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Impact of CDH1 Mutation Status on Gene Expression and Co-Expression Networks in Stomach Adenocarcinoma

CDH1 Status in Gastric Cancer

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Abstract: Objective: This study aims to explore how cadherin 1 (CDH1) mutation status influences gene expression and co-expression networks in Stomach Adenocarcinoma (STAD). By examining frequently mutated genes, we assess transcriptomic alterations and potential molecular rewiring associated with CDH1 mutations.

Method: Somatic mutation profiles and RNA-seq data for STAD patients were obtained from The Cancer Genome Atlas (TCGA). The 20 most frequently mutated genes were identified. Samples were stratified into CDH1-mutated (CDH1+) and non-mutated (CDH1−) groups. Gene expression differences were analyzed using the Wilcoxon rank-sum test. Spearman's correlation was used to construct gene co-expression networks for each group, with significance defined as FDR-adjusted $P \leq 0.05$ and $|\rho| > 0.5$.

Results: Seven genes showed significant differential expression between CDH1+ and CDH1− tumors. Among these, FAT3, SYNE1, ZFHX4, FAT4, and HMCN1 were upregulated in CDH1+ cases, while PCLO and DNAH5 were downregulated. Co-expression network analysis revealed 47 significant gene-pair correlations in CDH1+ tumors versus 19 in CDH1−.

Conclusion: CDH1 mutation status in STAD is associated with distinct gene expression profiles and co-expression patterns, particularly involving genes related to cell adhesion and cytoskeletal organization. These findings highlight the broader impact of CDH1 alterations beyond E-cadherin loss and suggest candidate genes and pathways that may serve as biomarkers or therapeutic targets in CDH1-mutant gastric cancer.

Keywords: CDH1, Correlation network, Gene expression, Stomach adenocarcinoma

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INTRODUCTION

Despite a decrease in the number of cases in certain parts of the world, gastric cancer continues to be a serious issue as it is still among the most widespread tumors (1). Majority of stomach cancer is made up by a histological type known as Stomach Adenocarcinoma (STAD) which is also characterized by a great molecular variability (2). Diagnosis, prognosis and treatment are difficult due to this diversity, which has led to extensive studies in order to determine its genetic and transcriptomic bases. The emergence of extensive sequencing initiatives like The Cancer Genome Atlas (TCGA) has enabled a thorough molecular analysis of STAD (3). This aids in uncovering various patterns of genetic changes and disrupted signaling pathways. These studies highlight the presence of mutations that occur over and over again in important genes like tumor protein p53 (TP53), AT-rich interactive domain-containing protein 1A (ARID1A), cadherin 1 (CDH1); as well as changes in chromatin remodeling and cell adhesion (4). By so doing, these findings not just clarified how stomach cancer begins but also facilitated the creation of some molecular classifications that reflect more on the nature of tumor (5).

CDH1 is one of the key genes that is known to cause gastric cancer when mutated. E-cadherin is encoded by CDH1 gene and it is a transmembrane glycoprotein that is very crucial in joining epithelial cells together and also for maintaining structure of tissues (6). Mutations in CDH1 are closely associated with the diffuse subtype of gastric cancer, characterized by poorly cohesive tumor cells and a lack of gland formation (7). Such mutations usually cause disruption of intercellular junctions and increased invasiveness, hence worsening prognosis (8). It is crucial to note that there is also an association between germline CDH1 mutations and hereditary diffuse gastric cancer (HDGC) syndrome, emphasizing their importance in both sporadic and familial cases (7). Even though it is known that CDH1 mutations disrupt cell adhesion and lead to loss of epithelial integrity, little is understood about how CDH1 mutations affect the broader genomic profile and gene expression networks in gastric tumors. The available literature mainly discusses individual gene roles or few molecular pathways, thereby creating a knowledge gap on how CDH1 mutation status may affect expression and interaction of commonly mutated genes in STAD (9).

The recent research indicates that CDH1 mutations may determine not only tumor phenotype but also broader molecular programs that can affect treatment and course of the disease (10). For example, other adhesion related genes may have altered expression or compensatory upregulation in structural proteins might occur within CDH1 dysfunctional tumors giving rise to unique molecular subtypes in STAD. Additionally, depending on CDH1 mutation status, gene co-expression networks could provide an indication of unique regulatory interactions relevant for targeted therapy.

Consequently, this research aims to establish the impact of CDH1 mutation on the expression and co-expression profiles of most frequently mutated genes in STAD. The study will compare CDH1+ tumors with CDH1− tumors in order to identify differentially expressed genes and build comparative correlation networks using TCGA information. This approach can determine if CDH1 mutations cause extensive transcriptional changes and molecular rewiring in STAD. Important regulatory hubs and compensatory mechanisms which might be responsible for the behavior of certain subtypes could also be exposed by the results obtained. Through this study, we hope to enhance our knowledge on the molecular diversity of STAD and isolate potential biomarkers or pathways for use in future diagnosis and treatment plans.

METHODS

Data Collection

Somatic mutation profiles and transcriptomic data for TCGA-STAD cases were obtained from TCGA database. Mutation datasets (Simple Nucleotide Variation and Masked Somatic Mutation) were

retrieved using the TCGAbiolinks R package (v2.34.1) (11). RNA-seq data (STAR-counts) and clinical annotations were downloaded via the UCSC Xena platform. All data corresponded to the TCGA-STAD cohort (3). Total 404 samples are evaluated in TCGA-STAD cohort after excluding samples that do not contain CDH1 mutation data or gene expression data for the most mutated 20 genes.

Identification of most mutated genes

Non-silent somatic mutations (i.e., mutations that alter the amino acid sequence of the encoded protein, such as missense, nonsense, frameshift, and splice site mutations) were extracted, and silent mutations were excluded. Mutation frequencies were calculated as the ratio of patients harboring mutations in each gene to the total cohort size. The 20 genes with the highest mutation rates were selected for downstream analyses.

Stratification by CDH1 mutation status

Patients were classified into two subgroups which are CDH1+ (n=38), comprising samples with non-silent mutations in *CDH1*, and CDH1- (n=366), consisting of samples lacking *CDH1* mutations or containing only silent mutations.

Differential gene expression analysis

Expression levels of the top 20 mutated genes were compared between CDH1+ and CDH1− subgroups. Raw RNA-seq counts were log2-transformed (log2[count + 1]) to approximate normality. Differential expression was assessed using the Wilcoxon rank-sum test, with significance thresholds set at *: P≤0.05, **: P≤0.01, and ***: P≤0.001. Results were visualized as boxplots (ggplot2 R package) (12).

Gene correlation network analysis

Pairwise Spearman's rank correlations (ρ) were computed for the 20 mutated genes within each subgroup. Significant correlations were defined as those with false discovery rate (FDR)-adjusted P≤0.05 and absolute correlation strength $|\rho| > 0.5$. Networks were constructed using the igraph R package, where nodes represented genes, edges represented significant correlations, and edge properties (color: red for positive, blue for negative; width: proportional to $|\rho|$) reflected correlation direction and magnitude (13).

Computational tools and statistical analysis

All analyses were performed in R (v4.4.3). Data retrieval and preprocessing utilized TCGAbiolinks and UCSC Xena. Statistical tests were implemented using the Hmisc package (v5.2-3). Visualizations were generated with ggplot2 (v3.5.1) and igraph (v2.1.4).

RESULTS

Analysis of TCGA-STAD data identified the 20 most frequently mutated genes and titin (TTN), TP53, and mucin 16 (MUC16) were marked as top three (Figure 1). Comparative expression analysis between CDH1+ and CDH1- tumors revealed 7 significantly differentially expressed genes (P≤0.05) (Figure 2): five upregulated in CDH1+ samples [FAT atypical cadherin 3 (FAT3), spectrin repeat containing nuclear envelope protein 1 (SYNE1), zinc finger homeobox 4 (ZFHX4), FAT atypical cadherin 4 (FAT4), and hemicentin 1 (HMCN1)] and two downregulated [piccolo presynaptic cytomatrix protein (PCLO) and dynein axonemal heavy chain 5 (DNAH5)]. 13 genes showed no significant expression difference between groups. Finally, the correlation network constructed based on the expression data of the 20 most frequently mutated genes in CDH1+ and CDH1- samples is presented in Figure 3. All data have been provided in the supplementary material section.

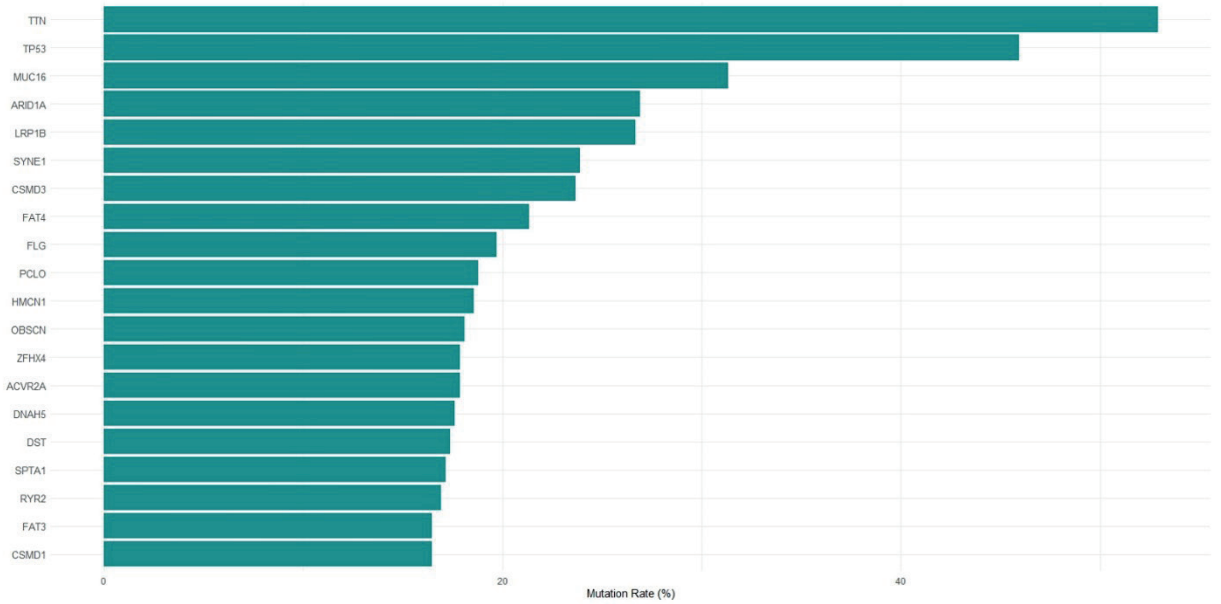

Figure 1. *The most frequently mutated 20 genes in the TCGA-STAD cohort.*

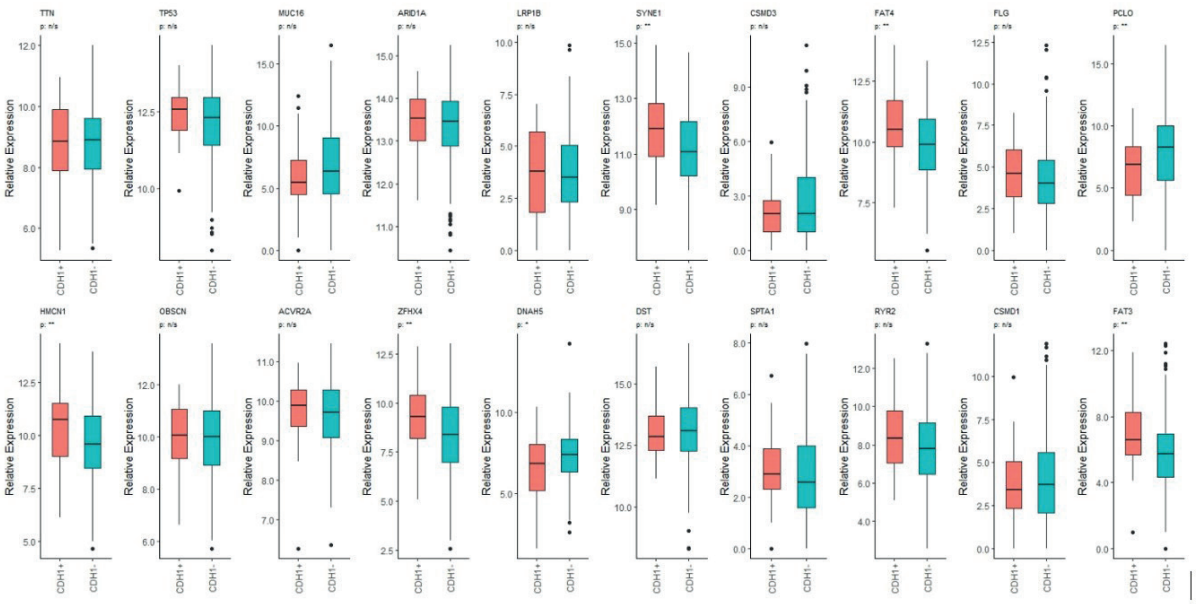

Figure 2. *Comparison of expression levels of the most frequently mutated 20 genes between CDH1+ and CDH1− samples in the TCGA-STAD cohort (*: P≤0.05, **: P≤0.01, ***: P≤0.001, n/s: Not Significant).*

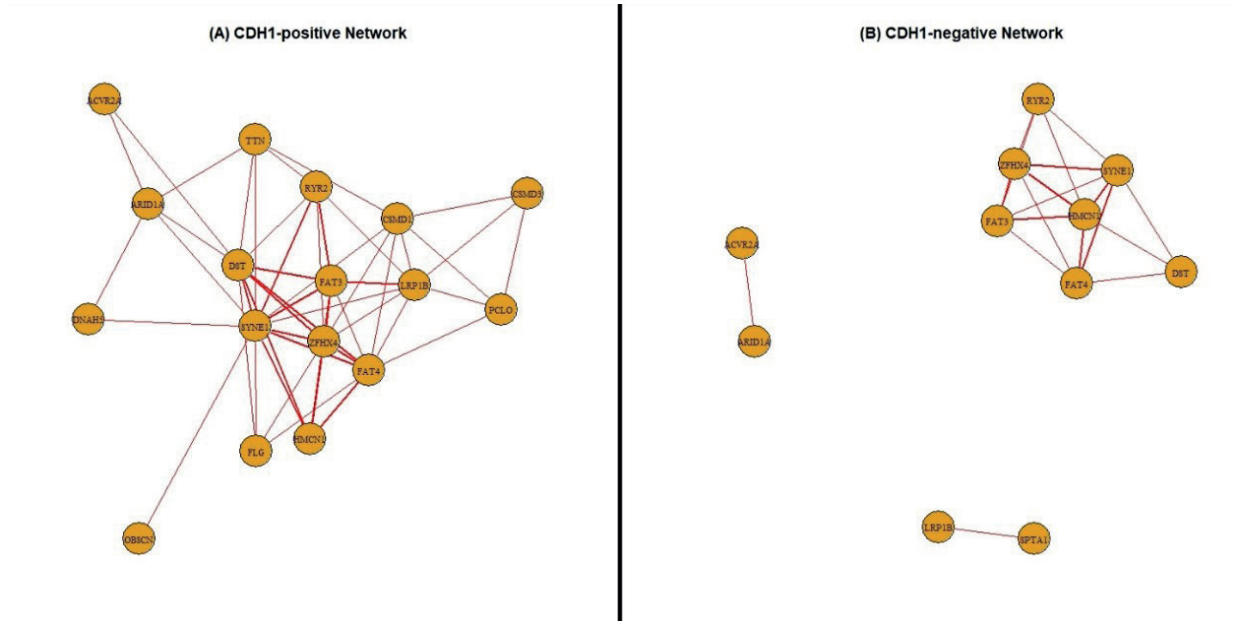

Figure 3. *Gene correlation networks of the most frequently mutated 20 genes in the TCGA-STAD cohort: (A) for CDH1+ samples, (B) for CDH1− samples (Positive correlations are shown in red, negative correlations in blue. Line thickness is proportional to the strength of the correlation coefficient).*

DISCUSSION

The mutational landscape of Stomach Adenocarcinoma (STAD) shows some distinct features that are in line with what we know about how gastric cancer develops. The TTN gene had the highest number of mutations in all cases examined. Although the TTN is very large and therefore prone to random mutations (as it encodes for titin, the largest known protein), there is emerging data that these changes could affect tumor progression through the mechanical properties of cancer cells. TP53 followed closely having mutations in around half of cases analyzed. It is a key cancer suppressor gene that when deactivated causes many cancer types including gastric cancer. Disruption of TP53 leads to resistance of apoptosis, and cells continue dividing even with unstable genomes (14).

The mutation rate of MUC16 is especially curious within the context of gastric cancer, given that this gene codes for CA-125, a glycoprotein related to cell adhesion (15). Loss of epithelial integrity may be enhanced by mutations in this gene, thereby promoting invasion and metastasis (16). The high prevalence of ARID1A mutations underscores the role chromatin remodeling dysregulation plays in STAD pathogenesis since ARID1A is a component of the SWI/SNF complex that controls gene expression by moving nucleosomes around (17). Another commonly changed gene is LDL receptor-related protein 1B (LRP1B) which functions in endocytosis and is linked to resistance when inactivated, hence conferring on tumor cells survival advantages (18). In addition, the fact that many of the highly mutated genes (FAT4, FAT3, DST, SYNE1) code for adhesion and structural proteins indicates that the breakdown of tissue structure is a key aspect in the development of gastric cancer (19). Such changes are expected to compromise contact inhibition and enhance invasiveness.

It is important to note that some commonly mutated genes follow certain patterns that are in line with the TCGA's proposed molecular classifications of gastric cancer, especially the genomically stable and chromosomal instability subtypes (3). The mutational profile is important for comparing

CDH1+ vs CDH1- samples since some of the highly mutated genes are known to interact with or work within CDH1-related pathways. CDH1 is a gene that codes for E-cadherin, which is an important molecule for cell adhesion but usually disrupted in diffuse type of gastric cancer (8). These interactions might expose separate biological pathways and susceptibility profiles particular to CDH1 status in gastric cancer.

The comparison of gene expression profiles in CDH1+ and CDH1- STAD indicates some interesting differences in the way the genes are expressed. These differences may have an impact on the nature of the disease and its outcome in patients. Among the top 20 most frequently mutated genes in STAD, there was a significant difference in 7 when cross-referenced with the CDH1 status ($P \leq 0.05$). It is important to note that out of these 7 genes, 5 (FAT3, SYNE1, ZFHX4, FAT4, and HMCN1) were observed to have increased expressions while 2 (PCLO and DNAH5) had reduced expressions in the CDH1+ subgroup.

The biggest difference was seen in FAT3, which belongs to the cadherin superfamily and is involved in cell adhesion and polarity (20). The observed increase in FAT3 expression in CDH1+ tumors may represent a compensatory effect whereby heightened FAT3 levels serve to partially re-establish the compromised adhesive properties linked with abnormal E-cadherin function. In the same way, FAT4 also showed high levels of expression in relation to CDH1+ samples. These FAT cadherin genes are upregulated together showing a collective response in the cell adhesion network, a probable feature of CDH1+ STAD (19,21).

CDH1+ tumors also had elevated levels of expression for SYNE1 and ZFHX4. SYNE1 codes for a nuclear envelope protein linking nucleoskeleton and cytoskeleton while ZFHX4 acts as a transcription factor involved in neuronal differentiation (22,23). The fact that they are upregulated indicates changes in nuclear structure and gene regulation particular to CDH1+ STAD (24). On top of that, HMCN1 gene, which is responsible for coding an extracellular matrix protein that aids in cell adhesion, portrayed increased expression in CDH1+ samples thereby underlining extensive cell-cell and cell-matrix interaction remodeling in this group (25).

On the other hand, CDH1+ tumors showed significant under-expression of PCLO and DNAH5. Neuronal function is the main function of the cytoskeletal protein that is encoded by PCLO, whereas DNAH5 encodes a component found in ciliary dynein motors. The decrease in their expression could be attributed to changes in cytoskeletal structure and reduced cell motility of CDH1+ STAD, which may affect its invasive and metastatic potential when compared to CDH1- tumors (26,27).

It is interesting to note that some of the highly mutated genes like TTN, TP53 and MUC16 had no significant difference in expression with relation to CDH1 status despite their known roles in STAD (24). This implies that even though STAD patients experience mutations of these genes with high frequency irrespective of CDH1 status, their transcriptional regulation may not be influenced by CDH1 related pathways (28). The observed similarities in the expression levels of important tumor suppressors such as TP53 and ARID1A across both CDH1+ and CDH1- subtypes indicate that these crucial cancer driver genes might act through analogous but different downstream effectors (29).

Another analysis was done on the correlation network of highly mutated genes in STAD. There was a great disparity in the way the genes are transcribed between CDH1+ and CDH1- tumors, which helps us understand better the unique molecular structures of these tumors. For CDH1+ tumors, we found a very tight co-expression network with 47 significant gene-pair correlations (FDR-adjusted $P \leq 0.05$, $|\rho| > 0.5$), as compared to only 19 in the CDH1- subgroup. The observed large difference in network complexity implies that CDH1+ STAD might experience very strict transcriptional control that could be linked to some extent with compensatory effect related to abnormal E-cadherin function (30).

In CDH1+ tumors, co-expression analysis unveiled multiple tight clusters of genes. The hub genes were noted to be SYNE1, FAT4, and ZFHX4, each of them showing strong relationships with no less than 7 other genes across the network. A very high correlation between HMCN1 and ZFHX4 (ρ=0.886) is seen which may imply an interaction between ECM organization and transcriptional regulation (22,25). High positive correlation seen in CDH1+ context between FAT4 and HMCN1 (ρ=0.842), SYNE1 and DST (ρ=0.852), as well as ZFHX4 and FAT4 (ρ=0.819) is also worth noting. These correlations indicate tightly coordinated expression patterns involving cell adhesion, cytoskeletal architecture, and nuclear organization in the CDH1+ tumors (31). Although the CDH1- tumors demonstrated fewer significant correlations, they maintained several key gene associations (such as SYNE1, FAT4, HMCN1, and ZFHX4) observed in CDH1+ tumors. The fact that these basic correlations remained intact across the two subtypes implies that they play a crucial role in STAD development independent of CDH1 mutation status. However, the strength of these correlations generally appeared reduced in CDH1- tumors.

It is important to note that some gene correlations seen in CDH1+ tumors were missing in the CDH1- subgroup. For example, TTN had positive correlation with 5 genes [ARID1A, SYNE1, DST, ryanodine receptor 2 (RYR2), CUB and Sushi multiple domains 1 (CSMD1)] in CDH1+ but not in CDH1-, which implies this commonly mutated gene might have a CDH1 dependent role in gastric carcinogenesis (32). Similarly, CUB and Sushi multiple domains 3 (CSMD3) demonstrated significant correlations with LRP1B, PCLO, and CSMD1 only in CDH1+ tumors, indicating potential functional relationships that are specific to this STAD subtype (33).

Conversely, there was a strong connection between LRP1B and spectrin alpha erythrocytic 1 (SPTA1) (ρ=0.518) in the CDH1- subgroup which was missing in CDH1+ tumors. Perhaps, this kind of correlation arises due to adaptive responses which are turned on only when E-cadherin does not work properly (9). The fact that these two STAD subtypes have dissimilarly high or low expression profiles for certain genes implies that they are inherently distinct at the molecular level, and this may have a role in why they differ so much with regard to treatment outcome as well as prognosis (9).

It is interesting that genes responsible for cell adhesion and cytoskeletal organization intertwined to form closely linked modules in the two subgroups, although they were arranged differently. In CDH1+ tumors, these modules included extensive correlations with nuclear envelope components (SYNE1) and transcriptional regulators (ZFHX4) (22,23). This suggests coordinated regulation of cell architecture and gene expression. The fact that there were tight correlations between SYNE1, FAT4, HMCN1, and ZFHX4 in both categories underlines the importance of cell adhesion and nuclear-cytoskeletal links in STAD progression (34). The subtype-specific differences in these coordination patterns may contribute to the distinct invasive behaviors associated with CDH1 status (35).

Limitations of the study

This study is limited by its reliance on TCGA data and lack protein-level information in its current form. The co-expression findings require experimental validation. Additionally, the CDH1-based grouping does not fully capture tumor heterogeneity or account for other genetic drivers.

CONCLUSIONS

This study reveals that STAD has unique characteristics depending on CDH1 mutation status, which go beyond mere E-cadherin malfunction. Genes related to nuclear structure, cytoskeletal organization, and cell adhesion exhibit varied expression patterns and co-expression interactions, suggesting that CDH1 status affects more cellular functions than previously thought. These results are important for the clinic since they could explain the different behaviors and treatment reactions of diffuse and intestinal STAD subtypes. Future treatment strategies specifically designed to target

identified hub genes and pathways might provide more successful treatments for patients depending on patients' CDH1 status. Furthermore, the above-mentioned strong correlations between specific genes can be used as possible biomarkers for forecasting the beginning of disease and treatment response. Bridging the present genomic information into enhanced clinical management of gastric cancer patients will require more research on the functional implications of the molecular variations found in this study.

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