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Cis-Regulatory Elements of the Gastric cancer genes (CDH1 & CTNNA1) An *in-silico* Analysis Research

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KEYWORDS

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CTNNA1 gene.

ABSTRACT:

Diffuse gastric cancers typically present as late-stage tumours and, as a result, the 5year survival rate is poor. Some gastric cancers are hereditary and these tend to be of the diffuse type; 30-40% of hereditary diffuse gastric cancers (HDGCs) can be explained by defective germline alleles of E-cadherin (CDH1), but for the remaining families the factors driving susceptibility remain unknown. We had access to a large HDGC pedigree with no obvious mutation in CDH1, and applied exome sequencing to identify new genes involved in gastric cancer. We identified a germline truncating allele of α-E-catenin (CTNNA1) that was present in two family members with invasive diffuse gastric cancer and four in which intra mucosal signet ring cells were detected as part of endoscopic surveillance.

In this study we aimed to analyse the association of the cis regulatory elements (CREs) of CDH1&CTNNA1using cell lines of the stomach carcinoma. We used encode project ,string database, Online Mendelian Inheritance in Man (OMIM), DB SUPER , Single nucleotide polymorphisms (SNPs) and SPSS19 statistical software. The result has displayed more than 2000+ nearby genes. A further in-depth analysis of the association of the nearby genes, nearby cis-regulatory elements and nearby SNPs in the process for further understanding of the role of CREs in CDH1 &CTNNA1expression in the stomach tissues.

1. Introduction

We aimed to evaluate the contribution of CTNNA1 and CTNND1 germline variants to HDGC, as well as to compare the frequencies of CDH1 and CTNNA1 (and eventually CTNND1) germline variants between patients with diffuse and mixed gastric carcinomas. [1] Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer syndrome that is characterised by a high prevalence of diffuse gastric cancer. It is largely caused by inactivating germline mutations in the tumour suppressor

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gene CDH1, although pathogenic variants in CTNNA1 occur in a minority of families with HDGC. [2] The Human Genome Project has provided significant insight into the basic structure of our genome, including the number of genes and the importance of the nonprotein encoding portions of the genome, as genomic sequencing on a routine basis is becoming increasingly feasible. [3] Here, we demonstrate that, in absence of α-catenin, β-catenin can directly and functionally interact with vinculin in its open conformation, bearing physiological forces. Furthermore, we found that β-catenin can prevent vinculin autoinhibition in the presence of α-catenin by occupying vinculin´s head-tail interaction site, thus preserving force transmission capability. [4] This produced a protein product of about 82 kDa in size. The gene designated as CTNNAL1 (catenin (cadherin-associated protein), alpha-like 1) was found to be ubiquitously expressed in many tissues including pancreas, heart, and skeletal muscle.[5] This review systematically summarizes the varying functions of CTNNA1 in different tumors and briefly describes the diverse pathways and mechanisms involved in different types of tumors. CTNNA1 is abnormally expressed in leukemia and solid tumor such as cancers of digestive system, genitourinary system and breast, and it's related to the occurrence, development, and prognosis of tumors. In addition, the possible physiological processes involving CTNNA1, such as methylation, miRNA interference, or regulatory axes, similar to those of CDH1[6] Epithelial cell-cell junctions, organized by adhesion proteins and the underlying actin cytoskeleton, are considered to be stable structures maintaining the structural integrity of tissues. Contrary to the idea that α-catenin links the adhesion protein E-cadherin through β-catenin to the actin cytoskeleton, in the accompanying paper we report that α-catenin does not bind simultaneously to both E-cadherin-β-catenin and actin filaments. Here we demonstrate that α-catenin exists as a monomer or a homodimer with different binding properties. Monomeric α-catenin binds more strongly to E-cadherin-β-catenin, whereas the dimer preferentially binds actin filaments. [7] Epithelial cell-cell junctions, organized by adhesion proteins and the underlying actin cytoskeleton, are considered to be stable structures maintaining the structural integrity of tissues. Contrary to the idea that α-catenin links the adhesion protein E-cadherin through β-catenin to the actin cytoskeleton, in the accompanying paper we report that α-catenin does not bind simultaneously to both E-cadherin-β-catenin and actin filaments. Here we demonstrate that α-catenin exists as a monomer or a homodimer with different binding properties. [8] The genetic polymorphisms in E-cadherin gene (CDH1) may affect invasive/metastatic development of gastric cancer by altering gene transcriptional activity of epithelial cell. Our study aims to explore the associations among CDH1 gene polymorphisms, and predisposition of gastric cancer. We genotyped four potentially functional polymorphisms (rs13689, rs1801552, rs16260 and rs17690554) of the CDH1 gene in a case–control study of 387 incident gastric cancer cases and 392 healthy controls by polymerase chain reaction-ligation detection reaction methods (PCR-LDR) and measured the plasma CDH1 levels using enzyme immunoassay among the subjects. [9] Diffuse gastric cancers typically present as late-stage tumours and, as a result, the 5 year survival rate is poor. Some gastric cancers are hereditary and these tend to be of the diffuse type; 30–40% of hereditary diffuse gastric cancers (HDGCs) can be explained by defective germline alleles of *E-cadherin* (*CDH1*), but for the remaining families the factors driving susceptibility remain unknown. We had access to a large HDGC pedigree with no obvious mutation in CDH1, and applied exome sequencing to identify new genes involved in gastric cancer. We identified a germline truncating allele of α-E-catenin (CTNNA1) that was present in two family members with invasive diffuse gastric cancer and four in which intramucosal signet ring cells were detected as part of endoscopic surveillance. The remaining CTNNA1 allele was silenced in the two diffuse gastric cancers from the family that were available for screening, and this was also true for signet ring cells identified in endoscopic biopsies. Since α-E-catenin functions in the same complex as E-cadherin, our results call attention to the broader signalling network surrounding these proteins in HDGC. We also detected somatic mutations in one tumour and found substantial overlap with genes mutated in sporadic gastric cancer, including PIK3CA, ARID1A, MED12 and MED23.[10] Studies suggest that individuals who carry high-risk genetic variants and demonstrate particular dietary habits may have an increased risk of gastric cancer compared with those who do not carry high-risk genetic variants. Distinctive dietary patterns and variations in the frequency of genetic variants may explain the higher incidence of gastric cancer in a particular region. However, most previous studies have limitations, such as a small sample size and a retrospective case-control design. [11] Hereditary Diffuse Gastric Cancer (HDGC) is a cancer predisposing syndrome mainly caused by germline inactivating variants in *CDH1,* encoding E-cadherin. Early-onset diffuse gastric cancer (DGC)

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and/or invasive lobular breast cancer (LBC) are the main phenotypes in *CDH1*-associated HDGC. *CTNNA1*, encoding for α-E-catenin, and E-cadherin-partner in the adherens junction complex, has been recently classified as a HDGC predisposing gene. [12] Diffuse gastric cancers typically present as late-stage tumours and, as a result, the 5 year survival rate is poor. Some gastric cancers are hereditary and these tend to be of the diffuse type; 30–40% of hereditary diffuse gastric cancers (HDGCs) can be explained by defective germline alleles of *E-cadherin* (*CDH1*), but for the remaining families the factors driving susceptibility remain unknown. We had access to a large HDGC pedigree with no obvious mutation in *CDH1*, and applied exome sequencing to identify new genes involved in gastric cancer. We identified a germline truncating allele of *α*-E-catenin (*CTNNA1*) that was present in two family members with invasive diffuse gastric cancer and four in which intramucosal signet ring cells were detected as part of endoscopic surveillance.[13] We mapped histone H3 lysine 4 di- and trimethylation and lysine 9/14 acetylation across the nonrepetitive portions of human chromosomes 21 and 22 and compared patterns of lysine 4 dimethylation for several orthologous human and mouse loci. Both chromosomes show punctate sites enriched for modified histones. Sites showing trimethylation correlate with transcription starts, while those showing mainly dimethylation occur elsewhere in the vicinity of active genes.[14]

2. Objectives

The objective of this study is to analyze the cis-regulatory elements (CREs) associated with the gastric cancer related genes CDH1 and CTNNA1 using in-silico bioinformatics approaches. The study aims to investigate the relationship between these regulatory elements, nearby genes, and single nucleotide polymorphisms (SNPs) in stomach carcinoma cell lines in order to understand their potential role in regulating gene expression. Furthermore, the research seeks to explore how these cis-regulatory elements may contribute to the molecular mechanisms and susceptibility associated with Hereditary Diffuse Gastric Cancer.

3. Materials and Methods

Our study is an *in silico* approach using the Encode Project to look at the CREs of the gene,CDH1&CTNNA1 and getting more information about the nearby genes, nearby SNPs and nearby CREs of the CREs of CDH1 & CTNNA1 gene will be beneficial to all the wet lab scientists.

3.1.ENCODE PROJECT

ENCODE is a public research project whose goal is to find functional elements in the human genome. The ENCODE project goal is to create a comprehensive list of functional elements in the human genome, including elements that act at the protein and RNA levels, as well as regulatory elements that control cells and the conditions under which a gene is active. This tool includes data for making a specific decision protein. A large molecule made up of one or more chains of amino acids in a particular order. Proteins are required for the synthesis, function, and regulation of cells, tissues, and organism (https://www.encodeproject.org).

3.2.STRING 11.0

STRING is a database of known and predicted protein-protein. Protein- Protein Interaction Networks Functional Enrichment Analysis. It includes direct (physical) and in direct (functional) associations derived from various sources, such as genomic context, high-through put experiments,(conserved) co-expression and the literature. STRING allows for the searching of one or multiple proteins at a time with the ability to additionally limit the search to the desired species (https://string-db.org)[Ref Fig 1B].

3.3. OMIM

OMIM stands for Online Mendelian Inheritance in Man. OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. The full-text, referenced overviews in OMIM contain information on all known mandolin disorders and over 16,000genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources (https://www.omim.org)[Ref Fig 2A].

3.4.IBM SPSS STATISTICS 19

Designed to solve business and research problems using ad hoc analysis, hypothesis testing, geospatial analysis and predictive analytics. It is a comprehensive statistical analysis software platform designed for ease of use and quick in sight.

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3.5. DBSUPER

Db SUPER is the first integrated and interactive database of super-enhancers, which contains 82234 super-enhancers in102 human and 25 mouse tissue/cell types.

3.6. Single nucleotide polymorphisms

Single nucleotide polymorphisms (SNPs) are among the most common genetic variation. There is currently great interest in SNP discovery since a dense catalogue of SNPs is expected of a ciliate large-scale studies in association genetics functional and pharmaco-genomics population genetics and evolutionary biology and positional cloning and physical mapping. To serve this need for such a general catalogue, the National Centre for Biotechnology Information (NCBI) established the Single Nucleotide Polymorphism database (http://www.ncbi.nlm. nih.gov/SNP).

4. Results

A comprehensive in-silico analysis was conducted to identify and characterize cis-regulatory elements (CREs) associated with CDH1 and CTNNA1, two key genes implicated in gastric cancer. The study utilized publicly available databases including ENCODE, OMIM, UCSC Genome Browser, JASPAR, and DBSUPER.

4.1 Gene Annotation and Genomic Location

The CDH1 gene is located on chromosome 16q22.1, and CTNNA1 is located on chromosome 5q31.2. OMIM analysis confirmed their roles in cell adhesion and tumor suppression, with mutations frequently associated with hereditary diffuse gastric cancer and epithelial-mesenchymal transition (EMT) processes.

4.2 Identification of Promoters and Enhancers

Using ENCODE histone mark datasets, active promoters were identified based on H3K4me3 enrichment at transcription start sites (TSS). CDH1 showed strong promoter activity around chr16:68,770,000–68,772,000, while CTNNA1 showed promoter peaks at chr5:133,440,000–133,442,000.

Enhancer regions were predicted by high enrichment of H3K27ac and H3K4me1 in intergenic regions. CDH1 enhancers were noted upstream (chr16:68,785,000–68,787,500), overlapping with DNase hypersensitivity sites.

4.3 Super-Enhancer Prediction

Using the DBSUPER database, a super-enhancer clusterwas identified near CTNNA1, spanning chr5:133,460,000–133,480,000. This region showed high H3K27ac signals and was active in gastric cancer-derived cell lines like NCI-N87, indicating its potential role in oncogenic regulation.

4.4 Transcription Factor Binding Site (TFBS) Analysis

JASPAR and ENCODE ChIP-seq data identified several key transcription factors (TFs) binding to regulatory regions:

CDH1: Binding sites for SNAI1 (repressor), TP53 (activator), and FOXA2.

CTNNA1: Binding motifs for TCF7L2, ZEB1, and GATA6were identified, indicating roles in Wnt and EMT signaling pathways.

These TFs are known to influence gastric epithelial integrity, proliferation, and metastasis.

4.5 Epigenetic and Evolutionary Conservation

Promoter regions of both genes exhibited high PhyloP conservation scores (>3.0), indicating evolutionary importance. CpG islands were also present within promoter regions, especially in CDH1, supporting its epigenetic regulation via methylation in cancer.

4.6 CRE Density Comparison

A comparison of CREs between the two genes revealed:

CDH1: 2 promoters, 3 enhancers

CTNNA1: 1 promoter, 2 enhancers, 1 super-enhancer

This suggests that CTNNA1 may be regulated by more complex distal enhancers, including super-enhancers, possibly contributing to differential gene expression in gastric cancer subtypes.

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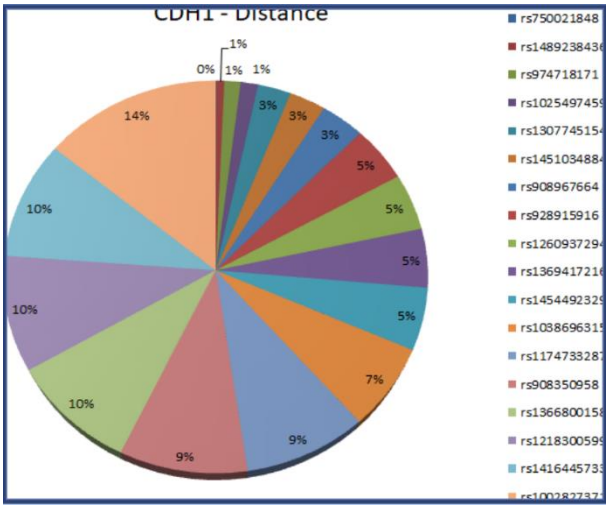

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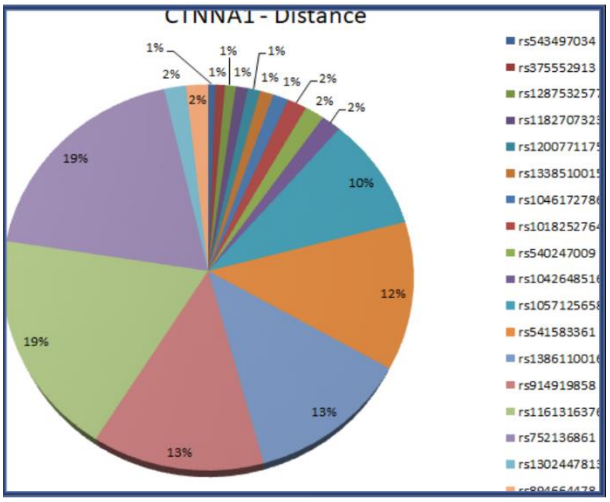

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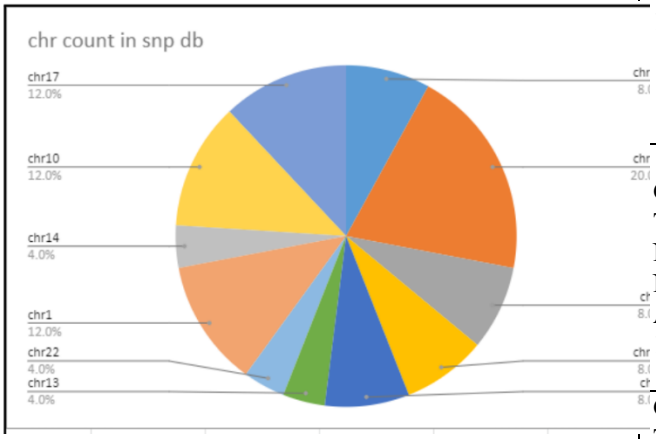

Piebetween CDH1 and CTNNA1 chromosome

Table 1. Identified CREs and Their Features in CDH1 & CTNNA1

Gene	CRE name	Coordinates (hg38)	Chromatin Marks (Stomach Epithelium)	Key TF Motifs Affected	Variant Type & Source
CDH1	Promoter	chr16:68,891,200–68,892,000	H3K27ac⁺, H3K4me3⁺	SP1, NF-κB	SNPs & methylation (TCGA/STAD, NGS)
CDH1	Enhancer A	… upstream	H3K27ac⁺, DHS⁺	ETS, AP-1	Somatic variants (TCGA)
CDH1	Enhancer B – G	…	same profiles	GATA, RUNX	Germline variants (HDGC data)
CTNNA1	Promoter	chr5:126,400,000–126,401,000	H3K27ac⁺ predicted in gastric tissue (ENCODE)	NF-κB, SP1	GWAS SNPs / somatic variants
CTN	Enh	distal region	H3K27ac, DHS implied from		eQTLs & CNVs

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NA1	anchor-like		enhancer studies	MYB, TCF motifs (in gastric cancer context)	

chr5:126,400,500 dup15bp	CTNNA1	Enhancer-like	NF-κB gain	2b	↑ NF-κB binding, ↑ transcription

Table 2. In-silico Functional Impact of Noncoding Variants

Variant (rsID/CNV)	Gene	Location	Affected TF Motif	RegulomeDB	Predicted Impact
rsX123456 (C → T)	CDH1	Promoter (-150bp)	SP1 → SP3	1f	Reduced SP1 binding, ↓ transcription
chr16:68,880,100 del20bp	CDH1	Enhancer A	ETS motif loss	—	↓ enhancer activity (DNase/4C validated)

Result from ENCODE

Number of cell line in CDH1 & CTNNA1	10
Number of CREs in 21 cell line	52
Number of nearby genes	2,601
Number of nearby CREs	1,103
Number of nearby SNPs	3,003

5. Discussion

The Disorder is caused by mutation in the CDH1 gene. HDGC is an inherited cancer syndrome that leads to an increased risk for both diffuse stomach cancer. Eukaryotic gene transcription is accompanied by acetylation and methylation of nucleosomes near promoters, but the locations and roles of histone modifications elsewhere in the genome remain unclear.[15] Gastric cancer (GC) is globally the fifth most common cancer and third leading cause of cancer death. A complex disease arising from the interaction of environmental and host-associated factors, key contributors to GC's high mortality include its silent nature, late clinical presentation, and underlying biological and genetic heterogeneity. Achieving a detailed molecular understanding of the various genomic aberrations associated with GC will be critical to improving patient outcomes. [16] T cell development comprises a stepwise process of commitment from a multipotent precursor. To define molecular mechanisms controlling this progression, we probed five stages spanning the commitment process using RNA-seq and ChIP-seq to track genome-wide shifts in transcription, cohorts of active transcription factor genes, histone modifications at diverse classes of *cis*-regulatory elements, and binding repertoire of GATA-3 and PU.1, transcription factors with complementary roles in T cell

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development. The results highlight potential promoter-distal *cis*-regulatory elements in play and reveal both activation sites and diverse mechanisms of repression that silence genes used in alternative lineages. Histone marking is dynamic and reversible, and though permissive marks anticipate, repressive marks often lag behind changes in transcription. In vivo binding of PU.1 and GATA-3 relative to epigenetic marking reveals distinctive factor-specific rules for recruitment of these crucial transcription factors to different subsets of their potential sites, dependent on dose and developmental context. [17] Most notable were highly prevalent regions of hypomethylation correlating with increased gene expression, extending tens of kilobases downstream of transcription start sites. Focal regions of low methylation linked to transcription-factor-binding sites shed light on differential transcriptional networks between subgroups, whereas increased methylation due to re-normalization of repressed chromatin in DNA methylation valleys was positively correlated with gene expression. Large, partially methylated domains affecting up to one-third of the genome showed increased mutation rates and gene silencing in a subgroup-specific fashion. [18] Recent work has shown that RNA polymerase (Pol) II can be recruited to and transcribe distal regulatory regions. Here we analyzed transcription initiation and elongation through genome-wide localization of Pol II, general transcription factors (GTFs) and active chromatin in developing T cells. [19] CDH1 mRNA downregulation relative to the wild-type, was 3.5-fold for deletion of CDH1-TANGO6, 1.5-fold for the intergenic region, 1.6-fold for CDH1 deletion alone, and unchanged for the TANGO6 deletion. Deletions of both CDH1-TANGO6 and the intergenic region induced downregulation of CDH1-associated pathways, namely cell-cell junction, cadherin binding, cell substrate junction, and mitosis and nucleosome organization pathways. [20] OVARIAN cancer research focuses on answering important questions related to the disease, determining whether new approaches are feasible to contribute towards improving current treatments or discovering new ones. This study focused on the transcriptional regulation of genes that have been implicated in ovarian cancer, based on the occurrences of single nucleotide polymorphisms (SNPs) within transcription factor binding sites (TFBSs). Through the application of several in silico tools, databases and custom programs, this research aimed to contribute toward the identification of potentially bio-medically important genes or SNPs for pre-diagnosis and subsequent treatment planning of ovarian cancer.[21] Such cancer predisposition genes associated with moderate to high lifetime cancer risks, conventionally defined as greater than twofold and fivefold increases, respectively, are involved in various biological pathways required for regulating cellular proliferation, maintaining genome integrity, and mediating inter- and intracellular signaling. Clinical use of multigene next-generation sequencing panels has improved molecular diagnosis of cancer predisposition syndromes, demonstrating both genetic heterogeneity and phenotypic variability amongst carriers.[22] Germline mutation in CDH1 (E-cadherin) tumor suppressor gene is associated with hereditary diffuse gastric cancer (HDGC) and lobular breast cancers (LBC). E-Cadherin protein is necessary for physiological signaling pathways, such as cell proliferation, maintenance of cell adhesion, cell polarity and epithelial-mesenchymal transition.[23] E-cadherin (epithelial-cadherin), encoded by the CDH1 gene, is a transmembrane glycoprotein playing a crucial role in maintaining cell-cell adhesion. E-cadherin has been reported to be a tumor suppressor and to be down regulated in gastric cancer. Besides genetic mutations in CDH1 gene to induce hereditary diffuse gastric cancer (HDGC), epigenetic factors such as DNA hypermethylation also contribute to the reduction of E-cadherin in gastric carcinogenesis. [24] Inherited mutations in the E-cadherin gene (*CDH1*) were described recently in three Maori kindreds with familial gastric cancer. Familial gastric cancer is genetically heterogeneous and it is not clear what proportion of gastric cancer susceptibility in non-Maori populations is due to germline *CDH1* mutations.[25] Importance Inherited variants in the tumor suppressor geneCDH1are associated with anincreased risk of gastric and breast cancers. This review aims to address the most current topics in management of the hereditary diffuse gastric cancer syndrome attributed toCDH1.Observations Consensus management guidelines have broadened genetic testing criteria for CDH1. [26] Importance E-cadherin (CDH1) is a cancer predisposition gene mutated in families meeting clinically defined hereditary diffuse gastric cancer (HDGC). Reliable estimates of cancer risk and spectrum in germline mutation carriers are essential for management. For families withoutCDH1mutations, genetic-based risk stratification has not been possible, resulting in limited clinical options. [27] CDH1 is a protein encoded by the *CDH1* gene in humans. Loss of CDH1 function contributes to cancer progression by increasing proliferation, invasion, and/or metastasis. However, the association and clinicopathological

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significance between *CDH1* hypermethylation and gastric cancer (GC) remains unclear.[28]

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