7)	82 (74.5)		
Alcohol use	Yes	50 (45.5)	28 (25.5)	9.614	**0.002**
	No	60 (54.5)	82 (74.5)		
Tobacco chewing	Yes	38 (34.5)	18 (16.4)	9.582	**0.002**
	No	72 (65.5)	92 (83.6)		
Family history of cancer	Yes	20 (18.2)	8 (7.3)	5.893	**0.015**
	No	90 (81.8)	102 (92.7)		

Bold values indicate statistical significance at P<0.05.

Table 1 describes the demographic and lifestyle characteristics of gastric cancer cases and controls. Cases were more frequently represented in the >60-year age group than controls (41.8% vs 23.6%), whereas a higher proportion of controls were aged ≤40 years (20.0% vs 7.3%; overall P=0.004). Despite this difference in age-group distribution, the mean ages of cases and controls were similar (56.8

vs 56.2 years; P=0.68). Sex distributions were comparable. Rural residence, smoking, alcohol use, tobacco chewing and family history of cancer were significantly more frequent among cases than controls.

B. Clinicopathological profile

Table 2: Clinicopathological characteristics of 110 gastric cancer cases

Characteristic	Category	Cases n (%)
Tumor site	Cardia	18 (16.4)
	Body	24 (21.8)
	Antrum	58 (52.7)
	Whole stomach	10 (9.1)
Lauren type	Intestinal	68 (61.8)
	Diffuse	34 (30.9)
	Mixed	8 (7.3)
TNM stage	I	12 (10.9)
	II	24 (21.8)
	III	46 (41.8)
	IV	28 (25.5)
Lymph-node metastasis	Present	74 (67.3)
	Absent	36 (32.7)
Distant metastasis	Present	28 (25.5)
	Absent	82 (74.5)

Table 2 describes Clinicopathological characteristics of 110 gastric cancer cases. The antrum was the most frequent tumour site (52.7%), and intestinal-type carcinoma was the predominant Lauren subtype (61.8%). Stage III was the largest single TNM category (41.8%), while 74 patients (67.3%) had stage III–IV disease. Lymph-node metastasis was present in 67.3% of cases, and distant metastasis was present in 25.5%.

C. CDH1 genotype and allele distributions

For rs16260, the overall three-genotype distribution was not statistically significant (P=0.077), whereas the A-allele frequency was significantly higher among cases than controls (35.5% vs 25.5%; P=0.023). For rs5030625, neither the genotype distribution (P=0.353) nor the allele distribution (P=0.128) differed

significantly between cases and controls. Control genotype distributions for both variants were in Hardy–Weinberg equilibrium (rs16260, P=0.661; rs5030625, P=0.208) (Table 3).

Table 3 CDH1 genotype and allele distributions among cases and controls

Variant	Genotype or allele	Cases n (%)	Controls n (%)	P value
rs16260	CC	46 (41.8)	62 (56.4)	0.077
	AC	50 (45.5)	40 (36.4)	
	AA	14 (12.7)	8 (7.3)	
	C allele	142 (64.5)	164 (74.5)	**0.023**
	A allele	78 (35.5)	56 (25.5)	
rs5030625	GG	58 (52.7)	68 (61.8)	0.353
	GGA	40 (36.4)	34 (30.9)	
	GAGA	12 (10.9)	8 (7.3)	
	G allele	156 (70.9)	170 (77.3)	0.128
	GA allele	64 (29.1)	50 (22.7)	

Bold values indicate statistical significance at P<0.05

D. Genetic-model associations

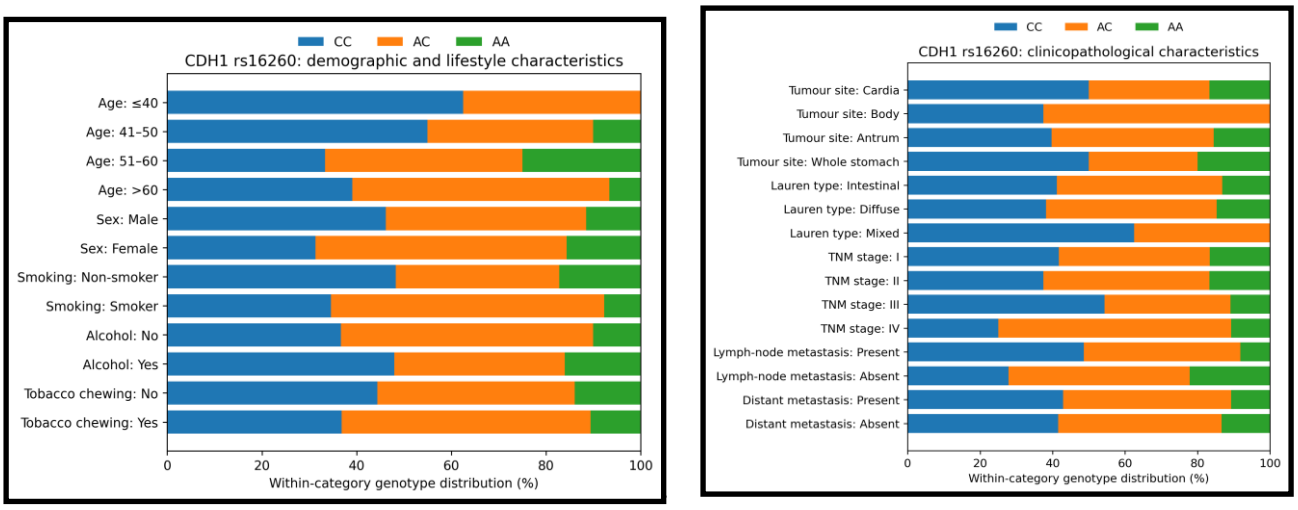
Table 4. Associations of CDH1 promoter polymorphisms with gastric cancer susceptibility under different genetic models

Variant	Model	Comparison	OR	95% CI	P value
rs16260	Codominant	AC vs CC	1.68	0.96-2.96	0.070
	Codominant	AA vs CC	2.36	0.91-6.09	0.076
	Dominant	AC+AA vs CC	1.80	1.05-3.07	**0.032**
	Recessive	AA vs others	1.86	0.75-4.63	0.183
	Over dominant	AC vs homozygotes	1.46	0.85-2.50	0.171
	Allelic	A vs C	1.61	1.07-2.42	**0.023**
rs5030625	Codominant	GGA vs GG	1.38	0.78-2.45	0.274
	Codominant	GAGA vs GG	1.76	0.67-4.60	0.249
	Dominant	GGA+GAGA vs GG	1.45	0.85-2.48	0.174
	Recessive	GAGA vs others	1.56	0.61-3.98	0.351
	Over dominant	GGA vs homozygotes	1.28	0.73-2.24	0.392
	Allelic	GA vs G	1.39	0.91-2.14	0.128

Associations of CDH1 promoter polymorphisms with gastric cancer susceptibility under different genetic models were described in Table 4. Analysis under different genetic models showed significant associations for rs16260 under the dominant model (AC+AA vs CC: OR=1.80, 95% CI=1.05–3.07; P=0.032) and the allelic model (A vs C: OR=1.61, 95% CI=1.07–2.42; P=0.023). The individual AC-versus-CC and AA-versus-CC comparisons, as well as the recessive and overdominant models, were not significant. For rs5030625, no significant associations were observed under any of the genetic models examined.

E. Exploratory case-only rs16260 comparisons

When rs16260 genotype distributions were compared across demographic, lifestyle and clinicopathological characteristics among gastric cancer cases, significant differences were observed according to smoking status (P=0.040) and lymph-node status (P=0.038). The AC genotype was more frequent among smokers, whereas the AA genotype was more frequent among non-smokers. For lymph-node status, the CC genotype was more frequent among node-positive cases, whereas the AA genotype was more frequent among node-negative cases. No significant differences were observed according to age group, sex, alcohol use, tobacco chewing, tumour site, Lauren histological type, TNM stage or distant metastasis (Figure 1).



(A) Demographic and lifestyle characteristics. **(B) Clinicopathological characteristics**

Figure 1. Distribution of CDH1 rs16260 genotypes according to demographic, lifestyle and clinicopathological characteristics among gastric cancer cases.

IV. Discussion

This study evaluated demographic and lifestyle characteristics, the clinicopathological profile of gastric cancer cases, and two common CDH1 promoter variants, rs16260 and rs5030625, in a South Indian hospital-based population. The main genetic finding was an association of rs16260 with gastric cancer

susceptibility under the dominant and allelic models, whereas rs5030625 showed no significant association. Both variants were in Hardy–Weinberg equilibrium among controls.

Rural residence was significantly more common among cases than controls. This difference may reflect variations in lifestyle, socioeconomic conditions, environmental exposures, dietary practices, tobacco use, access to healthcare, or other factors associated with place of residence.

Smoking was more common among cases (47.3%) than controls (25.5%), consistent with established evidence linking smoking with gastric cancer risk. An Indian study also reported an association between bidi smoking and gastric cancer, although the magnitude of risk varied according to the type of tobacco exposure [17]. Alcohol use was also more frequent among cases, in agreement with previous evidence suggesting that gastric cancer risk may vary according to the amount and pattern of alcohol consumption [18]. Tobacco chewing was similarly more common among cases than controls. These findings support the possible contribution of lifestyle-related exposures to gastric cancer susceptibility.

A family history of cancer was more common among cases than controls, suggesting a possible contribution of familial or shared environmental factors to gastric cancer susceptibility. However, the recorded family history included any type of cancer and was not specific to gastric cancer. Therefore, it cannot be directly related to hereditary gastric cancer syndromes. This distinction is particularly relevant because rare pathogenic germline CDH1 variants associated with hereditary diffuse gastric cancer and common CDH1 promoter polymorphisms represent different forms of genetic variation [12].

Clinicopathologically, antral tumours were the most common tumour site, while intestinal-type carcinoma was the predominant histological type. The predominance of intestinal-type gastric cancer is consistent with the well-established multistep pathway of inflammation, atrophy, intestinal metaplasia and dysplasia in gastric carcinogenesis [8]. A substantial proportion of patients presented with stage III–IV disease and lymph-node metastasis, indicating advanced disease at the time of diagnosis.

For rs16260, the A allele was more frequent among gastric cancer cases, and carriers of at least one A allele showed an increased risk under the dominant model. This finding is consistent with the functional study by Li et al. [13], which demonstrated that the −160 A allele significantly reduced CDH1 promoter transcriptional efficiency by approximately 68% compared with the C allele ($P<0.001$). Reduced CDH1 transcription may lead to lower E-cadherin expression and thereby provide a possible biological basis for the association observed in our study. However, the overall distribution of the three genotypes did not differ significantly between cases and controls.

Previous studies of rs16260 have reported inconsistent findings across populations. In the 2024 meta-analysis by Jiang et al. [14], no significant overall association with gastric cancer was observed, although

increased risk was reported in the Caucasian subgroup; no significant association was found in the Asian subgroup. The more recent 2026 meta-analysis by Ye and Wang [15] reported significant associations under the recessive and homozygous models. These differences across studies may reflect variations in genetic background, environmental exposures, sample size and study design.

For rs5030625, the GGA and GAGA genotypes and the GA allele were more frequent among cases than controls; however, none of the genotype, allele, or genetic-model comparisons reached statistical significance. In contrast, Shekarriz et al. reported an association between the heterozygous genotype and gastric cancer in a Northern Iranian population [21]. The 2024 meta-analysis reported a significant overall association under the heterozygous model, with additional associations observed in the Asian subgroup [14]. Similarly, the 2026 meta-analysis reported a significant overall association for the heterozygous genotype [15]. Differences among studies may reflect population-specific genetic backgrounds, sample size and study design.

In the case-only analysis, rs16260 genotype distributions differed significantly according to smoking status and lymph-node status, whereas no significant differences were observed according to tumour site, Lauren type, TNM stage or distant metastasis. These subgroup findings are exploratory and require further investigation.

The strengths of this study include histopathological confirmation of gastric cancer cases and the use of defined PCR-RFLP methods for genotyping. Reporting genotype and allele frequencies together with multiple genetic models enabled a comprehensive evaluation of the selected CDH1 variants.

This study has some limitations. The relatively modest sample size may have limited the statistical power for less frequent genotypes and subgroup comparisons. The hospital-based design may also limit the generalizability of the findings. In addition, information on certain potentially relevant factors, including H. pylori infection and detailed dietary exposures, was not available.

Future studies with larger, multicentre cohorts are needed to confirm these findings across diverse populations. Further investigation of gene–environment interactions and functional studies may help clarify the biological significance of these CDH1 variants in gastric cancer susceptibility.

V. Conclusion

In this South Indian hospital-based case-control study, CDH1 rs16260 was associated with gastric cancer susceptibility under the dominant and allelic models, whereas rs5030625 showed no significant association under the genetic models examined. Both variants were in Hardy–Weinberg equilibrium among controls. These findings suggest a possible role of rs16260 in gastric cancer susceptibility and warrant confirmation in larger, independent populations.

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