Comprehensive analysis of prognostic significance of cadherin (CDH) gene family in breast cancer

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ABSTRACT

Breast cancer is one of the leading deaths in all kinds of malignancies; therefore, it is important for early detection. At the primary tumor site, tumor cells could take on mesenchymal properties, termed the epithelial-to-mesenchymal transition (EMT). This process is partly regulated by members of the cadherin (CDH) family of genes, and it is an essential step in the formation of metastases. There has been a lot of study of the roles of some of the CDH family genes in cancer; however, a holistic approach examining the roles of distinct CDH family genes in the development of breast cancer remains largely unexplored. In the present study, we used a bioinformatics approach to examine expression profiles of CDH family genes using the Oncomine, Gene Expression Profiling Interactive Analysis 2 (GEPIA2), cBioPortal, MetaCore, and Tumor IMmune Estimation Resource (TIMER) platforms. We revealed that CDH1/2/4/11/12/13 messenger (m)RNA levels are overexpressed in breast cancer cells compared to normal cells and were correlated with poor prognoses in breast cancer patients’ distant metastasis-free survival. An enrichment analysis showed that high expressions of CDH1/2/4/11/12/13 were significantly correlated with cell adhesion, the extracellular matrix remodeling process, the EMT, WNT/beta-catenin, and interleukin-mediated immune responses. Collectively, CDH1/2/4/11/12/13 are thought to be potential biomarkers for breast cancer progression and metastasis.
INTRODUCTION

Breast cancer is one of the most common malignancies among women and the second leading cause of death after lung cancer [1, 2]. The prognosis of breast cancer is better with early detection and improved treatment. Because of the poor prognosis of advanced breast cancer, research on breast cancer has recently focused on precise detection of invasion and metastasis with accurate tumorogenic biomarkers [3–9]. Despite progress in developing diagnostic screening tools, distant metastases at the time of diagnosis indicates a worse prognosis with only 23% of patients surviving 5 years post-diagnosis [10]. Therefore, novel research on genetic alterations and signal transduction pathways is playing important roles in both early breast cancer detection and treatment in advanced stages [11–13].

The cadherins (CDHs) are a superfamily of calcium-dependent adhesion molecules which have functions in cell recognition, tissue morphogenesis, and tumor suppression [14, 15]. The CDH family consists of 23 members, from CDH1 to CDH26, as documented in the GeneCards database [16]. Basic characteristics of the CDH gene family, including gene IDs and aliases, are presented in Table 1. Classic cadherins have mostly been thoroughly studied, including epithelial (E)-cadherin (CDH1), neural (N)-cadherin (CDH2), placental (P)-cadherin (CDH3), and retinal (R)-cadherin (CDH4) [17].

It is widely accepted that the epithelial-to-mesenchymal transition (EMT) of epithelial cells results in strong cell-cell adhesion and more invasive features [18]. The EMT is essential for this phenomenon and is considered a promoter of metastasis, and metastic processes associated with mesenchymal features are similar among various cancers such as advanced breast cancer. The EMT has also received a lot of interest in cancer research and is thought to be an important step in metastases [19, 20]. As a result, finding new molecules that can inhibit this mechanism is an important subject of scientific study. A feature of the EMT is in part a result of downregulation of CDH1 and parallel upregulation of other cadherins like CDH2, which plays an essential role during early invasion and metastasis [21]. Loss of CDH1 alone might be insufficient to induce the EMT [22]. Instead, CDH1 expression was observed in invasive lobular carcinomas (ILCs) and invasive ductal carcinomas (IDCs) [23]. Other cadherins and molecules such as β-catenin, which forms an important membrane complex, are often detached from the cell membrane and are translocated to the nucleus to induce EMT signaling events [24–26].

Previous studies reported the roles of cadherins in breast cancer. However, interactions and pathways among all CDH family members and related molecules in tumorigenesis are still unclear, and challenges remain in discovering suitable biomarkers for precision treatment and detection.

The present study is the first study to perform a bioinformatics analysis of the entire CDH family in patients with breast cancer by analyzing several large online databases. A flowchart depicting the investigative strategies we utilized in this study, including expression levels, clinical survival, and functional enrichment analyses, of CDH family members in breast cancer is presented in Figure 1. First, original data were retrieved from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) and The Cancer Genome Atlas (TCGA) databases. Second, differential expression levels were analyzed using the Oncomine and Tumor Immune Estimation Resource (TIMER) databases. Third, Kaplan-Meier (KM) plots were utilized to reveal the significance of CDH family in the prognosis of breast cancer patients. Incorporating these results, we selected targeted genes due to higher expression levels and lower survival for further analysis. Then, the Cancer Cell Lines Encyclopedia (CCLE) and Gene Expression Profiling Interactive Analysis 2 (GEPIA2) databases were used to discover differences in expressions between breast cancer and normal tissues [27–31]. Afterwards, we used the MethSurv database to determine single CpG methylation expression patterns. In addition, we studied the gene potential thoroughly through a functional enrichment analysis and micro (mi)RNA-regulated networks, including biological processes (BPs), cellular components (CCs), molecular functions (MFs), signaling pathways, and potentially regulated miRNAs. Ultimately, we utilized the TIMER2.0 database to uncover correlations between CDH genes and immune cell markers in breast cancer. The flowchart is presented to offer insights into our comprehensive approach and possibly suggest a theoretical foundation for future research.

MATERIALS AND METHODS

Oncomine analysis

Oncomine (https://www.oncomine.com/) is an online database established to show information of gene expressions in major cancers compared to their respective normal samples [32]. In this study, individual expression levels of CDH family members in various cancers were obtained from the Oncomine database with p<0.05 and fold change (FC) defined as 1.5 [33–37].

TIMER and GEPIA2 analyses

The TIMER database was utilized to identify complements or regulatory factors that are upregulated
Table 1. Basic characteristics of the CDH gene family.

| Approved symbol | HGNC ID | Gene ID | Aliases | Location on chromosome |
|-----------------|---------|---------|---------|------------------------|
| CDH1            | 1748    | 999     | Cadherin 1; Uvomorulin; CD324; UVO; Cadherin 1, Type 1, E-Cadherin (Epithelial) | 16q22.1 |
| CDH2            | 1759    | 1000    | Cadherin 2; CDHN; CD325; NCAD; Cadherin 2, Type 1, N-Cadherin (Neuronal) | 18q12.1 |
| CDH3            | 1762    | 1001    | Cadherin 3; CDHP; PCAD; Cadherin 3, Type 1, P-Cadherin (Placental) | 16q22.1 |
| CDH4            | 1763    | 1002    | Cadherin 4; R-Cadherin; Cadherin 4, Type 1, R-Cadherin (Retinal) | 20q13.33 |
| CDH5            | 1764    | 1003    | Cadherin 5; VE-Cadherin; CD144; 7B4 | 16q21 |
| CDH6            | 1765    | 1004    | Cadherin 6; Cadherin 6, Type 2, K-Cadherin (Fetal Kidney) | 5p13.3 |
| CDH7            | 1766    | 1005    | Cadherin 7; Cadherin 7, Type 2; Cadherin-7; CDH7L1 | 18q22.1 |
| CDH8            | 1767    | 1006    | Cadherin 8; Cadherin 8, Type 2; Cadherin-8; Nbla04261 | 16q21 |
| CDH9            | 1768    | 1007    | Cadherin 9; Cadherin-9; Cadherin 9, Type 2 (T1-Cadherin) | 5p14.1 |
| CDH10           | 1749    | 1008    | Cadherin 10; Cadherin-10; T2-Cadherin; Cadherin 10, Type 2, (T2-Cadherin) | 5p14.2-5p14.1 |
| CDH11           | 1750    | 1009    | Cadherin 11; CAD11; OB; Cadherin 11, Type 2, OB-Cadherin (Osteoblast) | 16q21 |
| CDH12           | 1751    | 1010    | Cadherin 12; Br-Cadherin; CDHB; Neural Type Cadherin 2 | 5p14.3 |
| CDH13           | 1753    | 1012    | Cadherin 13; CDHH; T-Cadherin; H-Cadherin (Heart) | 16q23.3 |
| CDH14           | 1754    | 1013    | Cadherin 15; CDH 14; CDH3; Cadherin 15, Type 1, M-Cadherin (Myotubule) | 16q24.3 |
| CDH15           | 1755    | 1014    | Cadherin 16; Cadherin 16, KSP-Cadherin; Kidney-Specific Cadherin | 16q22.1 |
| CDH16           | 1756    | 1015    | Cadherin 17; HFT-1; Intestinal Peptide-Associated Transporter HFT-1 | 8q22.1 |
| CDH17           | 1757    | 1016    | Cadherin 18; CDH14; Cadherin 18, Type 2 | 5p14.3 |
| CDH18           | 1758    | 28513   | Cadherin 19; CDH7; Cadherin 19, Type 2 | 18q22.1 |
| CDH19           | 1760    | 28316   | Cadherin 20; CDH7L3; Cdh7 | 18q21.33 |
| CDH20           | 13251   | 64405   | Cadherin 22; DJ998H6.1; C20orf25 | 20q13.12 |
| CDH21           | 13733   | 64072   | Cadherin 23; CDHR23; Cadherin-Related Family Member 23 | 10q22.1 |
| CDH22           | 14265   | 64403   | Cadherin 24; CDHH11L; Cadherin 24, Type 2 | 14q1.2 |
| CDH23           | 15902   | 60437   | Cadherin 26; VR20; Cadherin-Like Protein VR20 | 20q13.33 |

or downregulated in tumor samples compared to normal tissues. To analyze differences in gene expressions of each CDH family member between breast cancer and normal tissues, differentially expressed genes (DEGs) in breast invasive carcinoma (BRCA) in TCGA dataset were identified via TIMER. The threshold |log2[FC]| was set to 1, and the value of q was 0.05. GEPIA2 (http://gepia2.cancer-pku.cn/#index) is a web platform that contains RNA sequencing (RNA-Seq) expression data from 9736 tumors and 8587 normal samples from TCGA and GTEx projects [38]. An independent t-test was used to calculate p values, and p<0.05 was considered statistically significant; Pr(>F)<0.05 was based on Student’s t-test [39–44].

KM plotter survival analysis

The KM plotter (http://kmplot.com/analysis/) contains 54,000 genes associated with survival in 21 types of cancer [45], including breast cancer samples (n=7830), which can be analyzed to examine the effects of CDH gene family members on survival times of patients with breast cancer. Results are presented by plotting the survival curve and hazard ratios (HRs) with 95% confidence intervals (CIs) and log-rank p values [46]. To assess the prognosis of breast cancer patients, distant metastasis-free survival (DMFS) was applied to evaluate the survival of advanced breast cancer patients.

Genetic alterations and protein expression analysis

The cBioPortal (http://www.cbioportal.org/) is an open platform providing large-scale visualization, analysis, and downloading of cancer genomic datasets for various types of cancer [47, 48]. Cancer genome profiles can be obtained by a portal query interface, allowing researchers to explore and compare genetic alterations across samples. This study used the cBioPortal to explore alterations, correlations, and networks of the CDH gene family. CDH family protein expressions were evaluated by the Human Protein Atlas (HPA) platform. HPA contains images of pathologic tissues labeled with antibodies in conjunction with 11,250 human proteins. Microarrays include sections from forty-six normal tissues and more than twenty types of human cancers [49–51]. This study used the HPA to obtain the intensities of labeled antibodies in pathologic malignant tissues. Bar charts represent the quantification of four classifications, “negative”, “weak”, “moderate”, and “strong”, of IHC staining intensities in breast cancer samples with different antibodies.

Expression modules in breast cancer gene-expression analysis

“Breast cancer gene-expression miner” (bc-GenExMiner), which contains published annotated breast
Figure 1. Flowchart of the study design and analytical steps in the present study. Gene data were retrieved from TCGA and METABRIC databases. To select targeted genes among the cadherin (CDH) family, we observed results of simultaneous higher expression levels in cancer cells than normal tissues and poorer prognoses in breast cancer patients. Afterwards, through four steps of a “differential expression analysis”, “survival analysis, protein levels, and DNA methylation”, “functional enrichment analysis”, and “tumor microenvironment”, a comprehensive analysis was conducted with the following databases and analytical methods. TCGA, The Cancer Genome Atlas; METABRIC, Molecular Taxonomy of Breast Cancer International Consortium; TIMER, Tumor IMmune Estimation Resource; CCLE, Cancer Cell Line Encyclopedia; GEPIA2, Gene Expression Profiling Interactive Analysis 2; KM, Kaplan-Meier; IHC, immunohistochemistry; BPs, biological processes; MFs, molecular functions; CCs, cellular components; KEGG, Kyoto Encyclopedia of Genes and Genomes; GSEA, Gene Set Enrichment Analysis; miRNA, micro-RNA.
cancer transcriptomic data (DNA microarrays \( n=11,359 \) and RNA-Seq \( n=4421 \)), is a breast cancer-associated web portal (http://bgenex.ico unicancer.fr) that conducts several differential gene expression analyses. We obtained data from Affymetrix® median probe data. To evaluate the difference in a gene’s expression among different groups, Welch’s test was used. Moreover, Dunnett-Tukey-Kramer’s test was used for two-by-two comparisons (allowing determination of the significance levels but not giving a precise \( p \) value) when there were more than three different groups and Welch’s \( p \) value was significant. Variant corresponding clinical or pathological data is contained in bc-GenExMiner version 4.5, which stresses that the Expression Module can be utilized for both exploratory and validation purposes [52].

Cancer cell line encyclopedia (CCLE) analysis

Over 1100 cell lines among 37 cancer types are contained in the CCLE database (https://portals.broadinstitute.org/ccle). The CCLE dataset provides extensive genomic data, computational analyses, and visualization [53]. For the present study, we used the CCLE dataset to investigate messenger (m)RNA expression levels of \( CDH \) family members to further verify their participation in cancer cell lines [54–57].

DNA methylation analysis

The MethSurv (https://biit.cs.ut.ee/methsurv/) database was utilized to determine single CpG methylation expression patterns and establish a heatmap of the different DNA methylated regions [58]. DNA methylation values are presented as beta values (ranging from 0 to 1). We used the formula of \( M / (M + U + 100) \) to calculate each single methylation of CpG, where \( M \) and \( U \) respectively represent methylated and unmethylated intensity values.

Functional enrichment and miRNA-regulated network analyses

The METABRIC and TCGA datasets in the cBioPortal database were accessed for functional enrichment analyses [59, 60]. There were two parts of the MetaCore analysis (https://portal.genego.com). The first part was to find overlapping genes coexpressed in the two datasets with Venny version 2.1. The second part was to uncover BPs, disease biomarker networks, breast neoplasm signaling pathways, and drug target networks [61–65]. Moreover, a gene ontology (GO) analysis was implemented to discover the functional significance of genes with BPs, MFs, CCs, and the Kyoto Encyclopedia of Genes and Genomes (KEGG) with \( p \) values of <0.05 indicating statistical significance [66–70]. Next, we used the median expression of targeted genes and then performed a differential analysis with an algorithm in the “DESeq2” package in R/Bioconductor. After the differential analysis, results were utilized for the gene set enrichment analysis (GSEA) with the Hallmark database [71–73]. Then, we used the “fgsea” packages in R Studio software to evaluate enriched pathways in transcriptional data by the GSEA, and online platform (http://www.bioinformatics.com.cn/) and used “SRplot” for visualization (http://www.bioinformatics.com.cn/ srplot) [74, 75]. The level of statistical significance was presented via \( p \) values, and a normalized enrichment score (NES) reflected the rank of gene classes. In addition, the gene potential of the \( CDH \) family was conducted using the miRWalk database (http://mirwalk.umm.uni heidelberg.de/) to investigate the regulatory potential of miRNAs and to analyze regulated pathways and networks by an Ingenuity Pathway Analysis (IPA) [76–79].

Cox regression analysis in TIMER

The TIMER web server was accessed for a Cox regression analysis [80, 81]. We used the “Survival” module to explore the clinical significance of covariates in a multivariable Cox proportional hazard model. Clinical factors such as age, gender, ethnicity, and tumor stage and gene expression were covariates in the analysis. TIMER presents Cox regression results including hazard ratios (HRs) and statistical significance. For outputs of the Cox model, Surv(CancerType)-variables is the formula of the user-defined Cox regression model, which is fitted by the function coxph() from the R package ‘survival’. In the results, the coefficient reads as a regression coefficient. The 95% confidence intervals (CIs) are shown.

Data availability

The present study is based on open-source data. Users could download relevant data in public databases for research.

RESULTS

Differential expressions of \( CDH \) family members in breast cancer

To understand differences in expressions between breast cancer and normal tissues, all 24 \( CDH \) family members were investigated in the Oncome database (Figure 2A, 2B). Findings of this database revealed that at the transcriptional level, \( CDH1/2/4/6/7/11/12/13/15/22/23/24 \) were overexpressed in breast cancer samples compared to normal tissues, while transcriptional levels of \( CDH1/3/5/8/9/10/16/17/18/19/20/26/28 \) were downregulated compared to normal tissues. In addition, complement expressions were explored across TCGA
Figure 2. mRNA transcription levels of cadherin (CDH) gene family members (ONCOMINE). A red background with numbers indicates studies including expression levels of CDH family members corresponding to our selection standards (with p values <0.05, fold changes of >1.5, and the expressed gene rank in the top 10% as selection thresholds) in cancer tissues; blue (the same selection threshold) in normal tissues. The number for the significant unique analyses means that the queried genes significantly differed in these studies. The number for the total unique analyses means the total number of queried genes in these studies. (**A**) mRNA transcription levels of CDH1/2/4/6/7/11/12 were overexpressed in breast cancer samples compared to normal tissues, while transcriptional levels of CDH1/3/4/5/6/9/10/12 were downregulated compared to normal tissues. (**B**) mRNA transcription levels of CDH13/15/22/23/24 were overexpressed in breast cancer samples compared to normal tissues, while transcriptional levels of CDH13/15/22/23/24 were downregulated compared to normal tissues. Red indicates upregulation, and blue indicates downregulation compared to normal tissues.
Figure 3. Expression levels of cadherin (CDH) gene family members in breast invasive carcinoma (BRCA). (A) In the TIMER database, a box plot shows transcripts of CDH gene family members in normal and breast cancer tissues. The Wilcoxon test was used to determine statistical significance; * p<0.05, *** p<0.001. (B) Expression levels of CDH gene family members in breast cancer cell lines are represented by a heatmap (CCLE). We used data from the CCLE database to generate mRNA expression values, which were then ranked. In CCLE, red denotes overexpression (top column), and blue denotes under-expression (bottom column).
database via the TIMER database (Figure 3A). We investigated expression levels of CDH family members in breast cancer cell lines using the CCLE database as well (Figure 3B). Results revealed that expression levels were upregulated or downregulated in BRCA samples compared to non-tumor samples. Compared to normal tissues, expression levels of CDH3/4/5/6/7/8/9/10/11/12/13/14/15/16/17/18/19/20/22/23/24/26 were significantly higher in BRCA tissues. In contrast, expression levels of CDH1/18 were significantly lower in BRCA tissues. The molecular subtypes of cell lines are also shown in Supplementary Figure 1. CDH1 and CDH7 were highly expressed in luminal A cell lines; CDH5 was mostly expressed in human epidermal growth factor receptor-2 (HER2) cell lines; CDH2/3/4/5/6/11/12/13/15/18/19/22/23 showed high expressions in multiple triple-negative breast cancer cell lines; and other CDH genes showed no specific expressions in molecular subtypes of breast cancer cell lines.

Prognostic analysis of the CDH family via Kaplan-Meier analyses

The impact of the entire CDH family on breast cancer survival was evaluated through the KM plotter database. Distant metastasis-free survival (DMFS) was analyzed due to its significance in clinical prognosis of advanced breast cancer. Results demonstrated that most CDH family genes were associated with the prognosis of BRCA patients including CDH1/2/3/4/5/6/7/9/10/11/12/13/14/15/16/17/18/19/20/22/23/24/26 (Figure 4 and Table 2). High expression levels of CDH1 (HR=1.32, 95% CI=1.13–1.55, p=0.0058), CDH2 (HR=1.39, 95% CI=1.17–1.64, p=0.00012), CDH3 (HR=1.55, 95% CI=1.32–1.82, p=6.4e-8), CDH4 (HR=1.27, 95% CI=1.08–1.5, p=0.0036), CDH7 (HR=1.34, 95% CI=1.14–1.58, p=0.00048), CDH9 (HR=1.21, 95% CI=1.03–1.43, p=0.02), CDH10 (HR=1.34, 95% CI=1.13–1.58, p=0.00059), CDH11 (HR=1.42, 95% CI=1.04–1.96, p=0.028), CDH12 (HR=1.21, 95% CI=1.03–1.41, p=0.019), CDH13 (HR=1.31, 95% CI=1.12–1.54, p=0.00089), CDH15 (HR=1.22, 95% CI=1.03–1.44, p=0.023), CDH16 (HR=1.28, 95% CI=1.09–1.5, p=0.003), and CDH26 (HR=1.68, 95% CI=1.28–2.19, p=0.00012) were correlated with poorer DMFS in BRCA patients. On the other hand, high expressions of CDH5 (HR=0.84, 95% CI=0.71–0.98, p=0.031) and CDH19 (HR=0.71, 95% CI=0.54–0.92, p=0.01) were associated with a good prognosis in BRCA patients. Other family members in the CDH family showed negative results.

A univariate Cox regression analysis was conducted to validate our results from clinical breast cancer patients, data of which were obtained from the TIMER database. The univariate Cox regression demonstrated that high levels of CDH13 were an independent risk factor for poor overall survival (OS) (Supplementary Table 1A) in breast cancer patients. In addition, subtypes of breast cancer, including luminal, HER2, and basal, were analyzed. The luminal subtype showed no significance among CDHs (Supplementary Table 1B). CDH12 was a significant risk factor for poor OS in the HER2 subtype (Supplementary Table 1C). CDH11 and CDH12 were significant risk factors for poor OS in the basal subtype (Supplementary Table 1D).

To further understand correlations of expression levels of CDH family members in breast cancer, some clinical and pathological factors were analyzed in specific genes among the CDH family. Among all CDH family members, CDH1/2/3/4/5/6/7/11/12/13/15/16/26 were significantly positively associated with a lower DMFS (Figure 4), and CDH1/2/4/5/6/7/11/12/13/15/22/23/24 mRNA expression levels were higher in breast cancer than in normal tissues in the Oncomine database (Figure 2A, 2B). Results demonstrated that the eight CDH1/2/4/7/11/12/13/15 genes simultaneously expressed significance in the gene database and clinical survival analysis. Therefore, in this study, these eight specific genes were further analyzed with an extensive database, clinical factors, and bioinformatics tools and were demonstrated to be potential biomarkers for breast cancer.

Correlations of CDH1, CDH2, CDH4, CDH7, CDH11, CDH12, CDH13, and CDH15 expressions with prognosis and different clinical and pathological factors

As CDH1/2/4/7/11/12/13/15 were positive in terms of both gene expressions and with the KM survival analysis, immunohistochemical (IHC) patterns from the HPA were utilized to validate clinical applications by pathology (Figure 5A, 5B). CDH1, CDH2, and CDH12 exhibited strong intensities in cell nuclei in breast cancer samples. Otherwise, other members of the CDH family showed negative or weak intensities in pathological samples. The relative staining intensities of CDH1 were negative (two cases), moderate (one case), and strong (eight cases) in breast cancer samples. CDH2 staining intensities were negative (nine cases), weak (three cases), and strong (one case) in breast cancer samples. CDH12 staining intensities were negative (one case), weak (three cases), moderate (one case), and strong (seven cases) in breast cancer samples. There was no IHC pattern for CDH4 obtained from the HPA. Other staining intensities of CDH family members are shown in Figure 5A, 5B. CDH staining expressions, magnification in 4x, were displayed among CDH family except CDH13 and CDH15 due to negative intensities.

Correlations of expression levels of CDH1/2/4/7/11/12/13/15 with pathological stages of breast cancer are
shown in violin plots in Figure 6A. mRNA levels of CDH1/11/13 were relatively high in breast cancer patients classified as stage IV with metastasis but without statistical significance.

Figure 4. Kaplan-Meier (KM) analysis of cadherin (CDH) family genes in the distant metastasis-free survival (DMFS) of breast cancer patients. The hazard ratio (HR) represents a prognostic value of breast cancer patients. Log[rank p] was utilized to find out the level of prognostic significance of breast cancer patients. In addition, log[rank p] of <0.05 was considered a significant difference in the prognosis of breast cancer patients. High expressions of CDH1/2/3/4/5/7/9/10/11/12/13/15/16/19/26 were significant compared to low expressions, which are highlighted with p values in red boxes. The HRs of CDH1/2/3/4/7/9/10/11/12/13/15/16/26 were significantly higher, which are marked in yellow boxes, indicating poor prognostic outcomes in breast cancer. In contrast, the HRs of CDH5/19 were significantly lower, which were marked in blue boxes, indicating better prognostic outcomes in breast cancer.
Scarff-Bloom-Richardson (SBR) grading is a clinical prognostic predictor associated with cell proliferation and an indicator of the response to chemotherapy (Figure 6B). A determination of an association between the SBR grade and responsiveness would be clinically useful [82]. SBR1 indicates good differentiation, SBR2 moderate differentiation, and SBR3 poor differentiation. Figure 6B demonstrates that CDH1, CDH2, and CDH11 with the poorest prognoses were assigned to grade SBR3.

The Nottingham prognostic index (NPI) is used to predict a prognosis after breast cancer surgery, and is calculated by three pathological factors: the tumor size, the number of involved lymph nodes, and the tumor grade (Figure 6C). Values are used to define three subsets of patients with different survival chances of breast cancer: 1) good prognosis, comprising 29% of patients with an 80% chance of 15-year survival; 2) moderate prognosis, 54% of patients with a 42% chance of 15-year survival; and 3) poor prognosis, 17% of patients with a 13% chance of 15-year survival [83]. The NPI can also be used to evaluate the effect of adjuvant treatment like chemotherapy or radiotherapy. Figure 6C demonstrates that only CDH1 expression was correlated with higher NPI values, indicating poor prognoses in patients with CDH1 gene expression. Otherwise, CDH11 and CDH13 expressions demonstrated lower NPI values with better prognoses. Other CDH family members showed no significance.

Other clinical predictors were also analyzed in terms of CDH family gene expressions in breast cancer (Supplementary Figure 2 in Supplementary Materials). Estrogen receptor (ER)/progesterone receptor (PR)-positive samples showed a high probability of positive effects of hormone therapy such as with tamoxifen. HER2 samples corresponded to positive effects of targeted therapy with trastuzumab. Subtypes of breast cancer including basal-like, HER2-E, luminal A, and luminal B were correlated with different pathological characteristics and clinical prognoses. Mutations of breast cancer gene-1 (BRCA1) and BRCA2 were also analyzed with respect to CDH family gene expressions, which represent breast cancer oncogenes (Supplementary Figure 2D). Supplementary Figure 2A demonstrates that ER-/PR- expressions were correlated with higher expressions of CDH2 and CDH11, indicating a poorer response to hormone therapy. Supplementary Figure 2B demonstrates that HER2-negative expression was found to be associated with CDH7 and CDH11, suggesting a poorer response to targeted therapy. Supplementary Figure 2C demonstrates relationships of different subtypes of breast invasive carcinoma with CDH family gene expressions. CDH1 was highly expressed by the HER2-E and luminal B types; CDH2 was highly expressed by the HER2-E type; CDH4 was highly expressed by the basal-like type; CDH7 and CDH11 were highly expressed by the luminal A type; CDH12 and CDH13 were highly expressed by the basal-like and luminal A types; and CDH15 expression was significantly associated with no types.

### Gene mutation analysis of CDH1/2/4/7/11/12/13/15 in breast cancer

Genomic changes in the CDH family were analyzed via the cBioPortal database, which demonstrated changes in CDH1 (14%), CDH2 (6%), CDH4 (11%), CDH7 (5%), CDH11 (5%), CDH12 (7%), CDH13 (4%), and CDH15 (4%) (Figure 7A). Our results of mutated gene

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**Table 2. Kaplan-Meier analysis of CDH family genes in distant metastasis-free survival (DMFS) in breast cancer.**

| Gene | HR (95% CI) | p value | Gene | HR (95% CI) | p value |
|------|-------------|---------|------|-------------|---------|
| CDH1 | 1.32 (1.13–1.55) | 0.0058 | CDH12 | 1.21 (1.03–1.41) | 0.019 |
| CDH2 | 1.39 (1.17–1.64) | 0.0012 | CDH13 | 1.31 (1.12–1.54) | 0.00089 |
| CDH3 | 1.55 (1.32–1.82) | 6.4e-08 | CDH15 | 1.22 (1.03–1.44) | 0.023 |
| CDH4 | 1.27 (1.08–1.5) | 0.0036 | CDH16 | 1.28 (1.09–1.5) | 0.003 |
| CDH5 | 0.84 (0.71–0.98) | 0.031 | CDH17 | 1.09 (0.93–1.27) | 0.29 |
| CDH6 | 1.09 (0.94–1.28) | 0.25 | CDH18 | 1.15 (0.98–1.35) | 0.08 |
| CDH7 | 1.34 (1.14–1.58) | 0.00048 | CDH19 | 0.71 (0.54–0.92) | 0.01 |
| CDH8 | 0.82 (0.62–1.1) | 0.18 | CDH22 | 0.89 (0.75–1.06) | 0.2 |
| CDH9 | 1.21 (1.03–1.43) | 0.02 | CDH23 | 0.78 (0.6–1.01) | 0.063 |
| CDH10 | 1.34 (1.13–1.58) | 0.00059 | CDH24 | 1.14 (0.87–1.5) | 0.34 |
| CDH11 | 1.42 (1.04–1.96) | 0.028 | CDH26 | 1.68 (1.28–2.19) | 0.00012 |

High expressions of CDH1/2/3/4/5/7/9/10/11/12/13/15/16/19/26 were significant compared to low expressions.
Figure 5. Protein expression levels of members of cadherin (CDH) family genes in all clinical breast cancer specimens from the Human Protein Atlas (HPA). (A) Images of immunohistochemistry (IHC) of CDH1/2/7/11 show their staining intensities. IHC images and patients’ information were obtained from the HPA. Normal and tumor samples are listed, and bar charts represent the quantification of IHC staining in breast cancer samples. There were strong intensities of CDH1 and CDH2 in breast cancer samples. (B) IHC images of CDH12/13/15 show their staining intensities. IHC images and patient information were obtained from the HPA. Normal and tumor samples are listed, and bar charts present quantification of IHC staining in breast cancer samples. There were strong intensities of CDH12 in breast cancer samples.
Figure 6. Expression of cadherin (CDH) family genes in subgroups of breast cancer patients. (A) Gene expression analysis among the stages of CDH genes in a breast cancer (GEPIA2) database. The violin plot displayed comparisons of CDH genes expressions from TCGA dataset of breast cancer. An independent t-test was utilized for p values; p<0.05 meant statistically significant; Pr(>F) <0.05 was based on Student’s t-test. (B) Scarff-Bloom-Richardson (SBR) grading of CDH family genes. Associations between CDH1/2/4/7/11/12/13/15 and SBR grading were analyzed via the bc-GenExMiner dataset. (C) The Nottingham prognostic index (NPI) of CDH family genes. Associations between CDH1/2/4/7/11/12/13/15 and NPI values were analyzed via the bc-GenExMiner dataset.
frequencies demonstrated that those of CDH1 and CDH4 were >10%. Altered genes at higher frequencies affect signaling pathways and cellular processes and can induce tumorigenesis based on previous studies [84–86]. CDH1 showed more gene alterations of truncating mutations and deep deletions, and low mRNA expression, while in contrast, CDH4 showed more amplifications and high mRNA expression. In the METABRIC dataset, CDH1 acted more like a TSG, and CDH4 acted like an oncogene in breast cancer. A previous study demonstrated that loss of E-cadherin was a key hallmark of ILCs [87]. In Giovanni et al. [86], CDH1 was one of the most recurrently mutated genes in breast cancer. In mixed ILC-IDC samples, genetic alterations of ILC tumors were found at a frequency of 14%. Mutations targeting CDH1 were mostly truncated mutations, and this result was similar to our mutation analysis.

We also used Pearson’s correlations to calculate correlations between CDH family members based on mRNA expressions (Figure 7B). CDH11 was significantly positively correlated with CDH13. Other genes in the CDH family otherwise showed no relative correlations with each other (Figure 7B). In addition, a protein-protein interacting (PPI) network analysis of the CDH family was conducted via STRING at various transcription levels to investigate potential relationships. The STRING analysis revealed that linkages among CDH gene family members were complicated. Using a three-group k-means algorithm, it was found that the group consisting of CDH1, CDH13, and CDH15 had a close relationship, and CDH2, CDH4, and CDH11 comprised another related group. A third group consisted of CDH7 and CDH12 (Figure 7C).

Figure 7. Genomic alterations of differentially expressed cadherin 1 (CDH1)/2/4/7/11/12/13/15 genes in breast cancer. (A) The cBioPortal database was used to reveal levels of gene amplification, deep deletions, and associated nucleotide substitutions of the CDH1/2/4/7/11/12/13/15 genes in breast cancer progression in the METABRIC dataset. (B) Correlation plot of the CDH1/2/4/7/11/12/13/15 genes in breast cancer (cBioPortal) database. Insignificant correlation values were displayed by crosses; p<0.01 was considered statistically significant. (C) Protein-protein interactions (PPIs) of CDH1/2/4/7/11/12/13/15 (STRING database). Highly interacting proteins were represented as hub protein nodes in the PPI network.
DNA methylation analysis of CDH1/2/4/11/12/13 in breast cancer

We present a heatmap of DNA methylated locations of CDH1/2/4/11/12/13 in breast cancer in Supplementary Figure 3 in “Supplementary Materials”. In total, 18 methylated CpG sites were determined for CDH1, with six CpG sites presenting high expressions. Among them, cg26508465 and cg09220040 showed the highest levels of DNA methylation. In total, 20 methylated CpG sites of CDH2 were determined with six CpG sites presenting high expressions. Among them, cg24776465 showed the highest level of DNA methylation. In total, there were 26 methylated CpG sites of CDH11, with 19 CpG sites sites presenting high expressions. Among them, cg02724025 showed the highest level of DNA methylation. Over half of the CpG sites of CDH11 presented high levels of methylation and relevance to breast cancer. These results provide a potential mechanism by which CDH11 can serve as an oncogene for breast cancer.

Regulated networks of CDH1/2/4/7/11/12/13/15 in breast cancer

To understand how DEG lists are linked to downstream CDH-regulated networks in various biological pathways and diseases, an enrichment analysis was performed using MetaCore software. After uploading genes coexpressed with CDH1 from Metabric and TCGA databases into MetaCore, we found that numerous pathways and networks were related to cell cycle (Figure 8 and Supplementary Table 2 in Supplementary Materials) including “Immune response_B cell antigen receptor (BCR) pathway”, “Oxidative stress ROS-induced cellular signaling”, “Development_negative regulation of WNT/Beta-catenin signaling in the cytoplasm”, and “Immune response_IFN-alpha/beta signaling via PI3K and NF-kB pathways”.

Similar pathway analyses of CDH2, CDH4, CDH7, CDH11, CDH12, CDH13, and CDH15 are displayed in “Supplementary Materials” (Supplementary Figures 4–9 and Supplementary Tables 3–9). Genes coexpressed with CDH2 were correlated with “Cell adhesion_ECM remodeling” and “Cytoskeleton remodeling_ Regulation of actin cytoskeleton organization by the kinase effectors of Rho GTPases” (Supplementary Figure 4). Genes coexpressed with CDH4 were correlated with “Protein folding and maturation POMC processing”, “Beta-catenin-dependent transcription regulation in colorectal cancer”, and “Cell adhesion_ECM remodeling” (Supplementary Figure 5). Genes coexpressed with CDH7 were correlated with “Cell cycle_Chromosome condensation in prometaphase” and “Cell cycle_ the metaphase checkpoint” (Supplementary Figure 6).

Genes coexpressed with CDH11 were correlated with “Cell adhesion_ECM remodeling”, “IL-1 beta-and endothelin-1-included fibroblast/myofibroblast production and extracellular matrix production in asthmatic airways”, and “Development regulation of epithelial to mesenchymal transition (EMT)” (Supplementary Figure 7). Genes coexpressed with CDH12 were coexpressed with “Cytoskeleton remodeling_ Regulation of actin cytoskeleton organization by the kinase effectors of Rho GTPases” and “Development negative regulation of WNT/Beta catenin signaling in the cytoplasm”. Genes coexpressed with CDH13 were correlated with “Development_Regulation of epithelial-to-mesenchymal transition (EMT)”, “Role of stellate cells in progression of pancreatic cancer”, and “Cell adhesion ECM remodeling” (Supplementary Figure 8). Genes coexpressed with CDH15 were correlated with “Transcription_HIF-1 targets”, “Oxidative stress ROS-induced cellular signaling”, and “Development_negative regulation of WNT/Beta catenin signaling in the cytoplasm”. In summary, genes coexpressed with CDH11 and CDH13 were both correlated with regulation of the EMT, while genes coexpressed with CDH2, CDH4, CDH11, and CDH13 were all correlated with cell adhesion.

Comprehensive results of CDH1/2/4/11/12/13 in the functional enrichment analysis

Gene ontology (GO) enrichment analysis

For comprehensive analysis, we obtained data from the METABRIC and TCGA datasets to acquire GO enrichment results including BPs, CCs, MFs, and KEGG (Supplementary Figures 9A–14A in Supplementary Materials). The BP analysis demonstrated that CDH1 was correlated with T-cell activation; the CC analysis showed correlations with cell-cell junctions and vacuolar membranes; MFs revealed significant relationships with phospholipid binding and actin binding, while KEGG ontology indicated the role of the mitogen-activated protein kinase (MAPK) signaling pathway and cytokine-cytokine receptor interactions (Supplementary Figure 9A). For CDH2, BPs demonstrated correlations with positive regulation of catalytic processes; the CC analysis showed correlations with mitochondrial matrix and cell-cell junctions; MFs revealed significant relationships with actin binding and protein serine/threonine kinase activity, while KEGG ontology indicated the role of the phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathway (Supplementary Figure 10A). For CDH4, BPs demonstrated correlations with proteasomal protein catalytic process; the CC analysis showed correlations with the mitochondrial inner membrane and mitochondrial matrix; MFs revealed significant relationships with actin binding and ion channel activity, while KEGG ontology indicated the
role of pathways of multiple neurodegenerative diseases (Supplementary Figure 11A). For CDH11, BPs demonstrated correlations with non-coding (nc)RNA metabolic processes; the CC analysis showed correlations with the mitochondrial inner membrane and mitochondrial matrix; MFs revealed significant relationships with transcription coregulator activity and actin binding, while KEGG ontology indicated the role of pathways of multiple neurodegenerative diseases (Supplementary Figure 12A). For CDH12, BPs demonstrated correlations with positive regulation of catabolic processes; the CC analysis showed correlations with cell-cell junctions and the mitochondrial matrix; MFs revealed significant relationships with phospholipid binding and actin binding, while KEGG ontology indicated the role of pathways of multiple neurodegenerative diseases (Supplementary Figure 13A). For CDH13, BPs demonstrated correlations with positive regulation of catabolic processes; the CC analysis showed correlations with cell-cell junctions and the mitochondrial matrix; MFs revealed significant relationships with transcription coregulator activity, while KEGG ontology indicated the role of neuroactive ligand-receptor interactions (Supplementary Figure 14A).

High expression levels of CDH2/4/11/12 were related to the epithelial-mesenchymal transition (EMT) in the GSEA analysis

GSEA results indicated that the Hallmark pathway analysis of CDH1 was significantly associated with

Figure 8. MetaCore enrichment pathway analysis of genes coexpressed with cadherin 1 (CDH1). The top 10% of expressed genes coexpressed with CDH1 from both Metabric (1804 genes) and TCGA (2003 genes) were extracted. Overlapping (805) genes were integrated to implement a pathway analysis, which formed a pathway list ordered by the -log p value. “Immune response B cell antigen receptor (BCR) pathway” was at the top of the pathway list when performing the “biological process” analysis. The figure demonstrates interactions between genes and proteins. Symbols represent proteins. Arrows depict protein interactions (green, activation; red, inhibition). Thermometer-like histograms indicate microarray gene expressions (blue, downregulated; red, upregulated).
protein secretion, estrogen response_early, and mammalian target of rapamycin C1 (mTORC1) signaling (Supplementary Figure 9B in Supplementary Materials). Yet the EMT revealed negative correlations with CDH1. The Hallmark pathway analysis of CDH2 revealed that it was significantly associated with the EMT, mTORC1 signaling, the G2/M checkpoint, and E2F targets (Supplementary Figure 10B). The Hallmark pathway analysis of CDH4 showed that it was significantly associated with the EMT, myogenesis, and apical junctions (Supplementary Figure 11B). The Hallmark pathway analysis of CDH11 indicated that it was significantly associated with the EMT, UV response_DN, coagulation, and angiogenesis (Supplementary Figure 12B). The Hallmark pathway analysis of CDH12 revealed that it was significantly associated with the EMT, tumor necrosis factor (TNF)-α signaling via nuclear factor (NF)-κB, and UV response_DN (Supplementary Figure 13B). The Hallmark pathway analysis of CDH13 showed that it was significantly associated with UV response_DN, DNA repair, adipogenesis, and IL-2 signal transduction and activator of transcription 5 (STAT5) signaling (Supplementary Figure 14B). CDH4/11/12/13 were all associated with EMT signaling in the GSEA and were seen to be important inflammation- and immune-related gene sets and cancer-related gene sets in tumor metastasis.

Micro-(mi)RNA-regulated network analysis of CDH1/2/4/11/12/13

We used the miRWalk database to identify associations with CDH1/2/4/11/12/13, and network regulation was analyzed by an IPA. Analysis of miRNA-regulated networks with CDHs (Supplementary Figure 15) indicated that hsa-miR-219a-2-3p regulated CDH1 and was thus associated with breast cancer development; hsa-miR-330-3p, has-miR-4429, and hsa-miR-199a-5p regulated CDH2; hsa-miR-4644, has-miR-211-5p, hsa-miR-520f-3p, hsa-miR-34e-5p, and hsa-miR-34a-5p regulated CDH4; hsa-miR-486-5p, hsa-miR-200c-3p, hsa-miR-200b-3p, hsa-miR-26a-5p, hsa-miR-140-5p, hsa-miR-128-3p, and hsa-miR-19a-3p regulated CDH11; and hsa-miR-30c-5p regulated CDH13. In a previous study, the miRNA hsa-miR-200 family was identified as being a definitive factor of the epithelial phenotype of malignant cells, which targeted the E-cadherin repressors, zinc finger E-box-binding homeobox 1 (ZEB1) and ZEB2 [88–90]. Meanwhile, hsa-miR-200 was identified as a repressor of the EMT and was downregulated in more-aggressive molecular subtypes of breast tumors such as HER2 and triple-negative [91]. Our results of miRNA-regulated networks that hsa-miR-200c-3p and hsa-miR-200b-3p regulated CDH11 were consistent with previous studies.

Levels of immune infiltration in breast cancer were related to CDH1/2/4/7/11/12/13/15 Expressions

The TIMER database was utilized to investigate the immunological microenvironment. We identified correlations of immune infiltration levels with expressions of CDH gene family members in breast cancer (Figure 9). Results of the analysis showed significant correlations of CDH1 with cluster of differentiation 4-positive (CD4+) T cells; CDH2 with CD4+ T cells, macrophages, neutrophils, and dendritic cells (DCs); CDH4 with CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and DCs; CDH7 with CD8+ T cells; CDH11 with CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and DCs; CDH12 with B cells and DCs; CDH13 with CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and DCs; and CDH15 with CD8+ T cells.

Drug target network analysis of CDH1/2/4/11/12/13

After comprehensive research on CDH family members, we were curious about drug targets and related mechanisms of drug resistance. Hence, drug target networks of CDH1/2/4/11/12/13 were analyzed by the MetaCore and MetaDrug system (Supplementary Figure 16 in Supplementary Materials). We found that “Signal transduction_c-myc, CREB1 signaling” was the top drug target of CDH1; “Cell adhesion_Fibrinogen, collagen signaling” was the top drug target of CDH2; “Metabolism_PPAR, RXR, VDR regulation of metabolism” was the top drug target of CDH4; “Cell adhesion_Fibrinogen, collagen signaling” was the top drug target of CDH11; “Transport_Potassium transport (core work 1)” was the top drug target of CDH12; and “Cell adhesion_Integrin signaling” was the top drug target of CDH13.

DISCUSSION

In previous studies, the CDH family was proven to be associated with invasiveness and metastasis [92–95]. The cadherin family as transmembrane glycoproteins mediate calcium-dependent cell-cell adhesion and regulates cell growth and differentiation. In the process of cell adhesion, cadherins act as essential factors to maintain stable homeostasis of tissue structures [96–98]. Once cell-cell adhesion is disturbed, adhesion-related pathways are subsequently interfered with. Disruption of cadherin signaling has determining influence on tumor progression and tumor immune responses [99–104].

In the present study, to determine whether CDH family members can serve as suitable biomarkers for breast cancer and pathways related to the EMT and metastasi
Figure 9. (A–H) Correlations between differentially expressed cadherin 1 (CDH1)/2/4/7/11/12/13/15 genes and immune cell infiltration in breast cancer. The figure showed that CDH1 (A); CDH2 (B); CDH4 (C); CDH7 (D); CDH11 (E); CDH12 (F); CDH13 (G); CDH15 (H) gene expressions were associated with tumor purity and tumor-infiltrating immune cell markers, such as cluster of differentiation 8-positive (CD8+) T cells, B cells, CD4+ T cells, neutrophils, macrophages, and dendritic cells. Spearman correlations were applied to describe correlations between the CDH1/2/4/7/11/12/13/15 genes and the abovementioned immune cells (p<0.05 was accepted as statistically significant).
comprehensive integrative data mining was utilized, including gene expressions, survival analyses, clinical and pathological factors, immune infiltration, and enrichment pathway analyses. In the Oncomine, TIMER, and prognostic analyses, significantly high expression levels of CDH1/2/4/7/11/12/13/15 were observed in breast cancer compared to normal tissue samples, and these were associated with poor DMFS outcomes. These results were confirmed by IHC staining in which CDH1, CDH2, and CDH12 exhibited strong intensities. Furthermore, results of the bc-GenExMiner database demonstrated that increased CDH4/12/13 expressions were associated with basal-like breast cancer, and increased CDH1/2/11 expressions suggested a high SBR grade status in patients. Genetic mutations of CDH1 and CDH4 at frequencies of >10% showed higher possibilities of altering cell signaling pathways and promoting proliferation in malignancies. CDH2, CDH4, and CDH11 had close relationships via the PPI network, and this was further confirmed by the MetaCore enrichment pathway analysis. These three CDH family genes, CDH2, CDH4 and CDH11, and genes coexpressed with CDH13 were correlated with the “Cell adhesion_ECM remodeling” process. CDH11 and CDH13 were also found to be closely related to CDH1 due to its roles in regulating of the EMT. The enrichment pathway results suggested that in addition to CDH1, genes coexpressed with CDH11 and CDH13 were also correlated with “Development_Regulation of the epithelial-to-mesenchymal transition (EMT)”. These correlations of CDH family genes could lead to a better understanding of breast cancer development and metastasis.

The ability to infiltrate different tissues is a critical step in cancer because it defines the metastatic potential of tumor cells [105–108]. This capacity can be achieved by the EMT [109–111]. Previous studies reported that the EMT is featured by the loss of CDH1 expression and the concomitant upregulation or de novo expression of CDH2, the so-called “cadherin switch”, which is associated with increased migration and invasiveness and thus poor prognoses [112–115]. The EMT causes disorganization of cell-cell adhesive junctions, thereby facilitating cancer metastasis. Irrespective of CDH1 expression, the migratory and invasive capacities are present in tumor cells by CDH2 expression. Therefore, CDH2 seems to be the key factor in epithelial cancer metastasis and disease progression. Those studies demonstrated the key roles of CDH2 in cancer metastasis, corresponding to our results with poor survival prognoses, strong intensities in pathological samples, and advanced SBR grading, indicating poor cell differentiation. Furthermore, we found that CDH2/4/11 had similar signaling pathways with cell adhesion, which was further correlated with the EMT. In other words, high expression levels of CDH2/4/11 are crucial for the EMT and cancer metastasis. To validate our results of positive correlations between CDH genes and the EMT, Pearson’s correlations were utilized to calculate correlations between CDH1/2/4/7/11/12/13/15 and EMT-regulated genes such as TWIST and SNAIL based on mRNA expression levels (Supplementary Figure 17 in Supplementary Materials). Other EMT-core genes associated with cell adhesion and migration were obtained from a previous study [116]. CDH11 displayed the greatest correlations with COL3A1, COL1A1, COL5A1, and ADAM12 with Spearman’s rank correlation coefficients of >0.5 among these eight genes. CDH13 showed mild positive correlations with COL3A1, COL1A1, COL5A1, ADAM12, SNAI2, COL6A1, and TWIST2. Conversely, traditional EMT markers, CDH1 and CDH2, demonstrated nearly no correlations with these common EMT-regulated genes. CDH1 only showed mild negative correlations with TWIST2 and SNAI3. Other genes otherwise showed relatively no correlations with EMT-core genes. It was interesting to discover that CDH11/13 demonstrated greater correlations with EMT-core genes rather than the traditional EMT-related cadherins, E-cadherin and N-cadherin, as mentioned in previous research [117, 118]. Our results supported the roles of CDH11 in inducing the EMT, which corresponded to other research not only in cancer [119] but in other diseases including melasma [120] and pulmonary fibrosis [121].

To understand drug targets of CDH family genes, we implemented a drug target network analysis (Supplementary Figure 16). Since drug target network analyses of the CDH2, CDH11, and CDH13 genes were all targeted to cell adhesion, we thus discussed the roles of cell adhesion in drug resistance. Cancer cells attaching to microenvironment components such as collagen type 1 (COL1) weakens the sensitivity of chemotherapeutic drugs like mitoxantrone, which is called cell adhesion-mediated drug resistance (CAM-DR) [122]. In consideration of the extensive presence of COL1 in mammary glands, breast cancer appears to have a high probability of presenting CAM-DR. The importance of COL1 is proven that patients with high-density breast tissues have higher risks of breast cancer [123–125] and poorer outcomes due to metastatic processes [126]. Regarding CAM-DR, the EMT plays a crucial part in drug resistance to breast cancer as well. The epithelial cell adhesion molecule (EpCAM) was implicated in tumor progression and drug resistance in breast cancer [127]. It was proven that EpCAM-knockdown resulted in upregulation of CDH1 and attenuation of CDH2 expression, which reversed the EMT. This process demonstrated that the EpCAM might possess the capability to induce the EMT in breast cancer to promote multidrug resistance. In addition,
transcriptional silencing of CDH1 was associated with the EMT in human breast cancer cells [128]. Previous research demonstrated that upregulation of E-cadherin by miR-200b and miR-200c via direct targeting the transcriptional repressors of E-cadherin, ZEB1 and ZEB2, inhibited the EMT [129]. In summary, CDH1/2/11/13 were associated with the cell adhesion network on drug targets and were thus associated with important factors in drug resistance.

CDH4 hypermethylation was significantly associated with increased risks for breast cancer in peripheral blood leukocyte DNA [130]. CDH11 was also known as one of the mediators that interacted with malignant cells and normal cells and was detected in various cancers, especially in metastatic cancer cell lines [131–133]. In particular, CDH11 was involved in the maintenance of high endogenous Rac activity and cytoskeletal reorganization in migratory breast cancer cells [134]. Moreover, because of the role of CDH11 as an inducer of metastatic signaling, targeting CDH11 triggered re-expression of the miR-335 tumor suppressor, which limited the CDH11-induced EMT. This phenomenon repressed cancer stem cell activities. CDH11-related pathways demonstrated the miR-335-mediated therapeutic value of anti-CDH11 antibody treatment and provided a therapeutic option in patients with metastatic breast cancer. Downregulation of CDH12 could inhibit the process of angiogenesis. Previous research implied that CDH12 might be influential in colorectal tumor metastasis [135]. CDH13 expression exhibited functions in cell adhesion and migration which were promoted by DNA polymerase beta (Pol β) by augmenting DNA demethylation of the CDH13 promoter [136]. Abnormal methylation of CDH13 promoter was observed in breast, colorectal, cervical and lung cancers, and chronic myeloid leukemia [137–139]. Those studies supported our results of the importance of CDH4/11/12/13 in tumorigenesis. We supposed that high mRNA expression levels of CDH4/11/12/13 were associated with breast cancer and poor survival.

As the tumor microenvironment plays important roles in tumorigenesis, we conducted an immune infiltration analysis in Figure 9. Previous studies also supported the associations between cadherin and immune pathways [140–142]. One of the most important pathways related to cadherin in immune responses is the Wnt pathway, which regulates cellular signaling by a canonical pathway with β-catenin [143]. β-Catenin plays a fundamental role in the cadherin protein complex, whose stabilization is crucial to activate the Wnt/β-catenin pathway. The WNT/β-catenin pathway mediates the self-renewal and relocation of cancer stem cells, promoting malignant progression and metastasis in breast cancer [144]. Our results of the enrichment pathway analysis were consistent with the importance of Wnt/β-catenin in breast cancer. Genes co-expressed with CDH1/12/15 were correlated with the pathway of “Development negative regulation of WNT/Beta catenin signaling in the cytoplasm”. Induction of Wnt/β-catenin signaling was crucial in maintenance of stemness of memory CD8 T cells by blocking T-cell differentiation [145]. Clinical responses to immune checkpoint inhibitors were correlated with tumors in the immune cell microenvironment [146, 147]. The Wnt/β-catenin pathway is considered to be a potential target for cancer treatment. In pancreatic cancer, effective immunotherapy is likely to require upregulation of CDH1 expression [148]. The roles of cadherin and Wnt/β-catenin signaling in regulating immune cell infiltrations of the tumor microenvironment aroused interest in immunotherapy treatment.

This study performed a comprehensive and systematic review of the genetic expressions, prognostic values, mutation levels, immune infiltration, and enrichment pathways of the CDH family. CDH1/2/4/11/12/13 expressions are significantly increased in breast cancer and are associated with poor clinical prognoses of DMFS. We concluded that CDH1/2/4/11/12/13 may be crucial for breast cancer tumorigenesis, providing novel insights into developing detection biomarkers or targeted therapies for breast cancer. Nevertheless, evidence from clinical applications such as in vitro data or large patient cohorts should be produced to validate associations between CDH1/2/4/11/12/13 and breast cancer.

CONCLUSIONS

CDH1/2/4/11/12/13 were overexpressed in breast cancer and were associated with poor prognoses in the distant metastasis-free survival analysis. Genes coexpressed with these CDH family members were correlated with regulation of the EMT and cell adhesion ECM remodeling, which were validated as playing critical roles in tumor metastasis. Although further evidence of clinical correlations for validation in the future should be determined to support our hypothesis, CDH1/2/4/11/12/13 are expected to be potential biomarkers for breast cancer progression and metastasis.

AUTHOR CONTRIBUTIONS

S.C.K., H.L.L., W.J.W., and C.Y.W. conceived the project and performed the bioinformatics analysis. S.C.K., H.L.L., C.Y.S., I.J.Y., M.C.Y., and wrote the manuscript. G.A., H.D.K.T., C.C.C., D.T.M.X., and F.B.P. performed the data analysis. W.J.W. and C.Y.W.
were responsible for manuscript editing and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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Supplementary Figure 1. (A–D) Molecular subtypes of breast cancer cell lines with expressions of CDH family. Colored columns on the right side displayed the molecular subtypes of each cell line. “Inconsistent” denoted cell lines that are inconsistently annotated regarding the status of markers. “Others” included two cell lines that were not breast cancers (HMEL, engineered breast; HS274T, breast fibroblast). TNBC, triple negative breast cancer.
Supplementary Figure 2. Clinical indicators for treatment and subtypes of breast invasive carcinoma patients with cadherin 1 (CDH1)/2/4/7/11/12/13/15 expressions. (A) Estrogen receptor (ER)/progesterone (PR) expression with CDH family genes co-expression. (B) Human epidermal growth factor receptor-2 (HER2) expression with CDH family genes co-expression. (C) Subtypes of breast invasive carcinoma with CDH family genes co-expression. (D) Breast cancer gene-1 (BRCA1)/ BRCA2 mutations with CDH family genes co-expression.
Supplementary Figure 3. Heatmap of DNA methylation expression levels of CDH1/2/4/11/12/13 in breast cancer by the MethSurv platform. Blue bars indicated low expressions, while red bars indicated high expressions. Different colored boxes indicated different ethnicities, races, ages, events, relation to UCSC CpG island and UCSC RefGene Groups. DNA methylation status was represented as β-values (ranging from 0 to 1). (A) Among CDH1, cg26508465 and cg09220040 showed the highest levels of DNA methylation; cg24776465 showed the highest level among CDH2; cg6140152 showed the highest level among CDH4; (B) cg02724025 showed the highest level among CDH11; cg17681524 showed the highest level among CDH12; cg16387516 showed the highest level among CDH13.
Supplementary Figure 4. MetaCore enrichment pathway analysis of genes co-expressed with cadherin 2 (CDH2). Top 10% of expression gene lists from both Metabric (1804 genes) and TCGA (2003 genes) were extracted. Overlapped (933) genes were integrated to implement pathway analysis, which formed a pathway list ordered by the \(-\log_{10} p\)-value. “Cell adhesion ECM remodeling” was at the top of the pathway list when performing the “biological process” analysis. The figure demonstrates the interactions between genes and proteins. Symbols represent proteins. Arrows depict protein interactions (green, activation; red, inhibition). Thermometer-like histograms indicate microarray gene expression (blue, down-regulation; red, up-regulation).
Supplementary Figure 5. MetaCore enrichment pathway analysis of genes co-expressed with cadherin 4 (CDH4). Top 10% of expression gene lists from both Metabric (1804 genes) and TCGA (2003 genes) were extracted. Overlapped (558) genes were integrated to implement pathway analysis, which formed a pathway list ordered by the -log \( p \)-value. “Protein folding and maturation_POMC processing” was at the top of the pathway list when performing the “biological process” analysis. The figure demonstrates the interactions between genes and proteins. Symbols represent proteins. Arrows depict protein interactions (green, activation; red, inhibition). Thermometer-like histograms indicate microarray gene expression (blue, down-regulation; red, up-regulation).
Supplementary Figure 6. MetaCore enrichment pathway analysis of genes co-expressed with cadherin 7 (CDH7). Top 10% of expression gene lists from both Metabric (1804 genes) and TCGA (2003 genes) were extracted. Overlapped (225) genes were integrated to implement pathway analysis, which formed a pathway list ordered by the -log p-value. “Cell cycle_Chromosome condensation in prometaphase” was at the top of the pathway list when performing the “biological process” analysis. The figure demonstrates the interactions between genes and proteins. Symbols represent proteins. Arrows depict protein interactions (green, activation; red, inhibition). Thermometer-like histograms indicate microarray gene expression (blue, down-regulation; red, up-regulation).
Supplementary Figure 7. MetaCore enrichment pathway analysis of genes co-expressed with cadherin 11 (CDH11). Top 10% of expression gene lists from both Metabric (1804 genes) and TCGA (2003 genes) were extracted. Overlapped (997) genes were integrated to implement pathway analysis, which formed a pathway list ordered by the log p-value. “Cell adhesion ECM remodeling” was at the top of the pathway list when performing the “biological process” analysis. The figure demonstrates the interactions between genes and proteins. Symbols represent proteins. Arrows depict protein interactions (green, activation; red, inhibition). Thermometer-like histograms indicate microarray gene expression (blue, down-regulation; red, up-regulation).
Supplementary Figure 8. MetaCore enrichment pathway analysis of genes co-expressed with cadherin 13 (CDH13). Top 10% of expression gene lists from both Metabric (1804 genes) and TCGA (2003 genes) were extracted. Overlapped (1015) genes were integrated to implement pathway analysis, which formed a pathway list ordered by the -log p-value. "Development_Regulation of epithelial-to-mesenchymal transition (EMT)" was at the top of the pathway list when performing the "biological process" analysis. The figure demonstrates the interactions between genes and proteins. Symbols represent proteins. Arrows depict protein interactions (green, activation; red, inhibition). Thermometer-like histograms indicate microarray gene expression (blue, down-regulation; red, up-regulation).
Supplementary Figure 9. (A, B) Gene Ontology (GO) analysis and Gene Set Enrichment Analysis (GSEA) based on genes co-expressed with CDH1. (A) Dot plots display biological processes, cellular components, molecular functions, and KEGG. The dot size is determined by the count of enriched genes in the pathway, and the color of the dots represents the significance of enrichment pathway. “clusterProfiler” package in R/Bioconductor was used to perform the GO analyses of dot plots. (B) Hallmark signaling pathway analysis of CDH1 in breast cancer. Results of the analysis showed significant values of gene classes in the Hallmark database. Statistical significance was presented by p value, and the normalized enrichment score (NES) reflected the rank of gene classes.
Supplementary Figure 10. (A, B) Gene Ontology (GO) analysis and Gene Set Enrichment Analysis (GSEA) based on genes co-expressed with CDH2. (A) Dot plots display biological processes, cellular components, molecular functions, and KEGG. The dot size is determined by the count of enriched genes in the pathway, and the color of the dots represents the significance of enrichment pathway. “clusterProfiler” package in R/Bioconductor was used to perform the GO analyses of dot plots. (B) Hallmark signaling pathway analysis of CDH2 in breast cancer. Results of the analysis showed significant values of gene classes in the Hallmark database. Statistical significance was presented by \( p \) value, and the normalized enrichment score (NES) reflected the rank of gene classes.
**Supplementary Figure 11.** (A, B) Gene Ontology (GO) analysis and Gene Set Enrichment Analysis (GSEA) based on genes co-expressed with CDH4. (A) Dot plots display biological processes, cellular components, molecular functions, and KEGG. The dot size is determined by the count of enriched genes in the pathway, and the color of the dots represents the significance of enrichment pathway. “clusterProfiler” package in R/Bioconductor was used to perform the GO analyses of dot plots. (B) Hallmark signaling pathway analysis of CDH4 in breast cancer. Results of the analysis showed significant values of gene classes in the Hallmark database. Statistical significance was presented by $p$ value, and the normalized enrichment score (NES) reflected the rank of gene classes.
The image displays a bar chart analysis of gene expression with categories under Biological Process, Molecular Function, Cellular Component, and KEGG Pathways.

Under Biological Process, categories include transcription coregulator activity, actin binding, protein serine/threonine kinase activity, catalytic activity, and RNA polymerase II-specific DNA-binding transcription factor binding.

In Molecular Function, categories such as DNA replication, rRNA metabolic process, rRNA processing, and carbon-carbon lyase activity are highlighted.

For Cellular Component, the chart showcases mitochondrial inner membrane, mitochondrial matrix, collagen-containing extracellular matrix, nuclear speck, transcription regulator complex, mitochondrial protein-containing complex, ribosome, ribosomal subunit, spliceosomal complex, large ribosomal subunit, cytosolic ribosome, organelar ribosome, nuclear ribosome, small ribosomal subunit, and organelle large ribosomal subunit.

The KEGG Pathways section includes Alzheimer disease, Amyotrophic lateral sclerosis, Huntington disease, Parkinson disease, Prion disease, Thermogenesis, Chemical carcinogenesis, Ribosome, Oxidative phosphorylation, Cell cycle, Carbon metabolism, Nucleotide metabolism, Proteasome, and Glyoxylate and dicarboxylate metabolism.
Supplementary Figure 12. (A, B) Gene Ontology (GO) analysis and Gene Set Enrichment Analysis (GSEA) based on genes co-expressed with CDH11. (A) Dot plots display biological processes, cellular components, molecular functions, and KEGG. The dot size is determined by the count of enriched genes in the pathway, and the color of the dots represents the significance of enrichment pathway. “clusterProfiler” package in R/Bioconductor was used to perform the GO analyses of dot plots. (B) Hallmark signaling pathway analysis of CDH11 in breast cancer. Results of the analysis showed significant values of gene classes in the Hallmark database. Statistical significance was presented by p value, and the normalized enrichment score (NES) reflected the rank of gene classes.
**Supplementary Figure 13.** (A, B) Gene Ontology (GO) analysis and Gene Set Enrichment Analysis (GSEA) based on genes co-expressed with CDH12. (A) Dot plots display biological processes, cellular components, molecular functions, and KEGG. The dot size is determined by the count of enriched genes in the pathway, and the color of the dots represents the significance of enrichment pathway. “clusterProfiler” package in R/Bioconductor was used to perform the GO analyses of dot plots. (B) Hallmark signaling pathway analysis of CDH12 in breast cancer. Results of the analysis showed significant values of gene classes in the Hallmark database. Statistical significance was presented by p value, and the normalized enrichment score (NES) reflected the rank of gene classes.
CDH13

**Biological Process**
- positive regulation of catabolic process
- proteasomal protein catabolic process
- response to nutrient levels
- positive regulation of kinase activity
- signal release
- axon development
- histone modification
- gland development
- pattern specification process
- embryonic organ development
- positive regulation of cellular catabolic process
- synapse organization
- axonogenesis
- proteasome-mediated ubiquitin-dependent protein catabolic process
- urogenital system development

**Molecular Function**
- transcription coregulator activity
- passive transmembrane transporter activity
- channel activity
- phospholipid binding
- DNA-binding transcription activator activity
- actin binding
- metal ion transmembrane transporter activity
- DNA-binding transcription factor binding
- phosphoridic ester hydrolase activity
- cadherin binding
- anion transmembrane transporter activity
- RNA polymerase II-specific DNA-binding transcription factor binding
- protein-macromolecule adaptor activity
- phosphatidylinositol binding
- actin filament binding

**Cellular Component**
- cell-cell junction
- mitochondrial matrix
- vacuolar membrane
- apical part of cell
- cell-substrate junction
- cell leading edge
- focal adhesion
- lysosomal membrane
- lytic vacuole membrane
- spindle
- synaptic membrane
- apical plasma membrane
- cell projection membrane
- glutamatergic synapse
- membrane raft

**KEGG**
- Neuroactive ligand-receptor interaction
- PI3K-Akt signaling pathway
- Human papillomavirus infection
- Cytokine-cytokine receptor interaction
- MAPK signaling pathway
- Salmonella infection
- Calcium signaling pathway
- Human cytomegalovirus infection
- cAMP signaling pathway
- Lipid and atherosclerosis
- Rap1 signaling pathway
- cGMP-PKG signaling pathway
- JAK-STAT signaling pathway
- Hepatitis B
- Cellular senescence

**GeneRatio**
- Count
- p.adjust
Supplementary Figure 14. (A, B) Gene Ontology (GO) analysis and Gene Set Enrichment Analysis (GSEA) based on genes co-expressed with CDH13. (A) Dot plots display biological processes, cellular components, molecular functions, and KEGG. The dot size is determined by the count of enriched genes in the pathway, and the color of the dots represents the significance of enrichment pathway. “clusterProfiler” package in R/Bioconductor was used to perform the GO analyses of dot plots. (B) Hallmark signaling pathway analysis of CDH13 in breast cancer. Results of the analysis showed significant values of gene classes in the Hallmark database. Statistical significance was presented by $p$ value, and the normalized enrichment score (NES) reflected the rank of gene classes.
Supplementary Figure 15. Analysis of micro-(mi)RNA networks with CDH1/2/4/11/13 in breast cancer. (A) CDH1 demonstrated network interaction with hsa-miR-219a-2-3p in breast cancer development; (B) CDH2 demonstrated network interaction with hsa-miR-330-3p, hsa-miR-4429, and hsa-miR-199a-5p; (C) CDH4 demonstrated network interaction with hsa-miR-4644, hsa-miR-211-5p, hsa-miR-520f-3p, hsa-miR-34e-5p, and hsa-miR-34a-5p; (D) CDH11 demonstrated network interaction with hsa-miR-486-5p, hsa-miR-200c-3p, hsa-miR-200b-3p, hsa-miR-26a-5p, hsa-miR-140-5p, hsa-miR-128-3p, and hsa-miR-19a-3p; (E) CDH13 demonstrated network interaction with hsa-miR-30c-5p.
**Supplementary Figure 16.** (A, B) Drug target networks analysis of genes co-expressed with cadherin (CDH) 1/2/4/11/12/13. Genes co-expressed with CDH1/2/4/11/12/13 were integrated to implement drug target networks analysis, which formed a pathway list ordered by the -log p-value on the left. (A) “Signal transduction_c-myc, CREB1 signaling” was at the top of the drug target of CDH1; “Cell adhesion_Fibrinogen, collagen signaling” was at the top of the drug target of CDH2; “Metabolism_PPAR, RXR, VDR regulation of metabolism” was at the top of the drug target of CDH4; (B) “Cell adhesion_Fibrinogen, collagen signaling” was at the top of the drug target of CDH11; “Transport_Potassium transport (core work 1)” was at the top of the drug target of CDH12; “Cell adhesion_Integrin signaling” was at the top of the drug target of CDH13. The figure demonstrates the interactions between genes and proteins. Symbols represent proteins. Arrows depict protein interactions (green, activation; red, inhibition).
Supplementary Figure 17. Correlations between cadherin (CDH) family and epithelial-mesenchymal transition (EMT)-regulated genes in breast cancer using TCGA dataset. The symmetric correlation matrix was created by the "corrplot" R package. The color represents the degree of pairwise correlation regarding Spearman's rank correlation coefficient. Darker red and larger dot size mean stronger positive correlation, while orange indicates stronger negative correlation. The cross symbols represent non-significant correlation coefficient values (p value > 0.01).
### Supplementary Table 1A. Univariate Cox regression analysis of CDH1/2/4/11/12/13 and age, gender, tumor stage with overall survival in breast cancer (BRCA) patients.

| Univariate      | Coefficient | Overall survival | p value |
|-----------------|-------------|------------------|---------|
|                 |             | HR               | (95% CI) |         |
| Age             | 0.036       | 1.037            | (1.023-1.050) | 0.000***|
| gender male     | -0.49       | 0.613            | (0.084-4.450) | 0.628    |
| stage2          | 0.668       | 1.951            | (1.117-3.405) | 0.019*   |
| stage3          | 1.374       | 3.95             | (2.189-7.126) | 0.000*** |
| stage4          | 2.718       | 15.143           | (7.074-32.417) | 0.000*** |
| CDH1            | 0.014       | 1.014            | (0.913-1.127) | 0.792    |
| CDH2            | 0.101       | 1.106            | (0.944-1.297) | 0.213    |
| CDH4            | -0.066      | 0.936            | (0.609-1.439) | 0.764    |
| CDH11           | -0.025      | 0.976            | (0.828-1.150) | 0.769    |
| CDH12           | -0.291      | 0.747            | (0.431-1.295) | 0.299    |
| CDH13           | 0.264       | 1.302            | (1.053-1.611) | 0.015*   |

The coefficient represents the regression coefficient. HR represents the hazard ratio, and 95% confidential interval are showed in (95% CI).

### Supplementary Table 1B. Univariate Cox regression analysis of CDH1/2/4/11/12/13 and age, gender, tumor stage with overall survival in molecular subtype-Luminal of breast cancer (BRCA) patients.

| Univariate      | Coefficient | Overall survival | p value |
|-----------------|-------------|------------------|---------|
|                 |             | HR               | (95% CI) |         |
| Age             | 0.039       | 1.039            | (1.020-1.059) | 0.000***|
| gender male     | -15.811     | 0                | (0.000-Inf) | 0.995    |
| stage2          | 0.559       | 1.749            | (0.899-3.403) | 0.1      |
| stage3          | 1.106       | 3.021            | (1.448-6.303) | 0.003**  |
| stage4          | 2.232       | 9.232            | (3.471-24.552) | 0.000*** |
| CDH1            | 0.069       | 1.071            | (0.917-1.252) | 0.387    |
| CDH2            | 0.159       | 1.172            | (0.947-1.451) | 0.144    |
| CDH4            | -0.197      | 0.821            | (0.312-2.160) | 0.69     |
| CDH11           | -0.032      | 0.969            | (0.761-1.234) | 0.798    |
| CDH12           | -0.419      | 0.658            | (0.297-1.454) | 0.3      |
| CDH13           | 0.331       | 1.392            | (0.973-1.992) | 0.071    |

The coefficient represents the regression coefficient. HR represents the hazard ratio, and 95% confidential interval are showed in (95% CI).
Supplementary Table 1C. Univariate Cox regression analysis of CDH1/2/4/11/12/13 and age, gender, tumor stage with overall survival in molecular subtype-HER2 of breast cancer (BRCA) patients.

| Univariate | Overall survival | HR      | (95% CI)     | p value |
|------------|-----------------|---------|--------------|---------|
| Age    | 0.086 | 1.09 | (1.018-1.168) | 0.014* |
| stage2 | -1.178 | 0.308 | (0.022-4.285) | 0.381 |
| stage3 | 0.474 | 1.606 | (0.112-22.999) | 0.727 |
| stage4 | 3.033 | 20.763 | (1.181-365.073) | 0.038* |
| CDH1 | -0.404 | 0.668 | (0.429-1.040) | 0.074 |
| CDH2 | 0.459 | 1.583 | (0.653-3.835) | 0.309 |
| CDH4 | -29.735 | 0 | (0.0-0.072) | 0.032* |
| CDH11 | 0.4 | 1.492 | (0.351-6.339) | 0.587 |
| CDH12 | 3.279 | 26.541 | (1.308-538.706) | 0.033* |
| CDH13 | -0.442 | 0.643 | (0.043-9.605) | 0.749 |

The coefficient represents the regression coefficient. HR represents the hazard ratio, and 95% confidential interval are showed in (95% CI).

Supplementary Table 1D. Univariate Cox regression analysis of CDH1/2/4/11/12/13 and age, gender, tumor stage with overall survival in molecular subtype-Basal of breast cancer (BRCA) patients.

| Univariate | Overall survival | HR      | (95% CI)     | p value |
|------------|-----------------|---------|--------------|---------|
| Age    | 0.023 | 1.023 | (0.986-1.063) | 0.226 |
| stage2 | 18.162 | 77244950 | (2.8e+07-2.1e+08) | 0.000*** |
| stage3 | 19.179 | 2.13e+08 | (7.5e+07-6.1e+08) | 0.000*** |
| stage4 | 22.124 | 4.06e+09 | (3.7e+08-4.5e+10) | 0.000*** |
| CDH1 | -0.048 | 0.953 | (0.651-1.395) | 0.805 |
| CDH2 | -0.26 | 0.771 | (0.553-1.074) | 0.124 |
| CDH4 | -0.089 | 0.915 | (0.617-1.358) | 0.659 |
| CDH11 | 0.427 | 1.533 | (1.064-2.209) | 0.022* |
| CDH12 | 0.899 | 2.457 | (1.224-4.935) | 0.012* |
| CDH13 | 0.156 | 1.169 | (0.684-2.000) | 0.567 |

The coefficient represents the regression coefficient. HR represents the hazard ratio, and 95% confidential interval are showed in (95% CI).
## Supplementary Table 2. Pathway analysis of genes co-expressed cadherin 1 (CDH1) from the MetaCore database (with p-value < 0.05 set as the cutoff value) (Supplementary Table 2 and Figure 8).

| #  | Maps                                  | p-Value        | Network objects from active data                                                                                     |
|----|---------------------------------------|----------------|---------------------------------------------------------------------------------------------------------------------|
| 1  | Immune response_B cell antigen receptor (BCR) pathway | 1.298E-16     | STIM1, Calcineurin A (catalytic), GRB2, alpha-5/beta-1 integrin, ICAM1, c-Rel (NF-κB subunit), H-Ras, NF-κB p65/Rel, erk1/2, egr1, c-Raf1, c-raf-1, BAP3, fibronectin, CD19, VAV-1, Rac1, 3P3 receptor, BAD, syk, cyclin D2, Shc, PI3K reg class IA (p85), GSK3 beta, Rb protein, CD79A, CD4, FκH, MEK6(MAP2K6), VAV-2, MEK2(MAP2K2), GSK3 alpha/beta, Bcl-2L, MEK1/2, CD42, Wasp, Actin cytoskeleton, NF-kB, AKT(PTK2), NF-kB p50/p65, PDK (PDPK1), TAK1(MAP3K7), NF-AT2(NFATC1), MEKK4(MAP3K4), MEK1(MAP2K1), VCA1, RelA(p65 NF-κB subunit), LRRK1, B-Raf, NF-kB1 (p50), K-RAS, ETS1, Lyn, PI3KIII, CIN85, CD79 complex, P2PA catalytic, PI3K, PKC-beta2, NFκB1, P3K3 alpha class IA (p110-delta), CARD1, CD6, HPK1(MAP4K1), PKC-beta, p70 S6 kinase1, Calmodulin, CalDAG-GEFIII, CKLFSF7, MEK11(MAP3K1), ATF2-4, MART1, IKB-beta, PLC-gamma, CD79B, Bcl-10, Calcineurin B (regulatory), PLC-gamma, p38MAPK, Elk-1 |
| 2  | Oxidative stressNDAROS-induced cellular signaling | 6.173E-16     | Casein kinase II, alpha chains, p38alpha (MAPK14), Tuberin, SREBP1 (nuclear), SDC, ERK1/2, EGR1, VEGF-A, PKA-reg (AMP-dependent), TNXIP (VDUP1), p21, Bak, Cytochrome c, FASN, E2F1, Syk, Bax, GSK3 beta, FTH1, IRP2, GRP75, MDM2, IL-6, NF-kB, AKT(PTK), Catalase, NF-kB p50/p65, Cyclin B1, c-Src, TNF-alpha, NOTCH1 (NICD), Thioredoxin, Chk2, ACACA, Rea1 (p65 NF-κB subunit), KEAP1, IRP1, HIF1A, SRX1, AMPK alpha subunit, Pin1, NIK(MAP3K4), Isorc, P66 Shc, Glutaredoxin 1, NFKBIA, HSPA1A, GSK3 beta, COX2 (PTGS2), ELAVL1 (HuR), HSFI, PKC-beta, NOTCH3 (3CD), PDK1, p70 S6 kinase1, G3X1, GSK, LKB1, PTK, TNF, MEK11(MAP3K1), HIS1, HSFI27, IKB-beta, DCL1 (Dynein LC8a), c-Abi, Cyclin D1, JNK(MAPK8-10), HIF-prolyl hydroxylase, HDAC1, SAEB, SP1, p53, NFR2, ADAM17, p38 MAPK, APEX, PAH1, NALP3 |
| 3  | Development_Negative regulation of WNT/Beta-catenin signaling in the cytoplasm | 6.950E-16     | Casein kinase I delta, NOTCH1 receptor, CCXX4, VHLH, DP1, N KD1, P1c cat, RIPK4, Presenilin 1, Alpha-1 catenin, Leforin, FAF1, Casein kinase I epsilon, Beta-catenin, CYLD, CCX5, DAB2, Nucleoredoxin, Dhs, Casein kinase I alpha, Rac1, YAP1 (Yap65), G-protein alpha-13, WWPP1, STK4, SIAH1, GSK3 alpha/beta, LATS2, G-protein beta/gamma, WDR26, Skp2/Tsc2/Fbxw7, TAZ, Axin, RAC1, HECTD1, LRP5/LRP6, Prickle-1, c-Cbl, STK3, Tcf(Lef), E2F1, Amer1, P2PA catalytic, SENP2, RNF185, A20, Cul1/Rbx1 E3 ligase, YAP1/TAZ, CDK6, ELAVL1 (HuR), PEG3, WNT5A, Malin, PKC-alpha, P orb-2, WNT, Beclin 1, Cyclin D1, p53, NKD2, DACT3, Frizzled, DACT1 |
| 4  | Immune response_IFN-alpha/beta signaling via PI3K and NF-kB pathways | 1.750E-15     | Tuberin, AKT1, Cyclin D3, ISG15, IRS-2, Tyk2, RPS6, DHRF, NML, eIF4E, ERK1/2, c-Rel, CD42A, IFN-alpha/beta receptor, p21, IFNAR1, PKC-epsilon, CDK1 (p34), IKB, p70 S6 kinase, PI3K reg class IA (p85), GSK3 beta, NF-kB2 (p100), Rb protein, CDK4, E2F4, PI3K, IKB (p49), AKT(PTK2), PKD (PDPK1), p107, p38, P38EF2A, IFI17, PI3K cat class IA, Rea1 (p65 NF-κB subunit), NF-kB2 (p52), PKC-delta, TRAF2, p100/2EF4, E2F1, p107/2EF4, IFNAR2, eIF4B, p90RSK1, eIF4G1, NIK(MAPK14), MKK1, CDK2, CD4, PCNc, 4E-BP, GSK3 alpha, IFIT1, IFIT2, E2F4, PKC-catalytic, Cyclin E, eIF4A, FOXO3A, IRF7, MNK2(GPR7), Cyclin A |
| 5  | Immune response_IFN-alpha/beta signaling via PI3K and NF-kB pathways | 2.174E-14     | ATP6V1B2, RARbeta, DHA2, MCM5, IL-4R type I, CCR2, PPAR-alpha, SOCS1, CD25A, p21, Cytochrome c, STAT1, Loricrin, CPT-1A, Filaggrin, EGR2 (Krox20), Bax, CDK6, FKB1, SOCS3, Bcl-XL, ACDAM, FasL(NFSEF6), Osteoprotegerin, AKT(PTK), PPAR-gamma, GATA3, A-FABP, MPP-13, PLEKHA4, ANGPTL4, MCM4, IL-4R type II, Cyclin D, CYPEP1, IL4RA, Bcl-6, SK4IK1, Cathepsin V, CDK2, CDK6, AP-1, Cyclin E, HSD3B1, FOXO3A, PERC, STAT5, Cyclin A, STAT6, LPL |
| 6  | Neurogenesis_NGFFrA MAPK-mediated signaling | 1.343E-13     | SPHK1, NEFL, TrkA, ERK5 (MAPK7), CDK5, GRB2, APS, Fra-1, H-Ras, ERK1/2, MEFC2, Ctkl, EGR1, PP2A regulatory, SGK1, PKA-reg (AMP-dependent), CRK, c-Raf-1, FRS2, DNAJA3 (TD1), p21, VGF, PKC-epsilon, Ephrin-A receptor 2, IP3 receptor, TYSH, Shc, MAPKAPK2, PLC-gamma 1, MEK6(MAP2K6), MAPK2S (MEK5), KIDINS220, CREB1, MEK1/2, PLAUR (uPAR), M-Ras, RGS2, p107, Stromelysin-1, c-Src, KCTD11, GAB2, SHPS-1, MATK, Rin, B-Raf, NF-kB1 (p50), JunB, K-RAS, PKC-delta, P2PA catalytic, C3G, SH2B, p90RSK, p130CAS, NGF, AP-1, Calmodulin, MAGI-2, PCK-lambda/iota, SHP-2, Cyclin D1, SORBS1, MPP-10, SP1, PVIR, JMD3, RIT, p38 MAPK, Elk-1, PKA-cat (AMP-dependent), FosB |
| 7  | Development_Differentiation of white adipocytes | 4.070E-13     | p38alpha (MAPK14), SREBP1 (nuclear), GRB2, BMP4, H-Ras, ERK1/2, FOX2C, c-Raf-1, SMAD4, PRKAR1A1, SREBP1 precursor, Scw, HIVEP2, Rb protein, Resistin, FTase-alpha, MEK2(MAP2K2), CREB1, MEK1/2, PPARGC1 (PGC1 alpha), INSIG1, p107, PPAR-gamma, TAK1(MAP3K7), MEK1(MAP2K1), A-FAB, CIDEB, p90RSK1, LPS, RIP140, PSAT, Factor D, FTase, TAB1, Angiotensinogen, LXR-alpha, BMP81A, SMAD1, Leptin, BMP2, LPL, Perilipin, C/EBPalpha, C/EBPdelta |
| 8  | Role of activation of WNT signaling in the progression of lung cancer | 1.531E-12     | DVL3, RUNX3, WNT3A, FZD6, O3/4, NKD1, SFRP2, Krm1, Lef-1, DVL-1, TCF7L2 (TCF4), DKK1, FZD8, Beta-catenin, Matrixin (MMP-7), VEGF-A, p21, Dsh, Rac1, ING4, GSK3 beta, Fzd2, Survivin, Axin2, Ezh2, Fzd9, Fzd7, DVL-2, Axin, CD147, RUVBL1, WNT4, ROR2, hASH1, WNT9A, Tcf(Lef), Porcn, WNT3, FZD3, ARID1, WNT1, SFRP4, WNT2B, WNT5A, LKB1, MEK11(MAP3K1), WNT, WNT10B, LRP6, SUZ2, Cyclin D, SFRP1, p38 MAPK, Frizzled, NOTCH3 |
| Page | Section | Gene/Protein | p-value |
|------|---------|--------------|---------|
| 9 | Development_Negative regulation of WNT/Beta-catenin signaling in the nucleus | ZNF703, Casein kinase I delta, AKT1, Calcineurin A (catalytic), RUNX3, Oct-3/4, VHL, Lef-1, PGAM5, Alpha-1 catenin, TCF7L2 (TCF4), 14-3-3, Jade-1, Casein kinase I epsilon, Beta-catenin, VEGF-A, BCL9/B9L, PC1-CTT, TLE, Dsh, Menin, GSK3 beta, Nephrocytin-4, HDAC2, HIC1, LAT52, RANBP3, CIBP, PJA2, HIC5, PPAR-gamma, Axin, TAK1(MAP3K7), SOX9, TCF7 (TCF1), KDM2, LRP5/LRP6, TRRAP, WWOX, NARF, c-Cbl, PKC-delta, Tcf(Lef), E2F1, SOX17, SENP2, Cul1/Rbx1 E3 ligase, NLK, RNS4F, WNT5A, SOX2, WNT, FOXO3A, eNOS, CHIBB, HDAC1, Plakoglobin, RUVBL2, CDX1, Frizzled, Histone H1, DACT1 | 2.248E-12 |
| 10 | Stellate cells activation and liver fibrosis | COL1A1, GRO-2, Biglycan, TNF-R2, GRB2, ICAM1, WNT3A, CCL2, H-Ras, Beta-catenin, c-Raf-1, TRADD, SMAD4, PDGF-R-alpha, DAB2, Dsh, Smoothen, i-kB, Shc, PI3K reg class IA (p85), GSK3 beta, RIKPI, MEK2(MAP2K2), MMP-2, COL1A2, ERK2 (MAPK1), AKT(PKB), PDGF receptor, NF-kb p50/p65, TNF-R1, ERK1 (MAPK3), TNF-alpha, MEK1(MAP2K1), PI3K cat class IA, PTCH1, TRAF2, Tcf(Lef), TGF-beta receptor type II, IL1RAP, KLF6, NIK(MAPK14), TIMP1, Traf1, ACTA2, Cyclin D1, IRAK1/2, SMAD3, SPI, Elk-1, Frizzled, TLR2, PDGFR-beta | 2.435E-12 |
| 11 | Development_Positive regulation of WNT/Beta-catenin signaling in the cytoplasm | Casein kinase II, alpha chains, Bcl-9, EGF, BIG1, GRB2, IRS-2, NKD1, UBE2B, PPI-1, cat, RIKP4, Alpha-1 catenin, 14-3-3, Beta-catenin, TCF7L2, SMAD4, Dsh, Rac1, YAP1 (YAP65), CDK1 (p34), PPP2R2A, SIAH1, USP25, GSK3 alpha/beta, ERK2 (MAPK1), AKT(PKB), Axin, GSKIP, HECTD1, ITGB1, LRP5/LRP6, SIAH2, Tcf(Lef), 14-3-3 zeta/delta, TGF, HSP105, PKA-reg type II (cAMP-dependent), PI3A catalytic, RNF220, COX-2 (PTGS2), Trabid, GIG2, Miz-1, USP9X, WNT, USP7, Jouberin, PIP2 alpha, INK(MAPK8-10), SMAD3, NKD2, MITF, PKA-cat (cAMP-dependent), Frizzled, SET7, DACT1 | 3.380E-12 |
| 12 | Apoptosis and survival_Regulation of apoptosis by mitochondrial proteins | p38alpha (MAPK14), Maspin, PLSCR3, Calcineurin A (catalytic), MPTP complex, Apaf-1, Cathepsin H, Granzyme B, ROCK1, ERK1/2, MUL1, RAD9A, P2OC, VDAC 2, Bik, Bak, Cytochrome c, Caspase-8, OPAL, Endonuclease G, NIP3, BAD, GZMH, Bax, SOD1, RASSF1, PINK1, PP1-p cat alpha, AMBRA1, Mitofusin 1, Caspase-2, Bcl-2X, MITC2, VDAC 1, MIDO, Calpain 1 (mu), Mcl-1, Cathepsin D, Granzyne K, Cathepsin L, IF27, Aif, GCL1BP, PKC-delta, 14-3-3 zeta/delta, MAPA, Pin1, PPIA catalytic, PARL, Caspase-9, Metaxin 1, BIM, JAK1, CD92, ATF-2, SLCL25A3, TIMM8A, tBid, Beclin 1, HtrA2, Cyclin A, JNK(MAPK8-10), JNK2(MAPK9), Caveolin-1, DNML1 (DRP1), Calcineurin B (regulatory), Smac/Diablo, p38 MAPK, Bid | 4.849E-12 |
| 13 | T follicular helper cell dysfunction in SLE | IL-7 receptor, MHC class II, ICOS-L, IL-7, Tyk2, IFN-gamma, BAF, CXCR5, CD28, OX40(TNFRSF4), KLF2, SLAM, IFN-alpha/beta receptor, STAT1, TRIM, I-kB, PI3K reg class IA (p85), FKHR, IFN-alpha, RIPK1, CD4, CD84, IL-6, CTLA-4, Fyn, NFKb-kB, AKT(PKB), ICOS, IL-2, CD40L(TNFRSF5), BAF(TNFRSF13B), CD80, Osteopontin, PI3K cat class IA, DDX6, PI3K reg class IA (p85-alpha), MCPIP, TRAF2, BAF-FR, IL4RA, NIK(MAPK3), Bcl-6, A20, JAK3, CARD11, RCH3, 4E-BPI, Hedls, c-Maf, p70 S6 kinase1, MALT1, IKK-beta, CXCL13, SAP, PD-1, Bcl-10, TRP1, CD40(TNFRSF4), IL-21 receptor, STAT6, CD86, BLIMP1 (PRDI-BF1) | 4.885E-12 |
| 14 | Signal transduction_Angiotensin in II/AGTR1 signaling via p38, ERK and PI3K | RECK, ERK5 (MAPK7), GRB2, CCL2, H-Ras, cF4E, ERK1/2, MEF2C, EGR1, MSK1/2 (RPS6K5A/S), c-Raf-1, HDAC4, p21, Angiotensin II, p47-phox, Syk, Shc, p70 S6 kinases, FKHR, eCRA, MEK6(MAP2K6), MAP2K5 (MEK5), MMP-2, CREB1, IL-6, MEK1/2, G-protein beta/gamma, HLA, c-Raf-1, AKT1, Bcl2, VEGF, PI3K, JAK2, MAP2K1, PI3K cat class IA | 2.049E-11 |
| 15 | Transcription_Negative regulation of HIF1A function | PARGC1 (PGC1-alpha), Fyn, AKT(PKB), Catalase, PDK (PDK1), c-src, PDGFR-D, MEK4(MAP3K4), Pyk2(FAK2), JAK2, Osteopontin, PI3K cat class IA, PI3K reg class IA (p58-alpha), PKC-delta, ETS1, EGF, AGTR1, MNK1, PLD2, p90Rsk, CaMKII delta, COX-2 (PTGS2), ELAVL1 (HuR), 4E-BPI, p130CAS, Calmodulin, SOD3 (EC-SOD), MMP-14, G-protein alpha-q, Cyclin D1, ATOX1, SP1, ADAM17, PI38 MAPK, Elk-1, PAI1, PKA-cat (cAMP-dependent), PDGF-R-beta, ATP7A, HIF3, Casein kinase I delta, Siruin3, MCM5, RUNX3, VHL, FBXW7, SART1, KLF2, VCP, SKP1, UBXD7, Ubiquitin, ING4, GSK3 beta, MCMT, LAMP2, OS-9, EAF2, MDM2, HSP40, MCM2, HSP90, Cul1/Rbx1 E3 ligase, AML1 (RUNX1), FHL1 (SLM1), PTEN, Siruin7, SSAT, Elongin C, HIF-prolyl hydroxylase, PRDX4, CHIP, RUVBL2, p53, CITED4 | 3.026E-11 |
Supplementary Table 3. Pathway analysis of genes co-expressed cadherin 2 (CDH2) from the MetaCore database (with p-value< 0.05 set as the cutoff value) (Supplementary Table 3 and Supplementary Figure 4).

| #   | Maps                                                                 | p-Value     | Network objects from active data                                                                                     |
|-----|----------------------------------------------------------------------|-------------|----------------------------------------------------------------------------------------------------------------------|
| 1   | Cell adhesion_ECM remodeling                                        | 2.504E-18   | MMP-13, TIMP3, SERPINE2, MSN (moesin), MMP-1, IL-8, MMP-14, MMP-2, Versican, MMP-12, IGF-1 receptor, Matrilysin (MMP-7), PLAU (uPAR), alpha-5/beta-1 integrin, Actin cytoskeletal, MMP-10, Collagen IV, TIMP2, Fibronectin, Nidogen, Stromelysin-1, LAMA4, MMP-9, PAI1, PLAU (UPA), Syndecan-2, Collagen I, Kallikrein 3 (PSA), Collagen III |
|     | Cytoskeleton remodeling_Regulation of actin cytoskeleton organization | 2.188E-15   | Talin, RhoA, WRCH-1, MRCKalpha, Rac1-related, Cdc42 subfamily, RhoJ, Vinculin, MSN (moesin), ERM proteins, F-Actin cytoskeleton, Spectrin, MRLC, ARP1B, RhoA-related, Caldesmon, Actin cytoskeletal, Alpha-actinin, Filamin A, RhoC, LIMK1, RhoB, TC10, MyHC, LIMK, MLCK, MRCK |
| 2   | IL-1 beta- and Endothelin-1-induced fibroblast/ myofibroblast migration and extracellular matrix production in asthmatic airways | 1.775E-12   | COL1A1, COL4A1, EDNRB, TIMP3, MMP-1, ERK1/2, MMP-2, Versican, IL-1RI, COL1A2, CTGF, PDGF-R-alpha, Thrombosphindon 1, Fibronectin, Stromelysin-1, PAI1, EDNRA, Collagen I, PDGF-R-beta, Collagen III |
| 3   | TGF-beta-induced fibroblast/ myofibroblast migration and extracellular matrix production in asthmatic airways | 4.672E-12   | COL1A1, Biglycan, TGF-beta 2, ITGB1, COL4A1, MMP-13, TIMP3, Tenasin-C, MMP-1, ERK1/2, MMP-2, COL1A2, COL5A1, Collagen IV, TIMP2, ITGA5, Fibronectin, Stromelysin-1, MMP-9, PAI1, Collagen I, MEK4(MAP2K4), Collagen III, Thrombosphindon 2 |
| 4   | Role of TGF-beta 1 in fibrosis development after myocardial infarction | 6.420E-12   | COL1A1, Biglycan, EDNRB, Tenasin-C, MMP-1, MMP-2, ACTA2, COL1A2, CTGF, Angiotensin II, TIMP2, Thrombosphindon 1, Fibronectin, Prolyl endopeptidase, MMP-9, PAI1, EDNRA, Collagen I, Collagen III |
| 5   | Glucocorticoid-induced elevation of intraocular pressure as glaucoma risk factor | 1.080E-11   | RhoA, ITGB1, WNT5A, ROR2, COL4A1, MMP-1, Filamin B (TABP), Antileukoprotease 1, SERPINA3 (ACT), WNT2, MMP-2, Actin cytoskeletal, Alpha-actinin, Filamin A, Srp40, Collagen IV, Thrombosphindon 1, Fibronectin, Stromelysin-1, PKC-epsilon, alpha-V/beta-5 integrin, PAI1, LAMA1, MLCK |
| 6   | Glucocorticoid-induced elevation of intraocular pressure as glaucoma risk factor | 3.805E-10   | G3P2, TIR1, TGF-beta 2, Adipophilin, Carbonic anhydrase XII, Lysyl oxidase, ROR-alpha, Adrenomedullin, HIF1A, P4HA2, REDD1, MMP-2, Galectin-1, PLAU (uPAR), P4HA1, 5'-NTD, GLUT3, ENO1, Angiotiopetin 2, CTGF, Thrombosphindon 1, MMP-9, PAI1, Carbonic anhydrase IX, Stanniocalcin 2, LRP1, PKM2, IBP3 |
| 7   | Transcription_HIF-1 targets                                          | 2.237E-09   | PAM, Trypsin, AVP-NPII, OT-NPII, GRP(1-27), AVP-Gly, GRP(18-27), GRP(1-27)Gly, AVP extracellular region, GRP precursor, OT, PCSK5, OT-Gly, GRP(1-17), Neurophysin-II, OT-Gly-Lys-Arg, NPI, ProGRP, AVP-Gly-Lys-Arg |
| 8   | Protein folding and maturation_Posttranslational processing of neuroendocrine peptides | 7.111E-09   | Biglycan, RECK, ROR2, FZD2, WNT7B, LYPD6, Tenasin-C, Glypican-3, Tcf(Lef), SFRP2, WNT, ERK1/2, WLS, TMEM59, RAP-2A, Filamin A, MKK7 (MAP2K7), GPR124, Stromelysin-1, WNT5B, Frizzled |
| 9   | Development_Positive regulation of WNT/Beta-catenin signaling at the receptor level | 1.170E-08   | RhoA, Rich1, JAM3, Cingulin, Tubulin alpha, F-Actin, ARP3, INADL, MRLC, ACTR3, CGNL1, ZO-3, Actin cytoskeletal, PARD6, Claudin-1, Actin, Tubulin (in microtubules) |
| 10  | Cell adhesion_Tight junctions                                         | 2.542E-08   | MTS1 (S100A4), LAMC2, LAMC2 (80kDa), Calcyclin, Tenasin-C, IL-8, TCF7L2 (TCF4), Fascin, MMP-14, Lamin A/C, Beta-catenin, PLAU (uPAR), LAMC2 (100kDa), Claudin-1, PLAU (UPA) |
|   | Cytoskeleton remodeling_Regulation of actin cytoskeleton nucleation and polymerization by Rho GTPases | 2.568E-08 |
|---|--------------------------------------------------------------------------------------------------|----------|
|   | RhoA, RhoD, DRF, RhoF (Rif), Profilin, Rac1-related, Cdc42 subfamily, BAIAP2, FMNL3, FMNL2, F-Actin cytoskeleton, RhoA-related, Actin cytoskeletal, RhoC, RhoB, TC10, FNBPI |          |

|   | Cell adhesion_Integrin-mediated cell adhesion and migration | 3.065E-08 |
|---|-------------------------------------------------------------|----------|
|   | Talin, RhoA, p130CAS, ITGB1, p190-RhoGEF, VCAM1, PKC, Vinculin, PINCH, Zyxin, F-Actin cytoskeleton, alpha-5/beta-1 integrin, Actin cytoskeletal, Alpha-parvin, Alpha-actinin, Collagen IV, Fibronectin, PARD6, Collagen I, Collagen III WWP1, Prickle-1, WNT5A, STK4, SIAH1, PKC-alpha, Tcf(Lef), WNT, Amer1, beta-TrCP, Alpha-1 catenin, Beclin 1, NEDD4L, LAT2, Beta-catenin, Skp2/TrCP/FBXW, Nucleoredoxin, SENP2, NFKB2, DACT3, Frizzled, DACT1, CDK6 |          |

|   | Development_Negative regulation of WNT/Beta-catenin signaling in the cytoplasm | 3.961E-08 |
|---|------------------------------------------------------------------------------|----------|
|   | Talin, RhoA, p130CAS, ITGB1, ARCGAP22, PKC-alpha, ERK1/2, MMP-14, MMP-2, alpha-5/beta-1 integrin, Actin cytoskeletal, TIMP2, RhoC, ITGA5, Fibronectin, PLAU (UPA) |          |

|   | FAK1 signaling in melanoma | 4.004E-08 |
|---|-----------------------------|----------|
|   | RhoA, p130CAS, ITGB1, ARCGAP22, PKC-alpha, ERK1/2, MMP-14, MMP-2, alpha-5/beta-1 integrin, Actin cytoskeletal, TIMP2, RhoC, ITGA5, Fibronectin, PLAU (UPA) |          |
Supplementary Table 4. Pathway analysis of genes co-expressed cadherin 4 (CDH4) from the MetaCore database (with p-value< 0.05 set as the cutoff value) (Supplementary Table 4 and Supplementary Figure 5).

| #  | Maps                                                                 | p-Value   | Network objects from active data                                                                 |
|----|----------------------------------------------------------------------|-----------|--------------------------------------------------------------------------------------------------|
| 1  | Protein folding and maturation_POMC processing                      | 2.428E-13| PAM, proACTH, POMC, N-POMC, beta-Endorphin extracellular region, gamma-LPH, ACTH 1-17, Joining   |
|    |                                                                      |           | peptide (JP), DA-alphaMSH, gamma-MSH, beta-LPH, gamma2-MSH, beta-MSH, N-POC, gamma3-MSH,       |
|    |                                                                      |           | ACTH, alpha-MSH, CLIP                                                                          |
| 2  | Beta-catenin-dependent transcription regulation in colorectal cancer | 1.638E-11| COX-2 (PTGS2), ID2, MTS1 (S100A4), LAMC2, LAMC2 (80kDa), Calcyten, Tenasin-C, IL-8, CDX2,       |
|    |                                                                      |           | L1CAM, Fascin, MMP-14, PLAU (uPAR), LAMC2 (100kDa), SOX9, PLAU (UPA), MDR1, YAP1 (Yap65)        |
|    |                                                                      |           | MMP-13, SERPINE2, Caveolin-2, MSN (moesin), MMP-1, IL-8, EGFR, MMP-14, MMP-2, MMP-12, HB-EFG,   |
|    |                                                                      |           | Matrilysin (MMP-7), PLAU (uPAR), Actin cytoskeletal, Collagen IV, TIMP2, Kalliikrein 1,          |
|    |                                                                      |           | Stromelysin-1, LAMA4, PLAU (UPA), Syndecan-2, Kalliikrein 3 (PSA)                                |
| 3  | Cell adhesion ECM remodeling                                        | 2.422E-11| ID2, Adipophilin, Lysyl oxidase, Transferrin, ROR-alpha, Endothelin-1, Adrenomedullin, HIF1A,   |
|    |                                                                      |           | P4HA2, LOXL4, MMP-2, Galectin-1, PLAU (uPAR), 5'-NTD, GLUT3, ENO1, CTGF, p21, IBP1, MGF, HGF   |
|    |                                                                      |           | receptor, OSF-1, Actin cytoskeletal, Collagen IV, TIMP2, Kalliikrein 1, Stromelysin-1, LAMA4,   |
|    |                                                                      |           | PLAU (UPA), Syndecan-2, Kalliikrein 3 (PSA)                                                    |
| 4  | Transcription_HIF-1 targets                                         | 2.755E-08| N-cadherin, Endothelin-1, E2A, WNT, TGF-beta receptor type II, SLUG, EGFR, SIP1 (ZFHXB1),       |
|    |                                                                      |           | MMP-2, PDGF-A, IL-1RI, Caldesmon, ACTA2, Tropomyosin-1, PDGF-R-alpha, TWIST1, HGF receptor (Met,|
|    |                                                                      |           | PGK1, SDF-1, MDR1, IBP3                                                                         |
| 5  | Development_Regulation of epithelial-to-mesenchymal transition (EMT) | 2.916E-08| RECK, MMP-13, CCL2, IL-8, TGF-beta receptor type II, EGFR, ERK1/2, MMP-2, PDGF-A, HB-EFG, IL-6,|
|    |                                                                      |           | Galectin-1, ACTA2, CTGF, PDGF-R-alpha, PDGF receptor, OSF-2, Stromelysin-1, TGF-beta receptor  |
|    |                                                                      |           | type I                                                                                         |
| 6  | Role of stellate cells in progression of pancreatic cancer           | 5.083E-08| ID2, TEF-3, Endothelin-1, FKHR, SOD2, HIF1A, CDX2, SLUG, SIP1 (ZFHXB1), Cyr61, ID3, HBP17, TAZ,|
|    |                                                                      |           | CTGF, TWIST1, SOX9, YAP1 (Yap65), CDK6                                                          |
| 7  | Development_YAP/TAZ-mediated co-regulation of transcription          | 8.820E-08| MLC2 (cat), MMP-13, PKC-alpha, IL-8, EGFR, G-protein alpha-1 family, MRLC, ERK1/2, MMP-2,       |
|    |                                                                      |           | Angiopeptin-1, Actin cytoskeletal, Coagulation factor X, ERK2 (MAPK1), G-protein alpha-q/11,      |
|    |                                                                      |           | Tissue factor, PLC-beta3, ERK1 (MAPK3), MLCK, IP3 receptor                                      |
| 8  | Role of Tissue factor-induced Thrombin signaling in cancerogenesis  | 2.122E-07| ITGB1, VEGF-C, GFPT2, IL-8, Cyr61, PLAU (uPAR), Coagulation factor X, CTGF, Tissue factor, PLAU  |
|    |                                                                      |           | (UPA)                                                                                           |
| 9  | Expression targets of Tissue factor signaling in cancer              | 1.791E-06| TMSB4X, EDNRB, Endothelin-1, Tenasin-C, MMP-1, TGF-beta receptor type II, MMP-2, ACTA2, Ac-SDKP,|
|    |                                                                      |           | CTGF, TIMP2, Thymosin beta-4, TGF-beta receptor type I                                           |
| 10 | Role of TGF-beta 1 in fibrosis development after myocardial infarction | 2.492E-06| Amphiregulin, EDNRB, PLC-beta, Endothelin-1, PKC-alpha, EGFR, G-protein alpha-1 family, ERK1/2,|
|    |                                                                      |           | PDGF-A, HB-EFG, PDGF-C, PDGF-R-alpha, PDGF receptor, p90Rsk, IP3 receptor, TGF-beta receptor    |
|    |                                                                      |           | type I                                                                                         |
| 11 | MAPK-mediated proliferation of normal and asthmatic smooth muscle cells | 2.689E-06| PGE2R4, Amphiregulin, EDNRB, Endothelin-1, IL-8, EGFR, G-protein alpha-1 family, NTSR1, ERK1/2,|
|    |                                                                      |           | MMP-2, PGE2R1, HB-EFG, Gaalipha(i)-specific peptideGPCRs, TGF-alpha, Galanin, Galalipha(q)-specific |
|    |                                                                      |           | peptide GPCR, G-protein alpha-q/11, HB-EFG(mature), SDF-1                                      |
| 12 | G protein-coupled receptors signaling in lung cancer                 | 2.940E-06|                                                                                                  |
| Page | Topic                                      | p-value      | Genes/Proteins                                                                 |
|------|-------------------------------------------|--------------|-----------------------------------------------------------------------------|
| 13   | Cell adhesion_Desmosomes                 | 3.919E-06    | Keratin 17, Desmocollin 3, Keratin 14, Keratin 5, Keratin 1, Plakophilin 1, Desmoglein 3, Vimentin, DSC2 |
|      |                                           |              | Endothelin-1, CCL2, WNT, G-protein alpha-i family, DKK1, PTHR1, PTHrP, SDF-1, Frizzled, IBP3, Kallikrein 3 (PSA) |
| 14   | Bone metastases in Prostate Cancer       | 4.695E-06    | COX-2 (PTGS2), SPHK1, MMP-13, ERK1/2, MMP-2, PDGF-A, PDGF-C, IL-6, EGR1, PDGF-R-alpha, ERK2 (MAPK1), p21, PDGF receptor, Tissue factor, Stromelysin-1, p90Rsk, Phox1 (PRRX1) |
| 15   | Signal transduction_PDGF signaling via MAPK cascades | 5.014E-06    |                                                                                   |
Supplementary Table 5. Pathway analysis of genes co-expressed cadherin 7 (CDH7) from the MetaCore database (with p-value< 0.05 set as the cutoff value) (Supplementary Table 5 and Supplementary Figure 6).

| #  | Maps                                                                 | p-Value         | Network objects from active data                                                                 |
|----|----------------------------------------------------------------------|-----------------|----------------------------------------------------------------------------------------------------|
| 1  | Cell cycle_Chromosome condensation in prometaphase                    | 2.632E-18       | Condensin, TOP1, Cyclin B, Histone H3, CAP-G-GAP-G2, CAP-H2, CAP-C, Cyclin A, CNAF1, CDK2/D3, Aurora-B, TOP2, BRRN1, Aurora-A, CAP-E, CDK1 (p34) |
| 2  | Cell cycle_The metaphase checkpoint                                   | 2.852E-16       | HZwint-1, ZW10, Survivin, Nek2A, CENP-A, CDC20, MAD2a, CENH, SPBC25, BUB3, Aurora-B, HEC, CENP-E, BUB1, Aurora-A, PLK1, CDC1A, CENP-F, Zwilch, AF15q14 |
| 3  | Cell cycle_Role of APC in cell cycle regulation                        | 2.885E-16       | Cyclin B, ORC1L, CKS1, Nek2A, CDC20, MAD2a, BUB3, Tome-1, Cyclin A, Aurora-B, CDC25A, BUB1, Geminin, Em1, Aurora-A, PLK1, Securin, CDK1 (p34), CDK2 |
| 4  | DNA damage_ATM/ATR regulation of G2/M checkpoint: cytoplasmic signaling | 9.173E-15       | CDC25, UBE2C, PP1-cat, Nucleolyein TIAR, 14-3-3, B56G, JAB1, PP2A regulatory, Aurora-B, JNK2(MAPK9), CDC25A, Cyclin B1, Aurora-A, PLK1, p38 MAPK, DCK, CDK1 (p34) |
| 5  | Cell cycle_Spindle assembly and chromosome separation                  | 1.398E-14       | Tubulin alpha, Cyclin B, Separase, ZW10, Nek2A, CDC20, MAD2a, Importin (karyopherin)-alpha, KNSL1, Aurora-B, HEC, TPX2, CSE1L, Aurora-A, Securin, Ran, CDK1 (p34), Tubulin (in microtubules) |
| 6  | DNA damage_Intra S-phase checkpoint                                    | 2.323E-13       | PCNA, Chk2, MCM3, Chk1, MCM7, Brc1, SM3C, CDC7, Histone H3, MCM5, FANC2D2, DTL (hCdt2), MCM4, FANCI (KIAA1794), PP1-cat, MCM10, PP1-cat alpha, Histone H2AX, Cyclin A, CDC25A, MCM2, Claspin, p38 MAPK, CDK2, CDC45L |
| 7  | DNA damage_ATM/ATR regulation of G2/M checkpoint: nuclear signaling    | 1.213E-11       | HSF1, Chk2, Chk1, Brc1, G2M-1, Cyclin B, Cyclin B2, CDC25C, PALB2, MDM2, Histone H2AX, Cyclin A, RBBP8 (Cdt1p), Cyclin B1, Claspin, PLK1, CDK1 (p34), CDK2 |
| 8  | Cell cycle_Role of Nek in cell cycle regulation                        | 4.024E-11       | Tubulin beta, Tubulin gamma, PI3K cat class IA, Tubulin alpha, Histone H3, Nek2A, CDC20, CDC25, Cyclin B1, TPX2, PDK (PDK1), Aurora-A, Ran, CDK1 (p34), Tubulin (in microtubules) |
| 9  | Cell cycle_Start of DNA replication in early S phase                   | 5.728E-10       | MCM3, CDC7, ORC1L, MCM5, RPA3, DP1, MCM4, MCM10, ORC6L, MCM4/6/7 complex, MCM2, Geminin, CDK2, CDC45L |
| 10 | Abnormalities in cell cycle in SCLC                                    | 1.651E-09       | PCNA, E2F2, Histone H3, CKS1, CDK4, BMI-1, MDM2, Cyclin A, Aurora-B, Cyclin B1, CDK1 (p34), Cyclin E2, CDK2 |
| 11 | Ubiquinone metabolism                                                 | 2.963E-09       | NDUF8A, NDUB3, NDUF5, NDUF7, NDP13, NDP5, NDUF1B, NDUF1B, NDUF10, NDUF13, COQ3, NDUF2, coenzyme Q2 homolog, prenyltransferase (yeast), NDUF8A, NDUF8B, NDUF8 |
| 12 | Cell cycle_Cell cycle (generic schema)                                 | 3.800E-09       | Cyclin B, E2F2, CDC25C, CDK4, E2F5, DP1, Cyclin A, CDC25A, p107, CDK1 (p34), CDK2 |
| 13 | ATP/ITP metabolism                                                     | 4.216E-09       | AK2, CSL4, POLR1A1, RRP4, RRM2B, PPA5, RRM2, RRP46, ADSS, ACYP2, Ribonucleotide reductase, POLR2I, POLR2B, RRP40, POLR2G, RPA16, RPA3, POLR2D, POLR2I, Adenosine kinase, PM/SCL-75, HPRT, POLR3K, Small RR subunit, RR1M, 5' NT1B |
| 14 | Cell cycle_ Initiation of mitosis                                       | 4.695E-09       | Wee1, Cyclin B2, Histone H3, CDC25C, FOXM1, Kinase MYT1, Lamin B, KNSL1, Cyclin B1, PLK1, CDK1 (p34), CDK7 |
| 15 | Cell cycle_Sister chromatid cohesion                                   | 1.312E-08       | PCNA, TOP1, SMC3, Cyclin B, RF3, Separase, Histone H3, DERPC, DCC1, Securin, CDK1 (p34) |
### Supplementary Table 6. Pathway analysis of genes co-expressed cadherin 11 (CDH11) from the MetaCore database (with p-value < 0.05 set as the cutoff value) (Supplementary Table 6 and Supplementary Figure 7).

| #  | Maps                                                                 | p-Value   | Network objects from active data                                                                                                                                 |
|----|----------------------------------------------------------------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1  | Cell adhesion_ECM remodeling                                         | 2.784E-19| MMP-13, TIMP3, SERPINE2, Caveolin-2, PLAT (TPA), MSN (moesin), MMP-1, IL-8, IGF-2, MMP-14, MMP-2, Versican, MMP-12, Matrilysin (MMP-7), PLAU (uPAR), alpha-5/beta-1 integrin, MMP-10, TIMP2, IGF-1, Fibronectin, Kallikrein 1, Nidogen, Stromelysin-1, LAMA4, PAI1, PLAU (UPA), Syndecan-2, Collagen I, Kallikrein 3 (PSA), Collagen III |
| 2  | IL-1 beta- and Endothelin-1-induced fibroblast/ myofibroblast migration and extracellular matrix production in asthmatic airways | 2.862E-18| COL1A1, IL-1 beta, AP-1, EDNRB, TIMP3, Decorin, CCL2, MMP-1, HAS2, c-Jun, MMP-2, Versican, IL-1RI, c-Jun/c-Fos, COL1A2, CTGF, PDGF-R-alpha, Thrombospondin 1, Fibronectin, Stromelysin-1, PAI1, EDNRA, Collagen I, PDGF-R-beta, Collagen III |
| 3  | Development_Regulation of epithelial-to-mesenchymal transition (EMT)  | 6.645E-18| IL-1 beta, HEY1, VE-cadherin, N-cadherin, TGF-beta 2, TGF-beta 3, WNT, TGF-beta receptor type II, SLUG, ZO-1, Lef-1, c-Jun, Sno-N, SIP1 (ZFHX1B), MMP-2, IL-1RI, Cadhesome, ACTA2, Tropomyosin-1, PDGF-R-alpha, TWIST1, Fibronectin, Vimentin, TCF8, Claudin-1, PAI1, PDGF-D, Frizzled, EDNRA, FGFR1, PDGF-R-beta |
| 4  | Role of TGF-beta 1 in fibrosis development after myocardial infarction| 4.860E-14| COL1A1, Biglycan, TMSB4X, EDNRB, Tenasin-C, MMP-1, SMAD7, TGF-beta receptor type II, MMP-2, ACTA2, Ac-SDKP, COL1A2, CTGF, TIMP2, Thymosin beta-4, Thrombospondin 1, Fibronectin, PAI1, EDNRA, Collagen I, Collagen III |
| 5  | TGF-beta-induced fibroblast/ myofibroblast migration and extracellular matrix production in asthmatic airways | 8.853E-14| COL1A1, Biglycan, TGF-beta 2, ITGB1, AP-1, MMP-13, TIMP3, Decorin, TGF-beta 3, Tenasin-C, MMP-1, HAS2, TGF-beta receptor type II, c-Jun, MMP-2, c-Jun/c-Fos, COL1A2, COL5A1, TIMP2, ITGA5, Fibronectin, Stromelysin-1, PAI1, Collagen I, Collagen III, Thrombospondin 2 |
| 6  | Development_TGF-beta-dependent induction of EMT via SMADs              | 1.227E-12| ID2, HEY1, N-cadherin, TGF-beta 2, TGF-beta 3, ETS1, TGF-beta receptor type II, SLUG, Lef-1, SIP1 (ZFHX1B), MMP-2, TGF-beta, TWIST1, Fibronectin, Vimentin, TCF8, Claudin-1, PAI1, ILK |
| 7  | Role of adhesion of SCLC cells in tumor progression                   | 1.634E-11| RhoA, N-cadherin, ITGB1, VCAM1, alpha-4/beta-1 integrin, Tenasin-C, alpha-V/beta-1 integrin, MMP-14, MMP-2, CDC42, alpha-5/beta-1 integrin, PTHRp, CD9, Caveolin-1, Fibronectin, Stromelysin-1, SDF-1, CXCR4 |
| 8  | TGF-beta 1-mediated induction of EMT in normal and asthmatic airway epithelium | 2.237E-11| COL1A1, IL-1 beta, N-cadherin, AP-1, Tenasin-C, SMAD7, ETS1, TGF-beta receptor type II, SLUG, ZO-1, c-Jun, MMP-2, ACTA2, c-Jun/c-Fos, CTGF, TWIST1, DAB2, Fibronectin, Vimentin, PAI1 |
| 9  | Development_Role of proteases in hematopoietic stem cell mobilization | 2.666E-11| Cathepsin G, VCAM1, alpha-4/beta-1 integrin, MMP-14, MMP-2, alpha-5/beta-1 integrin, DPP4, MGF, Fibronectin, c-Kit, Cathepsin K, SDF-1, CXCR4 |
| 10 | Role of stellate cells in progression of pancreatic cancer            | 5.084E-11| COL1A1, RECK, MMP-13, c-Fos, CCL2, IL-8, TGF-beta receptor type II, c-Jun, MMP-2, Galectin-1, ID1, ACTA2, alpha-5/beta-1 integrin, COL1A2, CTGF, PDGF-R-alpha, PDGF receptor, OSF-2, Fibronectin, Stromelysin-1, Collagen I, PDGF-R-beta, Collagen III |
| 11 | Signal transduction_WNT/Beta-catenin signaling in tissue homeostasis  | 7.895E-11| Cyclin D2, FGF18, Cyclin A2, FKHR, BACE1, Tcf(Lef), IL-8, WNT, SLUG, Lef-1, Pitx2, TCF7L2 (TCF4), Connexin 43, MMP-2, Versican, Beta-catenin, KLF4, PAI1, Frizzled |
|   | Description                                                                 | Score |
|---|-----------------------------------------------------------------------------|-------|
| 12 | TGF-beta signaling via SMADs in breast cancer                              | 9.85E-11 |
| 13 | Glucocorticoid-induced elevation of intraocular pressure as glaucoma risk factor | 1.112E-10 |
| 14 | Production and activation of TGF-beta in airway smooth muscle cells         | 1.946E-10 |
| 15 | Development_TGF-beta-dependent induction of EMT via RhoA, PI3K and ILK     | 5.404E-10 |
Supplementary Table 7. Pathway analysis of genes co-expressed cadherin 12 (CDH12) from the MetaCore database (with p-value< 0.05 set as the cutoff value) (Supplementary Table 7).

| #  | Maps                                                                 | p-Value       | Network objects from active data                                                                                                                                                                                                 |
|----|----------------------------------------------------------------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1  | Cytoskeleton remodeling_Regulation of actin cytoskeleton organization by the kinase effectors of Rho GTPases | 1.414E-09     | RhoA, WRCH-1, DMPK, PAK, Rac1-related, Cdc42 subfamily, RhoJ, ERM proteins, Spectrin, MRLC, SLC9A1, RhoA-related, Alpha adducin, RhoC, RhoB, TC10, MyHC, MRCK                                                                                           |
| 2  | Development_Negative regulation of WNT/Beta-catenin signaling in the cytoplasm | 5.128E-07     | ELAVL1 (HuR), KLHL12, WWP1, STK4, Porf-2, WNT, beta-TrCP, Itch, Alpha-1 catenin, NEDD4L, SKG3 alpha/beta, Skp2/TrCP/FBXW, TAZ, Cyclin D1, CXXC5, RNF185, Axin, YAP1/TAZ                                                                 |
| 3  | LRRK2 in neurons in Parkinson’s disease                               | 1.038E-06     | GSK3 beta, AP-2 alpha subunits, Beta-adaptin 2, PKC-zeta, MARKK, Tau (MAPT), RAB-5B, AP2A2, CHIP, PKA-cat (cAMP-dependent), VIL2 (ezrin)                                                                                                                                   |
| 4  | Development_Positive regulation of WNT/Beta-catenin signaling in the cytoplasm | 3.932E-06     | PPP2R2A, TBL1X, Bcl-9, Trabid, USP25, WNT, USP7, Alpha-1 catenin, Joubierin, FAK1, SKG3 alpha/beta, IGF-1 receptor, SMAD3, Makorin-1, Axin, PKA-cat (cAMP-dependent)                                                                                                           |
| 5  | Cytoskeleton remodeling_Regulation of actin cytoskeleton nucleation and polymerization by Rho GTPases | 6.154E-06     | RhoA, RhoD, RhoF (Rif), CYFIP2, Rac1-related, Cdc42 subfamily, BAIAP2, RhoA-related, RhoC, RhoB, TC10, FNBPI                                                                                                                                                    |
| 6  | Development_Positive regulation of STK3/4 (Hippo) pathway and negative regulation of YAP/TAZ function | 7.507E-06     | RhoA, STK4, AMPK beta subunit, Adenylate cyclase, beta-TrCP, CCDC85C, Itch, Alpha-1 catenin, EBP50, Skp2/TrCP/FBXW, TAZ, MARKK, PKA-cat (cAMP-dependent), Alpha-catenin                                                                                     |
| 7  | Development_Negative regulation of WNT/Beta-catenin signaling in the nucleus | 7.966E-06     | NF-AT5, TBL1X, GSK3 beta, Oct-3/4, WNT, Alpha-1 catenin, Jade-1, P15RS, CHIBBY, BCL9/B9L, GLI-3R, PC1-CTT, CHD8, TLE, HIC5, Axin, Histone H1                                                                                                                                  |
| 8  | PI3K signaling in gastric cancer                                      | 1.560E-05     | ELAVL1 (HuR), PI3K reg class IA (p85), GSK3 beta, PI3K reg class IA, PTEN, HSP27, FAK1, ErbB3, Cyclin D1, PRNP, G-protein alpha-q/11, MDR1                                                                                                                                   |
| 9  | Signal transduction_mTORC2 downstream signaling                      | 2.056E-05     | RhoA, Tuberin, GSK3 beta, SREBP1 (nuclear), PKC, STK4, NEDD4L, GSK3 alpha/beta, PKC-zeta, IGF-1 receptor, Cyclin D1, Adenylate cyclase type IX, PKA-cat (cAMP-dependent), PREX1                                                                 |
| 10 | Signal transduction_Cyclic AMP signaling                             | 3.383E-05     | PKC, cAMP-GEFI, PHK alpha, PHK gamma, GSK3 alpha/beta, Adenylate cyclase type VI, PKC-zeta, CREB1, Adenylate cyclase type IX, PKA-cat (cAMP-dependent)                                                                                                                      |
| 11 | Regulation of lipid metabolism_Regulation of lipid metabolism via LXR, NF-Y and SREBP | 3.383E-05     | SREBP1 precursor, Importin (karyopherin)-beta, ALCY, SREBP1 (nuclear), AMPK beta subunit, RARalpha, RXRA, CREB1, SP1, SREBP1 (Golgi membrane)                                                                                                                        |
| 12 | Signal transduction_IGF-1 receptor signaling pathway                 | 7.566E-05     | Androgen receptor, PI3K reg class IA (p85), GSK3 beta, SREBP1 (nuclear), Bcl-2, Cyclin D, FAK1, PKC-zeta, IGF-1 receptor, MNK2 (GPRK7), MKK7 (MAP2K7), ACSA                                                                                                              |
| 13 | WNT signaling in gastric cancer                                      | 1.292E-04     | GSK3 beta, CD44, WNT, beta-TrCP, WNT3, Skp2/TrCP/FBXW, Cyclin D1, Axin, FBXW11                                                                                                                                                                                        |
| 14 | DNA damage_ATM/ATR regulation of G1/S checkpoint                      | 1.306E-04     | ELAVL1 (HuR), Chk2, SMG1, FBXW7, PP2A structural, beta-TrCP, PP2A regulatory, Cyclin D1, PER3, FBXW11                                                                                                                                                                     |
| 15 | Main pathways of Schwann cell transformation in neurofibromatosis type 1 | 1.344E-04     | Tuberin, PI3K reg class IA (p85), Amhregulin, GSK3 beta, ErbB2, PTEN, Bcl-2, FAK1, ErbB3, Neurofibromin, IGF-1 receptor, BRD4, Cyclin D1, ErbB4                                                                                                                                 |
Supplementary Table 8. Pathway analysis of genes co-expressed cadherin 13 (CDH13) from the MetaCore database (with p-value< 0.05 set as the cutoff value) (Supplementary Table 8 and Supplementary Figure 8).

| #  | Maps                                                                 | p-Value   | Network objects from active data                                                                 |
|----|----------------------------------------------------------------------|-----------|--------------------------------------------------------------------------------------------------|
| 1  | Development_Regulation of epithelial-to-mesenchymal transition (EMT) | 3.068E-16 | IL-1 beta, HEY1, VE-cadherin, N-cadherin, TGF-beta 2, WNT, TGF-beta receptor type II, SLUG, ZO-1, SIP1 (ZFH1B), MMP-2, PDGF-A, Caldesmon, ACTA2, Tropomyosin-1, PDGF-R-alpha, TWIST1, Fibronectin, Jagged1, Vimentin, TCF8, Dll4, Claudin-1, PAI1, PDGF-D, Frizzled, EDNRA, FGFR1, PDGF-R-beta |
| 2  | Role of stellate cells in progression of pancreatic cancer          | 3.846E-16 | COL1A1, MEK1(MAP2K1), NGF, RECK, MMP-13, c-Fos, IL-8, TGF-beta receptor type II, alpha-V/beta-3 integrin, MEK2(MAP2K2), MMP-2, PDGF-A, HB-EGF, Galectin-1, ID1, ACTA2, alpha-5/beta-1 integrin, SOS, COL1A2, CTGF, PDGF-R-alpha, PDGF receptor, OSF-2, Fibronectin, NFKBIA, Collagen I, PDGF-R-beta, Collagen III |
| 3  | Cell adhesion_ECM remodeling                                       | 2.966E-15 | MMP-13, TIMP3, SERPINE2, Caveolin-2, PLAT (TPA), IL-8, MMP-2, Versican, MMP-12, HB-EGF, PLAUR (uPAR), alpha-5/beta-1 integrin, Actin cytoskeletal, MMP-10, Collagen IV, TIMP2, Fibronectin, Kalliikrein 1, Nidogen, LAMA4, PAI1, PLAU (UPA), Syndecan-2, Collagen I, Kalliikrein 3 (PSA), Collagen III |
| 4  | IL-1 beta- and Endothelin-1-induced fibroblast/myofibroblast migration and extracellular matrix production in asthmatic airways | 9.808E-14 | COL1A1, IL-1 beta, AP-1, COL4A1, EDNRB, TIMP3, Decorin, HAS2, MMP-2, Versican, COL1A2, NF-kb, CTGF, PDGF-R-alpha, Thrombospondin 1, Fibronectin, PAI1, EDNRA, Collagen I, PDGF-R-beta, Collagen III |
| 5  | TGF-beta-induced fibroblast/myofibroblast migration and extracellular matrix production in asthmatic airways      | 2.572E-11 | COL1A1, Biglycan, TGF-beta 2, ITGB1, AP-1, COL4A1, MMP-13, TIMP3, Decorin, Tenascin-C, HAS2, TGF-beta receptor type II, MMP-2, COL1A2, COL5A1, Collagen IV, TIMP2, ITGA5, Fibronectin, PAI1, Collagen I, Collagen III, Thrombospondin 2 |
| 6  | Role of TGF-beta 1 in fibrosis development after myocardial infarction | 5.509E-11 | COL1A1, Biglycan, EDNRB, Tenascin-C, TGF-beta receptor type II, MMP-2, AGTR1, ACTA2, COL1A2, CTGF, Angiotensin II, TIMP2, Thrombospondin 1, Fibronectin, PAI1, EDNRA, Collagen I, Collagen III |
| 7  | MAPK-mediated proliferation of normal and asthmatic smooth muscle cells | 3.070E-10 | LPAR2, Rb protein, EDNRB, c-Fos, PLAT (TPA), G-protein alpha-I family, MKP-1, PDGF-A, HB-EGF, PDGF-C, MEK1/2, G-protein beta/gamma, SOS, PDGF-R-alpha, PDGF receptor, Elk-1, PAI1, p90Rsk, EDNRA, FGFR1, PDGF-R-beta |
| 8  | Stimulation of TGF-beta signaling in lung cancer                   | 7.310E-10 | IL-1 beta, N-cadherin, TGF-beta 2, I-kb, ITGB1, Vinculin, TGF-beta receptor type II, SLUG, MMP-2, ACTA2, EGR1, VEGF-A, TGF-beta, Tropomyosin-1, MMP-28, Fibronectin, Vimentin, PAI1, Tropomyosin-2 |
| 9  | Cell adhesion_PLAU signaling                                       | 1.144E-09 | STAT3, MEK1(MAP2K1), LAMC2, NF-kb2 (p52), alpha-V/beta-1 integrin, alpha-V/beta-3 integrin, G-protein alpha-I family, F-Actin cytoskeleton, MRLC, PLAUR (uPAR), alpha-5/beta-1 integrin, VEGFR-2, SOS, NF-kb, Caveolin-1, MLCK, STAT1, PDGF-R-beta |
| 10 | Glucocorticoid-induced elevation of intraocular pressure as glaucoma risk factor | 2.691E-09 | ITGB1, WNT5A, COL4A1, GCR Beta, GCR, PLAT (TPA), ITGB3, alpha-V/beta-3 integrin, WNT2, MMP-2, ACTA2, EDNRA, Collagen IV, Thrombospondin 1, Fibronectin, alpha-V/beta-5 integrin, PAI1, LAMA1, MLCK, FGFR1 |
| 11 | Stromal-epithelial interaction in Prostate Cancer                   | 3.849E-09 | Keratin 17, TGF-beta 2, Tenascin-C, TGF-beta receptor type II, MMP-2, Versican, PDGF-A, ACTA2, PDGF-R-alpha, HIC5, TIMP2, Fibronectin, Vimentin, PDGF-D, FGFR1, Collagen I, PDGF-R-beta |
| Page | Development | TGF-beta-dependent induction of EMT via MAPK | 3.859E-09 |
|------|-------------|----------------------------------|-----------|
| 12   | TGF-beta 1-mediated induction of EMT in normal and asthmatic airway epithelium | 8.956E-09 |
| 13   | Development_TGF-beta-dependent induction of EMT via SMADs | 1.255E-08 |
| 14   | Signal transduction_Angiotensin II/AGTR1 signaling via Notch, Beta-catenin and NF-kB pathways | 2.318E-08 |

- MEK1(MAP2K1), TGF-beta 2, ITGB1, MLK3(MAP3K11), AP-1, c-Fos, NOX4, ITGB3, alpha-V/beta-1 integrin, TGF-beta receptor type II, MEK2(MAP2K2), MMP-2, TGF-beta, SOS, Fibronectin, Vimentin, Claudin-1, PAI1
- COL1A1, IL-1 beta, N-cadherin, AP-1, Tenascin-C, ITGB3, TGF-beta receptor type II, SLUG, ZO-1, MMP-2, ACTA2, CTGF, TWIST1, Fibronectin, Jagged1, Vimentin, PAI1, HEY1, N-cadherin, TGF-beta 2, TGF-beta receptor type II, SLUG, SIP1 (ZFHX1B), MMP-2, TGF-beta, TWIST1, Fibronectin, Jagged1, Vimentin, TCF8, Claudin-1, PAI1, COL1A1, HEY1, I-kB, PRKD1, NF-kB2 (p100), NF-kB2 (p52), IL-8, Connexin 43, MMP-2, AGTR1, Axin2, Beta-catenin, ACTA2, HEY2, Angiotensinogen, VEGF-A, NF-kB, CTGF, NIK(MAP3K14), Angiotensin II, Fibronectin, YAP1 (Yap65)
| # | Maps | p-Value | Network objects from active data |
|---|---|---|---|
| 1 | Transcription_HIF-1 targets | 6.658E-17 | PDK1, NIX, P4HA2, PFKL, REDD1, SLC9A1, VEGF-A, Cyclin G2, 5'-NTD, GLUT3, ENO1, p21, MSH6, Carbonic anhydrase IX, PGK1, Stanniocalcin 2, NIP3, MDR1, AK3, IBP3, ID2, Adipophilin, LOXL4, MMP-2, PLAUR (uPAR), WT1, Alpha-1B adrenergic receptor, DECl (StrA13), ALDOC, c-Myc, Epo, SDF-1, CXCR4, LRPI, PKM2, G3P2, ARNT, Heme oxygenase 1, TGF-beta 2, Ceruloplasmin, Lysyl oxidase, ROR-alpha, Adrenomedullin, CITED2, HIF1A, HXK1, HIF-1, GPI, PAHA1, FGFB, Angiopoietin 2, IBP1, MGF, Thrombomodulin 1, TIR1, GLUT1, Carbonic anhydrase XII, Transferin, SOX2, CX3CR1, TGM2, Galectin-1, NOXA, CTGF, MCT4, LDHA, ABCG2, p53, HGF receptor (Meit), Leptin, MMP-9, PAI |
| 2 | Oxidative stress_ROS-induced cellular signaling | 7.281E-17 | Casein kinase II, alpha chains, Tuberin, SREBP1 (nuclear), SCD, ERK1/2, EGR1, VEGF-A, PKA-reg (cAMP-dependent), TXNIP (VDUP1), IKK (cat), p21, Bak, Cytochrome c, FASN, E2I, Carbonic anhydrase IX, Syk, IL-1 beta, Bax, GS1K3 beta, FTL, IKK-alpha, FTH1, IRP2, GRP75, MDM2, IL-6, GADD45 alpha, NF-kB, AKT(PKB), Catalase, Cyclin B1, c-Src, PUMA, NOTCH1 (NICD), Thioredoxin, Heme oxygenase 1, PLK3 (CNK), Chk2, Adrenomedullin, HIF1A, IL-8, SRX1, AMPK alpha subunit, Pin1, NIK(MAP3K14), Glutaredoxin 1, p300, NFKBIA, HSPA1A, GSTP1, TIR1, ELAVL1 (HuR), HSFL1, PKC-beta, PRKD1, Sirtuin1, GPK1, PKC, LKB1, PTEN, MEKK1(MAP3K1), HES1, IKK-beta, DCL1 (Dynein LC8a), NOXA, Cyclin D1, HIF-prolyl hydroxylase, HDAC1, SAE2, SP1, p53, NRF2, ADAM17, p38 MAPK, APEX, PAI1, mTOR, NALP3 |
| 3 | Development_Negative regulation of WNT/Beta-catenin signaling in the cytoplasm | 6.919E-14 | Casein kinase I delta, NOTCH1 receptor, CXXC4, NKD1, P1P1-cat, RIPK4, APC protein, Alpha-1 catenin, Casein kinase I epsilon, Beta-catenin, CYLD, CXXC5, Nur77, Caspase (microtubules), Importin (karyopherin)-beta, Nox1, Casein kinase I alpha, WW1P1, STK4, SIAH1, Itch, GSK3 beta, G-protein beta/gamma, WDR26, Spk2/TrCP/FBXW, TAZ, Axin, KCTD1, RACK1, KLHL12, E-cadherin, HECTD1, Prickle-1, HIPK2, STK3, Tc(Lef), HUWE1, Amel1, beta-TrCP, P2PA catalytic, PR72, SENP2, A20, Cul1/Rbx1 E3 ligase, YAPI/TAZ, MAP1LC3A, CDK6, ELAVL1 (HuR), PEG3, WNT5A, PKC-alpha, Porf-b, WNT, Beclin 1, NEDD4L, Cyclin D1, p53, NIKD2, DACT3, Frizzled, Siah1/SIP/Ebi3 E3 ligase, DACT1 |
| 4 | Neurophysiological process_Dynein-dynactin motor complex in axonal transport in neurons | 8.348E-13 | NudE, ERK1/2, DCTN1(p150Glued), Importin (karyopherin)-alpha, HDAC6, APP, DYNCL11, Vimentin, Ubiquitin, Har-1, TMEM108, Centractins, DYNLT, ORP1, Dynin 1, cytoplasmic, heavy chain, Tctex-1, Alpha-centractin, MAPRE3(E3B), DYNLT1, HAP40, PRNPR, ACT(PKB), Snapin, PAFAH alpha (LIS1), MAPREPE1(EB1), DY2B, Tubulin (in microtubules), Importin (karyopherin)-beta, Dynin 1, cytoplasmic, light chains, Trck, Sortilin, BAG1, TrkB, JASAP1, NGF, RILP (Rab interacting lysosomal protein), Kinesin heavy chain, Bassoon, Kinesin light chain, Carboxytepsidase H, Dynin 1, cytoplasmic, intermediate chains, BDNF, NUDEL, SPTBN2 |
| 5 | G protein-coupled receptors signaling in lung cancer | 1.444E-12 | SSTR2, c-Fos, CD44, ERK1/2, PGE2R1, HB-EGF, VEGF-A, PKA-reg (cAMP-dependent), BDKRB2, Galanin, G-protein alpha-q/11, CCL5, I-6, GRP-R, CaMK II, Amphiregulin, CRN1, IKK-alpha, GALR2, NTS1, MMP-2, Bcl-XL, G-protein beta/gamma, Galphai(s)-specific peptide GPCRs, VIP, TGF-alpha, Galphai(s)-specific cannabis GPCRs, Akt(PKB), PDK (D1PDGFR), c-Src, SDF-1, CXCR4, RhoA, PDK4, PRKCI, PKG2, PRG2, G-protein alpha-12 family, IL-8, G-protein alpha-12, EGR2, G-protein alpha family, Galphai(s)-specific peptide GPCRs, PGR2B3, HB-EGF(mature), SSTR3, STAT3, EDNRB, Calmodulin, GRP(1-27), NT, VIP receptor 1, Cyclin D1, VIP receptor 2, SSTR5, ADAM17, PKA-cat (cAMP-dependent), EDNR |
| 6 | Transcription_Negative regulation of HIF1A function | 2.066E-12 | FHL3, p14ARF, Casein gene I delta, Sirtuin3, MCM5, RUNX3, COMMD1 (MURR1), FBXW7, SART1, KLF2, VCP, Sirtuin6, SKP1, UBXD7, Ubiquitin, ING4, GSK3 beta, EGLN2, MCM7, Elongin B, LAMPP2, EA2F, MDM2, MCM2, HSP90, Calpain 1(mu), HSP70, SAT2, EGLN1, RACK1, PLK3 (CNK), HSC70, PRDX2, CITED2, HIF1A, MTG16 (CBFA2T3), ARD1, PSA7, Sirtuin2, HSP90 beta, Cul1/Rbx1 E3 ligase, AML1 (RUNX1), Sirtuin1, HIF3A, PTEN, SSAT, Elongin C, HIF-prolyl hydroxylase, PRDX4, CHIP, p53, CITED4 |
| 7 | Chemotaxis_Lysophosphatidic acid signaling via GPCRs | 4.803E-12 | LPAR3, c-Fos, H-Ras, LARG, ROCK1, ERK1/2, PRK1, HB-EGF, Beta-catenin, EGR1, HDAC7, G-protein alpha-q/11, p21, PKC-epsilon, TRIP6, IP3 receptor, LPAR2, PLK1 reg class IA (p85), Bax, GS1K3 beta, PLC-beta, FKHR, PLEKHH2, DAI1, HAS2, Caspase-3, Cyrl6, CREB1, Bcl-XL, MEK1/2, G-protein beta/gamma, CDC42, Actin cytoskeletal, N-CoR, TAZ, MSK1, AKT(PKB), PDK (DPPK1), c-Src, RhoA, Tiam1, E-cadherin, cPKC (conventional), G-protein alpha-12 family, PLC-eta 1, PKC-delta, Tcf(Lef), IL-8, EGR2, G-protein alpha family, F-Actin cytoskeleton, MLK1, p120RasGAP, Caspase-3, LIMK, PLD2, CD36, G-protein gamma 12, MEK4(MAP2K4), 4E-BP1, p130CAS, ROCK, PRK1D1, FAK, PDZ-RhoGEF, PKC, Vinculin, ATP-2, PLC-delta 1, Bcl-2, FasR(CD95), SIVA1, Rhomammase, MLK1, CTGF, p53, PLC-beta3, ADAM17, p38 MAPK, Elk-1, mTOR, PREX1 |
Development, Positive regulation of WNT/Beta-catenin signaling in the cytoplasm

8.794E-12

| Gene/Interaction | Score |
|------------------|-------|
| Casein kinase II, alpha chains, TBL1X, Bcl-9, BIG1, IRS-2, NKD1, IRS-1, UBE2B, PPI1-cat, RIPK4, APC protein, Alpha-1 catenin, 14-3-3, Beta-catenin, TGIF, SMAD4, Makorin-1, Dsh, USP47, ZBED3, CDK1 (p34), PPP2R2A, SIAH1, USP25, PR130, Insulin receptor, GSK3alpha/beta, IGFr-1 receptor, ERK2 (MAPK1), AKT (PKB), Axin, HECTD1, ITGB1, SIAH2, HIPK2, Tcf(Lef), 14-3-3 zeta/delta, TGT, HSP105, PKA-reg type II (cAMP-dependent), PP2A catalytic, Trabid, BR2, USP9X, WNT, Jouberin, PP2C alpha, SMAD3, Parathyroid hormone, NKD2, MITF, PKA-cat (cAMP-dependent), Fizzled, SET7, DACT1, IP10, ISG15, TCF7L2 (TCF4), RIG-G, ERK1/2, GCH1, Beta-catenin, Matriixin (MMP-7), PRMT1, ZNF145, SMAD4, PIAS1, Apo-2L(TNFSF10), p21, IFNAR1, VAV-1, STAT1, PL, scramblase 1, ULK1, IKK-epsilon, Ubiquitin, TAP1 (PSF1), MAPKAPK2, PKC-theta, IFN-alpha, ISG54, Axin2, p130, MSK1, RASD2, AKT (PKB), p27KIP1, FZD7, HIP-2, Lck, CD45, PKR, PKC-delta, MEK3(MAP2K3), IRAF, MEK4(MAP2K4), Ku80, MEKK1(MAP3K1), SP5, Filamin-B (TABP), FOXO3A, FasR(CD95), IRF7, Cyclin D1, HDAC1, SMAD3, p38 MAPK, mTOR |

1.507E-11

| Gene/Interaction | Score |
|------------------|-------|
| IP10, ISG15, TCF7L2 (TCF4), RIG-G, ERK1/2, GCH1, Beta-catenin, Matriixin (MMP-7), PRMT1, ZNF145, SMAD4, PIAS1, Apo-2L(TNFSF10), p21, IFNAR1, VAV-1, STAT1, PL, scramblase 1, ULK1, IKK-epsilon, Ubiquitin, TAP1 (PSF1), MAPKAPK2, PKC-theta, IFN-alpha, ISG54, Axin2, p130, MSK1, RASD2, AKT (PKB), p27KIP1, FZD7, HIP-2, Lck, CD45, PKR, PKC-delta, MEK3(MAP2K3), IRAF, MEK4(MAP2K4), Ku80, MEKK1(MAP3K1), SP5, Filamin-B (TABP), FOXO3A, FasR(CD95), IRF7, Cyclin D1, HDAC1, SMAD3, p38 MAPK, mTOR, CLEC12A, Fc epsilon RI gamma, MSR1, Endoplasmin, gp91-phox, FCGR3A, Rac2, CLEC4C, VCP, TAP, Rab-3C, VAV-1, p47-phox, Syk, Rab-6, IP-30, Adipophilin, HOYU1, IRAF, MyD88, C1q, CALCA, Calreticulin, HMC class I, HSP60, TLR9, HSP90, Syntaxin 4, HSP70, RabBb, LRP1, EHD1, Cathepsin L, Dectin-1, Rab-4Aa, SEC61 complex, FCGR7, LIR1, Cytochrome b-558, CLEC9A, HSP105, Rab-32, Fe gamma RII alpha, Rab-35, RanBP2, Rab-33A, Cathepsin B, HSPA1A, SEC22B, Fe gamma RI, DAP12, CD47, Rab-11A, CD8, UFO, Rab-10, OLR1, IKK-beta, TLR7, CD40(TNFRSF5), Rab-5B, TRIF (TICAM1), CHIP, SNAP-23, Rab-34, TLR2 |

8.917E-11

| Gene/Interaction | Score |
|------------------|-------|
| GAB1, CD44, ERK1/2, Beta-catenin, EGR1, Fibronectin, PI3K reg class IA (p85), GSK3 beta, N-Ras, Bcl-XL, TWIST1 (PKB), alpha-MSH, MClr, HGF, MEK1(MAP2K1), N-cadherin, E-cadherin, PI3K cat class IA, Desmoglein 1, HIF1A, C/EBPbeta, RXRA, PKC-beta2, PKC-alpha, ATF-2, SLUG, Cyclin D1, Plakoglobin, HGF receptor (Met), p38 MAPK, Elk-1, MITF |

2.580E-11

| Gene/Interaction | Score |
|------------------|-------|
| MHC class II, IL-1 alpha, Calcinurine A (catalytic), ICAM1, CD44, D288, MSK1/2 (RPS6KA5/4), HDAC7, IP3 receptor, I-kB, PI3K reg class IA (p85), PKC-theta, MyD88, Ikk-alpha, PLC-gamma 1, NR2, ITK, Caspase-3, IL-1RI, CREB1, G-protein beta/gamma, CD83, NF-kb, AKT (PKB), HSP70, SDF-1, CXCR4, RhoA, Pyk2(FAK2), CD80, PI3K cat class IA, Lck, CD45, Sip76, HIP1, MEK3(MAP2K3), PSMC2, MEF2, NIK(MAP3K14), LAT, NR2A, RhoGDI alpha, MEK4(MAP2K4), ROCK, Calmodulin, PKC-alpha, CD3, Ikk-beta, PI3R1, PSD-95, IRAK1/2, CD40(TNFRSF5), Calcinurine B (regulatory), p38 MAPK, TLR2, SPHK1, NEFL, c-Fos, Fra-1, H-Ras, ERK1/2, MEF2C, HB-EGF, EGR1, PI3P regulator, SGK1, PKA-reg (cAMP-dependent), FRS2, p21, VGF, PKC-epsilon, Ehrin-A receptor 2, IP3 receptor, TTYH1, MAPKAPK2, PLC-gamma 1, CalDAG-GEFII, N-Ras, SNX26 (TCGAP), MAP2K5 (MEK5), KIDINS220, CREB1, MEK1/2, PLAUR (uPAR), Flotillin-1, N-Ras, MSK1, RGS2, p107, Stromelysin-1, c-Src, GAB2, Squeostesome 1p162, SHPS-1, MATK, Efs/Sin, RIN, NF-kb1 (p50), K-RAS, PKC-delta, MEK3(MAP2K3), SOS, PI3 catalytic, C3G, SH2B, p90Rsk, p130CAS, NFG, Calmodulin, MAGI-2, SHP-2, SUR-8, Cyclin D1, SORBS1, SP1, PVR, JUND3, SHB, RIT, p38 MAPK, Elk-1, PKA-cat (cAMP-dependent), FosB |

9.062E-11

| Gene/Interaction | Score |
|------------------|-------|
| CHDI_Correlations, Replication data, Causal network (positive correlations) |

9.356E-11

| Gene/Interaction | Score |
|------------------|-------|
| Neurogenesis, NGF/TrkA MAPK-mediated signaling |

1.033E-10

| Gene/Interaction | Score |
|------------------|-------|
| Role of tumor-infiltrating B cells in anti-tumor immunity |

1.105E-10

| Gene/Interaction | Score |
|------------------|-------|
| IL-6 signaling in breast cancer cells |