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Original Article

Molecular and clinical analysis of genes involved in gastric cancer

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ABSTRACT

Gastric cancer is the abnormal growth of stomach cells. The symptoms of this disease include difficulty in swallowing, heartburn, stomach pain, indigestion, nausea, vomiting, and blood in the stool. Gastric cancer is a multifactorial and genetic disease, and many genes and factors are involved in it. *DCC* and *CDH1* are the genes silenced by hypermethylation in gastric cancer and play an influential role in suppressing gastric cancer tumors. The aim of this study was bioinformatics analysis at the genome and proteome level and evaluation and comparison of the expression of *DCC* and *CDH1* genes in different human body tissues. The results of this study showed that the *CDH1* gene is more expressed in the thyroid gland and Parathyroid gland and the *DCC* gene is more expressed in the testis, hippocampal formation, basal ganglia, midbrain, cerebral cortex, and hypothalamus. The expression analysis of these genes showed that both genes generally are more active in glands and have little expression in other body organs. Cellular analysis of *DCC* and *CDH1* genes by antibodies that bind to the proteins of the target genes showed that both genes are active in the Golgi apparatus, with the difference that the *DCC* gene is more present in the nucleus and the *CDH1* gene is more present in the plasma membrane. The expression level of the *CDH1* gene is relatively higher than that of the *DCC* gene. Also, phenotypic studies of the DCC gene showed that this gene is related to colorectal cancer, and it was found that the *CDH1* gene is effective in Blepharocheilodontic syndrome 1. Finally, considering the role of *CDH1* and *DCC* genes as tumor suppressor genes, these items can be used for targeted treatments in gastric cancer.

1. Introduction

Gastric cancer is the second leading cause of death worldwide. According to the statistics of the Cancer Center in 2020, Gastric cancer is one of the five most common cancers in the world [1, 2]. Men are generally affected by this disease twice as often as women. Stomach cancer in blacks is twice as much as in whites, with the sex ratio (male to female 2:1) [3]. Gastric cancer can develop in all parts of the stomach. In most parts of the world, gastric cancers form in the main part of the stomach. Most people who get gastric cancer are between 65 and 74 years old [4]. First-degree relatives of patients with gastric cancer are two to three times more likely to develop this disease [4]. Studies have shown that people with blood type A are more likely to get gastric cancer [5, 6]. Figure 1 shows the effective factors in gastric cancer. There is a lot of evidence that gastric cancer is a multifactorial disease and the result of

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multiple genetic and epigenetic changes in tumor suppressor genes. A number of tumor suppressor genes, including *hMLM1, p14, p15, p16, DAP-K, THBS1, TIMP-3, RARβ, MGMT, CHFR, DCC, GSTP1, RASSF1, COX-2, APC, CDH1, CDH4, RUNX3, TSLC1* and *RASSF1* are silenced by hyper methylation in gastric cancer. In this study, we investigate the two main tumor suppressor genes *DCC* and *CDH1* [7].

DCC gene

DCC gene with accession number NM_005215.4 is located on chromosome 18 (18q21.2) and its inheritance is autosomal dominant. The number of amino acids, molecular weight, and isoelectric point of the number of exons were determined in Table 1 for the *DCC* gene. *DCC* netrin receptor is known as *DCC* and is considered to suppress colorectal cancer. The *DCC* netrin receptor is a protein encoded by the *DCC* gene in humans. The *DCC* netrin receptor is a single membrane receptor. Transmembrane protein is a member of the immunoglobulin superfamily of cell adhesion molecules and mediates axonal guidance [6]. Figure 2A shows the location of this gene on the chromosome.

CDH1 gene

Cadherin 1 is also known as (E-cadherin) and (Uvomorulin). The CDH1 gene codes this protein in humans [8, 9]. *CDH1* with accession number NM_004360.5 is located in a gene cluster with other cadherin family members on chromosome 16(16q22.1) Figure (2 B). The number of amino acids, molecular weight, and isoelectric point of the number of exons were determined in Table 1 for the *CDH1* gene. This gene is a cancer growth suppressor and encodes a cadherin from the cadherin superfamily. Any dysfunction of this gene leads to increased proliferation and invasion in cancer and metastasis [10]. This calcium-dependent cell adhesion protein consists of five extracellular cadherin repeats, a transmembrane region, and a highly conserved cytoplasmic tail. When the production of this protein decreases, the adhesion of cells to each other decreases and cancer cells pass through the basement membrane and invade the adjacent tissues [11]. Mutations in this gene are directly related to stomach, breast, colorectal, colon, thyroid, and ovarian cancer. Researchers use cadherin 1 to differentiate breast cancers from each other. For example, cadherin 1 gene expression is much lower in invasive ductal carcinomas than in invasive lobular carcinomas [12].

Materials and methods

First, the sequences of *DCC* (NM_005215.4) and *CDH1* (NM_004360.5) genes were obtained from the NCBI database. The lengths of these proteins were 1447 and 882 amino acids, respectively. The exact location of these genes was then determined using the UCSC database. The three-dimensional structure of the proteins and drawing of a diagram of Ramachandran were determined using the MBC database, and the molecular weight and isoelectric point of the proteins were determined using the ProtScale database. Cell comparison of *DCC* and *CDH1* genes and expression of these genes were examined by Human Protein Atlas OMIM database.

Table 1. Genes sequence results of *DCC*, and *CDH1*

Name	*DCC*	*CDH1*
ORGANISM	Homo sapiens (Human)	Homo sapiens (Human)
Accession number nucleotide	NM_005215.4	NM_004360.5
Accession number protein	NP_005206.2	NP_004351.1
Gene ID	1630	999
Chromosome	18	16
Inheritance	Autosomal dominant	Autosomal dominant
Cytogenetic location	18q21.2	16q22.1
Chromosome location bp	52340197 - 53535903	68737292 - 68835537
nucleotide length	10181bp	4811bp
protein length	1447aa	882aa
Molecular weight (Da)	158456.54	97456.15
Isoelectric point	6.32	4.57
Total Exon	29	16

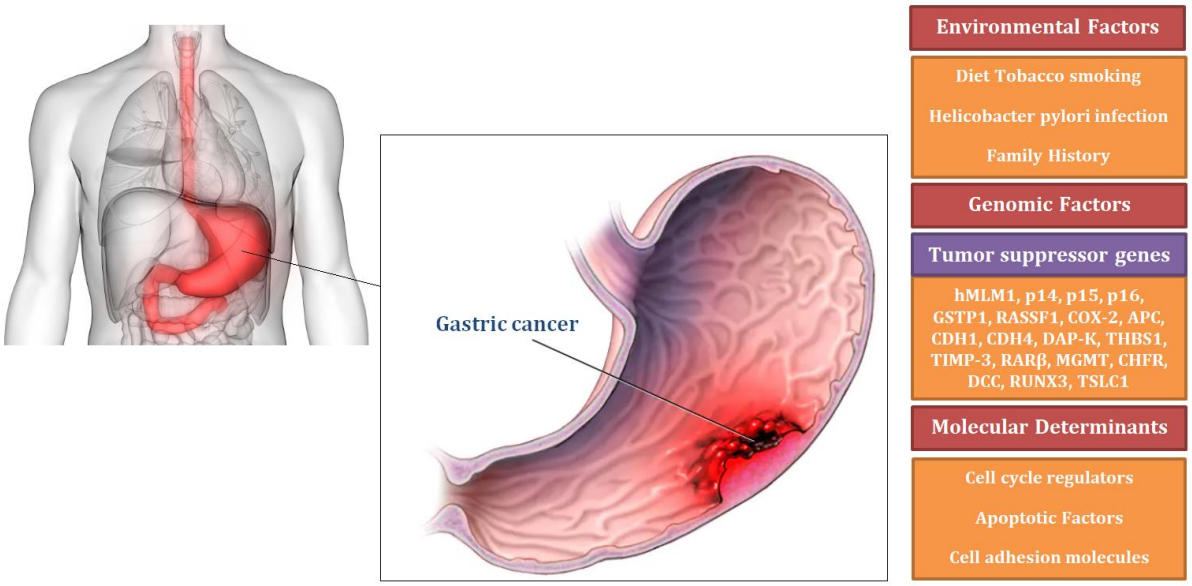

Fig. 1. Factors that cause the development of gastric cancer

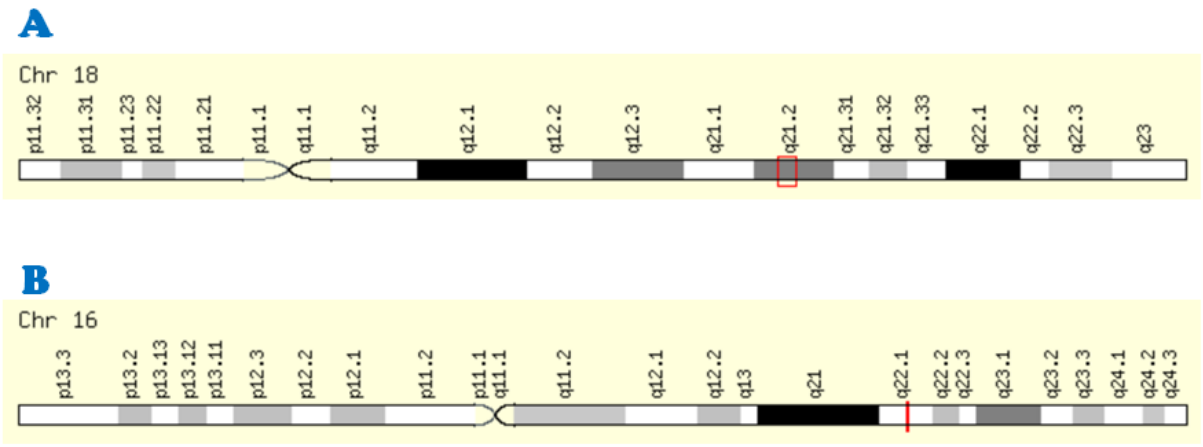

Fig. 2. A) Chromosome 18, the red area, is where the *DCC* gene is located (18q21.2). B) Chromosome 16, the red area, is where the *CDH1* gene is located (16q22.1).

Results

Biological process in DCC gene

DCC gene is involved in biological processes such as neuron migration, apoptotic process, multicellular organism development, nervous system development, axonogenesis, axon guidance, negative regulation of neuron projection development, spinal cord ventral commissure morphogenesis, dorsal/ventral axon guidance, anterior/posterior axon guidance, netrin-activated signaling pathway, negative regulation of collateral sprouting, extrinsic apoptotic signaling pathway in the absence of ligand, regulation of neuron death and negative regulation of dendrite development [13, 14].

Biological process in *CDH1* gene

CDH1 gene is involved in biological processes such as cell adhesion, synapse assembly, response to toxic substance, response to organic substance, pituitary gland development, extracellular matrix organization, neuron projection development, adherens junction organization, entry of bacterium into the host cell, positive regulation of protein import into nucleus, response to the drug, positive regulation of transcription, DNA-templated, cellular response to lithium-ion, cellular response to indole-3-methanol, protein localization to the plasma membrane and cell-cell adhesion [15, 16].

Three-dimensional structure

Molecular homologation modeling using the SWISS-MODEL server in Expasy resulted in a three-dimensional structure of *DCC* and *CDH1* proteins based on sample 1a02 with the highest similarity. Then the proteins related to DCC and CDH1 were determined [17](Figure 3). The estimation of protein quality was determined according to the QMEAN z-scores scale. The value of QMEAN z-scores for the *DCC* gene is equal to 0.55±0.05 and for the *CDH1* gene is equal to 0.74±0.05. According to the QMEAN z-scores, it was found that there is a good match between the model structure and the experimental structures of the same size. Diagrams 1 and 2 show different QMEAN z-scores, which include QMEAN, C-beta interactions, interactions between all atoms, solvation, and torsion, for *DCC* and *CDH1* genes. Then Ramachandran diagram related to *DCC* and *CDH1* proteins was determined to determine the energy level and stability in terms of two angles φ and ψ in proteins. Considering that in *DCC* protein, the percentage of amino acids in Ramachandran favoured was 92.84% and in *CDH1* protein the percentage of amino acids Ramachandran favoured was 86.95%. Therefore, the proposed model is suitable for three-dimensional structures for proteins (Figure 4).

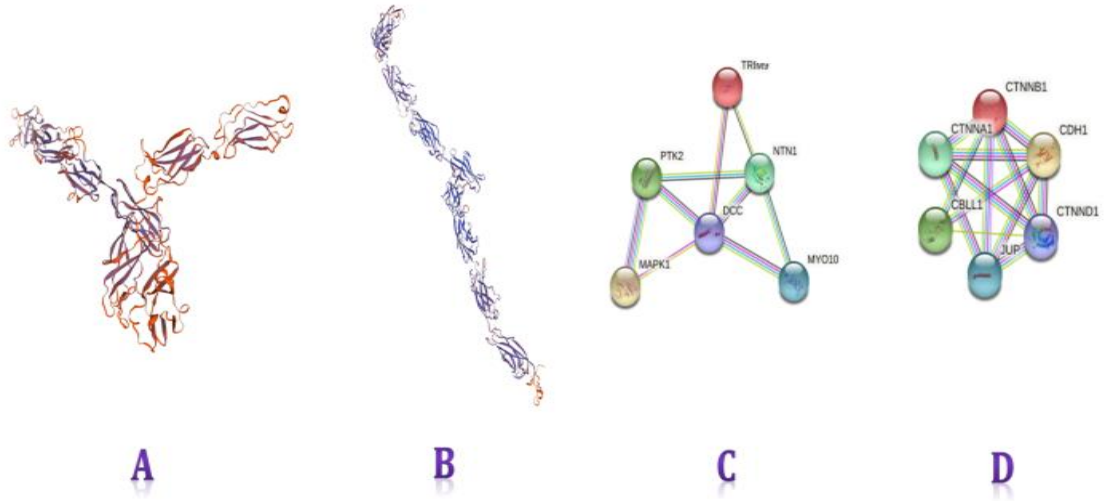

Fig 3. A) Three-dimensional structure of *DCC* protein. B) Three-dimensional structure of *CDH1* protein. C) Interacting proteins for *DCC* Gene. D) Interacting proteins for *CDH1* Gene.

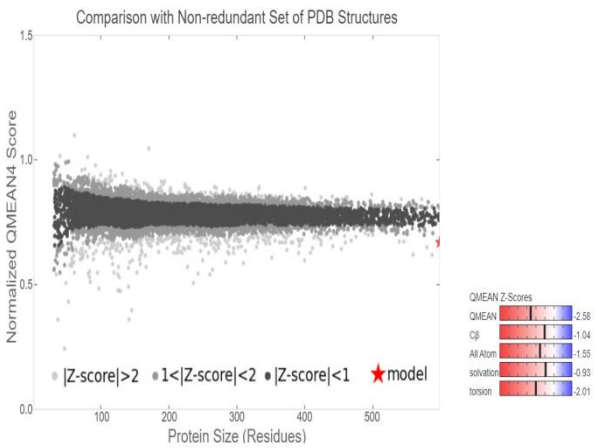

Diagram 1: Plot showing the QMEAN value and Z-score for the *CDH1* gene.

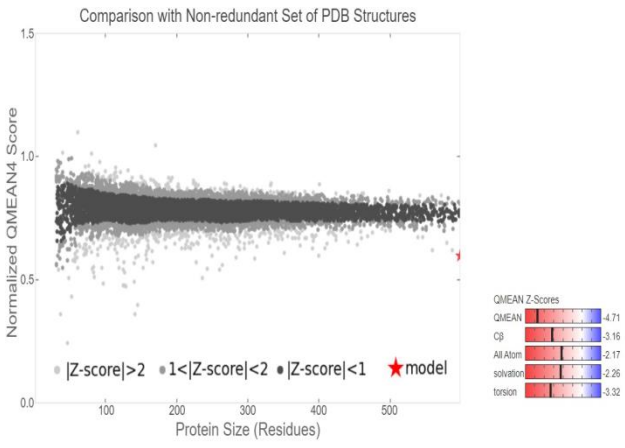

Diagram 2: Plot showing the QMEAN value and Z-score for the *DCC* gene.

Gene expression analysis

The analysis of gene expression showed that *DCC* gene expression is high in certain parts such as the Testis, Hippocampal formation, Basal ganglia, Midbrain, Cerebral cortex, and Hypothalamus and generally has low expression in other organs. Also, regarding *CDH1* gene expression, the highest level of expression was observed in the Thyroid gland and Parathyroid gland. In general, *CDH1* gene expression was higher than the *DCC* gene in different organs. The study of gene expression by microarray expression data also confirmed these findings (Diagrams 3-4).

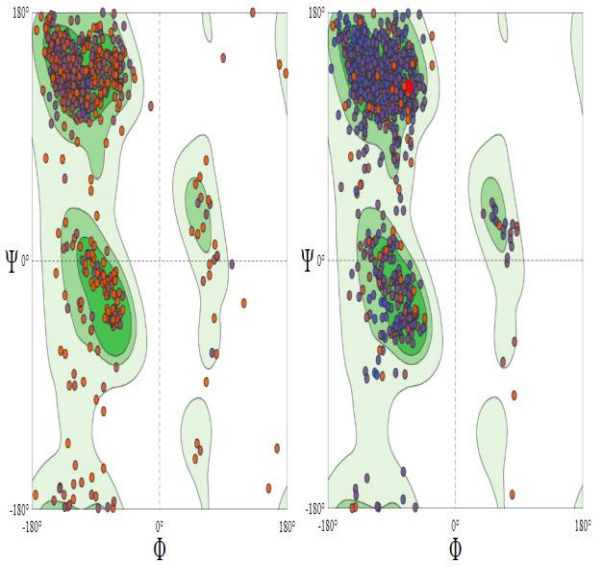

Fig. 4. The right side of the *DCC* protein Ramachandran diagram left side of the *CDH1* protein Ramachandran diagram.

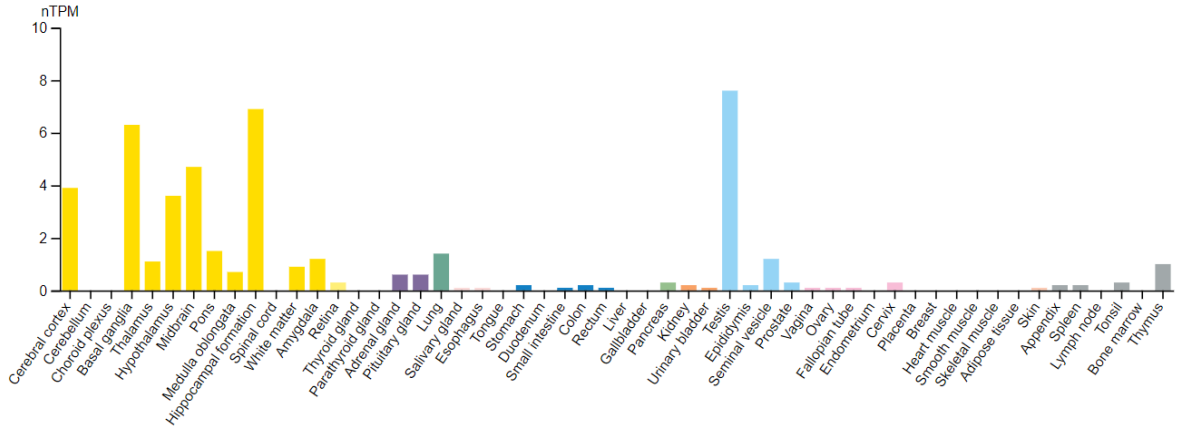

Diagram 3. Results of the study of *DCC* gene expression

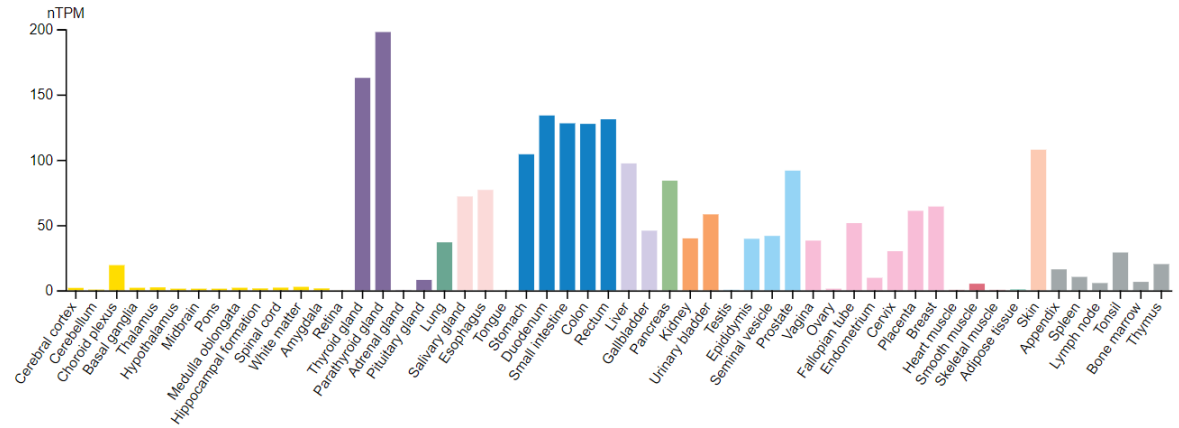

Diagram 4. Results of the study of *CDH1* gene expression

Cellular comparison of *DCC* and *CDH1* genes

Immunofluorescence staining of human cell line AF22 showed DCC gene localization to the Golgi apparatus (Figure 5A-B) [18]. Also, immunofluorescence staining of human cell line A-431 showed CDH1 gene localization to the plasma membrane, the Golgi apparatus, and cell junctions (Figure 5C) [19, 20].

Clinical and phenotypic investigations

The phenotypic investigation of the *DCC* gene showed that this gene is related to colorectal cancer, esophageal carcinoma, Gaze palsy, progressive scoliosis 2, and Mirror movements 1 and/or agenesis of the corpus callosum, and it was found that *CDH1* gene is effective in blepharochilodentic syndrome 1, Breast cancer, lobular, Diffuse gastric and lobular breast cancer syndrome with or without cleft lip and/or palate, Endometrial carcinoma, and ovarian cancer [21, 22] (Figure 6).

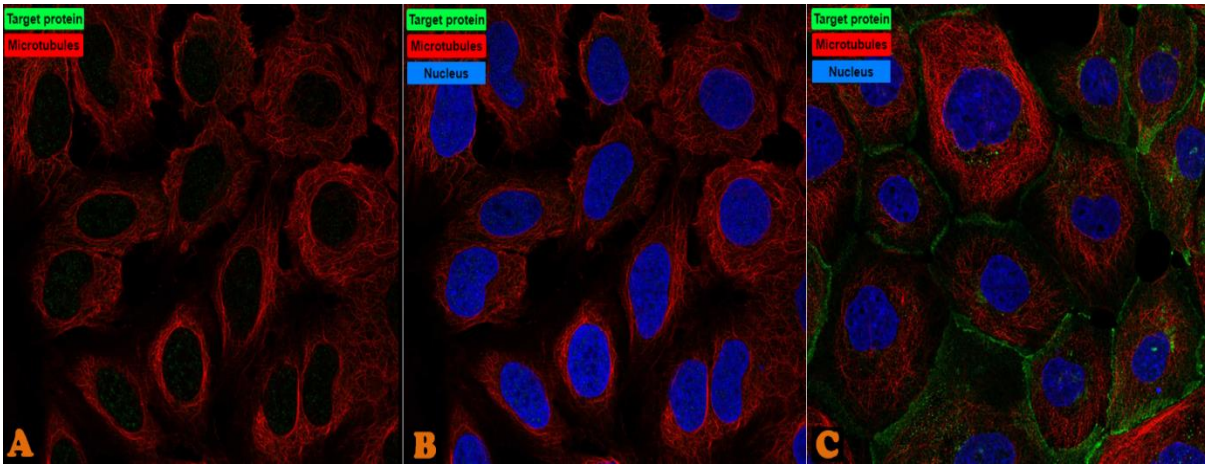

Fig. 5. A) Cellular analysis of the *DCC* gene without nuclear labeling by antibodies that bind to target gene proteins. B) Cellular analysis of the *DCC* gene in the presence of the nucleus by antibodies that bind to the proteins of the target genes. C) Cellular analysis of the *CDH1* gene by antibodies that bind to the proteins of the target genes.

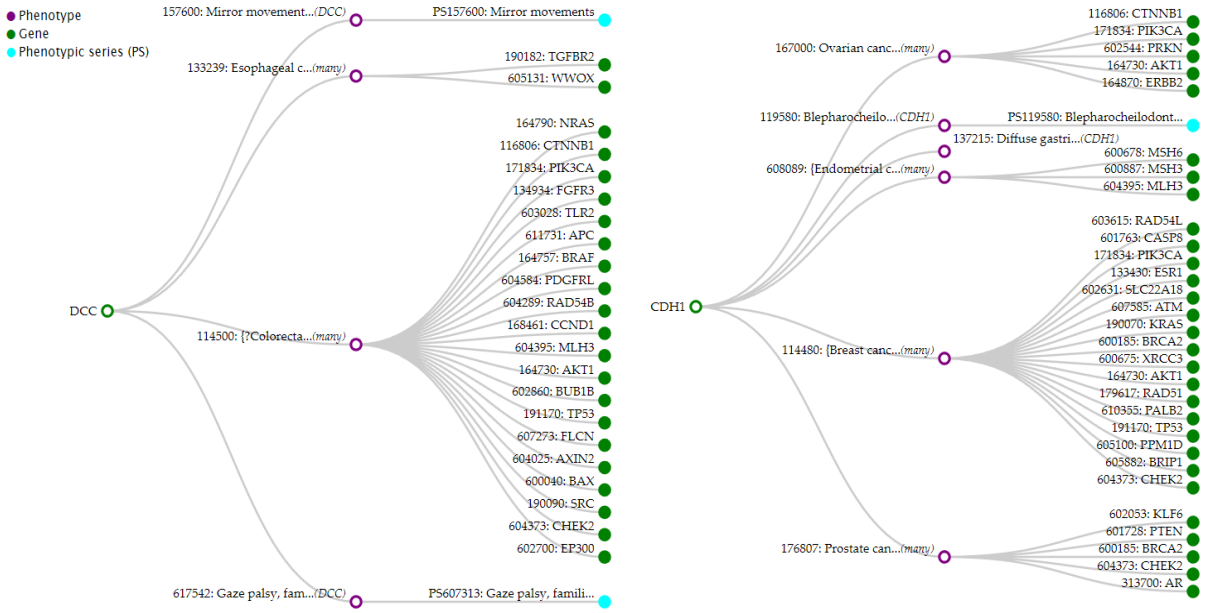

Fig. 6. Clinical and Phenotypic results of *DCC* and *CDH1* genes

Discussion

Gastric cancer is one of the most common malignant tumors in the world, and it has spread a lot in the last few years [23]. Aberrant methylation in the promoter and decreased expression of cancer-related genes is the cause of many human cancers. The obtained results show that methylation acts in the *CDH1* promoter and mutation in the *CDH1* gene as two important factors in the occurrence of gastric cancer [24]. Regarding the *DCC* gene, researchers have shown that the loss of *DCC* gene expression is related to gastric cancer and the reduction of its expression leads to malignant developments in this type of cancer [25]. This research showed that *CDH1* gene expression is higher than the *DCC* gene, and it is also present in the membranous area of the Golgi apparatus in addition to the nucleus. Since the promoter of KCNMA1 leads to the reduction of gastric cancer by suppressing the expression of *PTK2* and the *DCC* gene is also related to this protein, it can be concluded that the *DCC* gene can probably prevent the destructive effects of *PTK2* expression [26].

Benusiglio et al. showed that the mutation in *CDH1* and *CTNNA1* genes produce similar results and the reduction of expression in these genes causes an increase in tumor genesis, which can be justified considering the protein relationship of *CDH1* and *CTNNA1* [27]. The results of phenotypic and clinical examination of the *DCC* gene also showed that this gene is related to colorectal cancer and the *CDH1* gene is related to ovarian cancer and lobular breast cancer. In general, considering that two genes, *DCC* and *CDH1*, are effective in preventing the development of gastric cancer, at this time, the identification of specific molecular factors and biomarkers in gastric cancer is considered vital. This information may be a new solution for more awareness and targeted treatment [23].

Conclusion

Finally, considering the role of *CDH1* and *DCC* genes as tumor suppressor genes, these items can be used for targeted treatments in gastric cancer.

Abbreviations

DCC: Deleted in Colorectal Carcinoma

CDH: Cadherin

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

The authors declare not to use any patients in this research.

Ethics approval and consent to participate

No human or animals were used in the present research.

Consent for publication

All authors read and approved the final manuscript for publication.

Availability of data and material

All the data are embedded in the manuscript.

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Author contributions

All authors are equally involved in the preparation of this manuscript and endorse the manuscript.

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