Research Paper

Prognostic and immune infiltration signatures of proteasome 26S subunit, non-ATPase (PSMD) family genes in breast cancer patients

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ABSTRACT

The complexity of breast cancer includes many interacting biological processes that make it difficult to find appropriate therapeutic treatments. Therefore, identifying potential diagnostic and prognostic biomarkers is urgently needed. Previous studies demonstrated that 26S proteasome delta subunit, non-ATPase (PSMD) family members significantly contribute to the degradation of damaged, misfolded, abnormal, and foreign proteins. However, transcriptional expressions of PSMD family genes in breast cancer still remain largely unexplored. Consequently, we used a holistic bioinformatics approach to explore PSMD genes involved in breast cancer patients by integrating several high-throughput databases, including The Cancer Genome Atlas (TCGA), cBioPortal, Oncomine, and Kaplan-Meier plotter. These data demonstrated that PSMD1, PSMD2, PSMD3, PSMD7, PSMD10, PSMD12, and PSMD14 were expressed at significantly higher levels in breast cancer tissue compared to normal tissues. Notably, the increased expressions of PSMD family genes were correlated with poor prognoses of breast cancer patients, which suggests their roles in tumorigenesis. Meanwhile, network and pathway

analyses also indicated that PSMD family genes were positively correlated with ubiquinone metabolism, immune system, and cell-cycle regulatory pathways. Collectively, this study revealed that PSMD family members are potential prognostic biomarkers for breast cancer progression and possible promising clinical therapeutic targets.

INTRODUCTION

According to statistical data of cancer incidence and mortality, breast cancer (BRCA) accounts for 30% of newly diagnosed cases of cancer among American women [1, 2]. The currently used stratification system is still undergoing changes due to the heterogeneity of this disease, which can be observed at both the molecular and histological levels. Based on the presence or absence of prevalent listed biomarkers, including: the estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER)-2, and some other markers. Stratifying BRCA not only helps in selecting treatment options but also assists in approximating treatment responses and predicting prognostic statuses.

Many different treatment strategies besides surgery are available for patients with BRCA. Treatment options are personalized and often based on a multi-modality approach, depending on several factors, including the stage and biology of the tumor (hormone receptor and nodal status); genomic markers (Oncotype DX™ or MammaPrint™) [3, 4]; patient age, physical condition, menopausal status, and the presence of inherited genetic mutations (such as BRCA1 or BRCA2); and a patient's acceptance and tolerance of treatment regimens. Some treatments are standard, such as surgical therapy, radiotherapy, systemic therapy (endocrine therapy, chemotherapy, and targeted therapy), and immuno-therapy, while others are undergoing clinical trials. As one of the potential approaches, targeted therapies are selective inhibitors which only affect altered cancer cells [5, 6]. They precisely identify and attack specific molecules to block cancer growth, progression, and metastasis. Most targeted therapies are either monoclonal antibodies (mAbs) or small-molecule drugs (tyrosine kinase inhibitors, cyclin-dependent kinase inhibitors, poly (ADP-ribose) polymerase (PARP) inhibitors) and mammalian target of rapamycin (mTOR) inhibitors [7–9]. Nevertheless, drugs resistance which may develop soon after onset of this therapy is the main challenge to current research. Meanwhile, immunotherapeutic strategies, which are drugs designed to strengthen the body's natural defenses to fight cancer, have appreciably raised our expectations of successfully treating various cancer types [10–15]. In general, immunotherapies are further categorized into various subtypes, such as mAbs, immune checkpoint blockade (anti-cytotoxic T-lymphocyte-associated (CTLA)-4, anti-programmed death (PD)-1, anti-PD-ligand 1 (L1)), cytokine therapy, T-cell transfer therapy (including tumor-infiltrating lymphocytes (or TIL) therapy and chimeric antigen receptor (CAR) T Cell Therapy), and therapeutic vaccines. For instance, the immune checkpoint inhibitors that target the PD-1 pathway (pembrolizumab, atezolizumab, dostarlimab) are approved by the US Food and Drug Administration (FDA) for patients with metastatic TNBC [16–21]. According to recent literature, the abovementioned treatments for early BRCA determined by sub-classification have significantly improved the prognosis of BRCA patients with a 5-year survival rate of more than 85%. Therefore, it is crucial for us to understand the occurrence and development of breast cancer and to find biomarkers that indicates the sensitivity of current therapies and long-term outcomes in the early stage of the disease [22–28].

The ubiquitin-proteasome system is an indispensable mechanism of highly regulated intracellular protein degradation and turn over, thus dominates human antigen processing, signal transduction and cell-cycle regulation. The 26S proteasome is composed of one proteolytically active cylinder-shaped particle (the 20S proteasome), and one or two ATPase-containing complexes (known as the 19S cap complexes). The 20S core is constructed from inner α-rings and outer β-rings, which are both divided into 7 structurally similar subunits: proteasome 20S subunit α (PSMA1~7) and β (PSMB1~7), respectively. The 19S cap complexes is composed of a base and a lid subcomplex, further categorized into ATPase subunits (PSMC1~6) and non-ATPase subunits (PSMD1~14) [29–33]. In recent studies, dysfunction of the ubiquitin-proteasome system, which manifests as up- and/or downregulation of the aforementioned genes, has been described in various oncogenic situations. Hence, extensive research need to be conducted to fully assess the oncogenic potential of this family genes.

The PSMD family, which is comprised of 14 members in total, was proven to be partially involved in the formation of the regulatory complex. Both components occupy an important place in modulating the proteasome that performs several essential functions, such as catalyzing the unfolding and translocation of substrates into the 20S proteasome. Recent studies showed that *PSMD1* and

PSMD3 act as oncogenes in chronic myeloid leukemia by stabilizing nuclear factor (NF)-κB [34]. In gastric cancer, interactions between PSMD2 and asporin induced cell proliferation [35]. PSMD4 influenced cell malignancy of esophageal cancer via suppressing endoplasmic reticular (ER) stress [36]. PSMD5 inactivation promoted 26S proteasome assembly during colorectal tumor progression [37]. PSMD6, PSMD9, PSMD11, and PSMD14 expressions were significantly related to decreased survival chances in pancreatic ductal adenocarcinoma [38]. High-throughput technologies are widely used as systematic approaches to explore differences in expressions of thousands of genes in both biological and genomics systems [39–41]. Abnormal gene expressions are generally related to oncogenes and tumor-suppressor genes which regulate tumor maturation [42–47].

However, no studies have yet been conducted to develop data of how messenger (m)RNA levels of each *PSMD* family gene change in BRCA development. Therefore, this study aimed to make relevant comparisons of gene expressions in BRCA and normal tissues, by extracting information from public datasets, including numerous RNA-sequencing (RNA-Seq) and microarrays data of BRCA patients.

Moreover, we also explored the interactive cooperation or gene regulatory networks in which the targeted family genes were involved to identify completely novel biomarkers [48–53]. By adopting a meta-analytical approach, downstream molecules associated with *PSMD* genes were effectively screened. The study findings revealed that these PSMD family members and their regulated gene counterparts are worth considering as novel therapeutic targets for BRCA patients.

RESULTS

PSMD family members are involved in important processes in the developmental stages of BRCA

Prior studies discovered PSMD family members in human and significant roles in cancer progression of some of them. To provide further identification of *PSMD* family gene signatures related to breast neoplasms, a meta-analysis was carried out. As reported by an Oncomine analysis of mRNA expressions among PSMD family members, including PSMD1, PSMD2, PSMD3, PSMD5, PSMD10, PSMD12, and PSMD14 are highly upregulated in BRCA tissues. It was suggested that their overexpression promotes tumor growth. Therefore, we decided to perform further bioinformatics analyses on BRCA (Figure 1). Since the Kaplan-Meier curves are univariate analysis, the univariate and multivariate Cox proportional hazards regression analysis, which works for both quantitative predictor variables and for categorical variables, was subsequently verified by TCGA-based breast cancer samples. Results was presented in Supplementary Table 1.

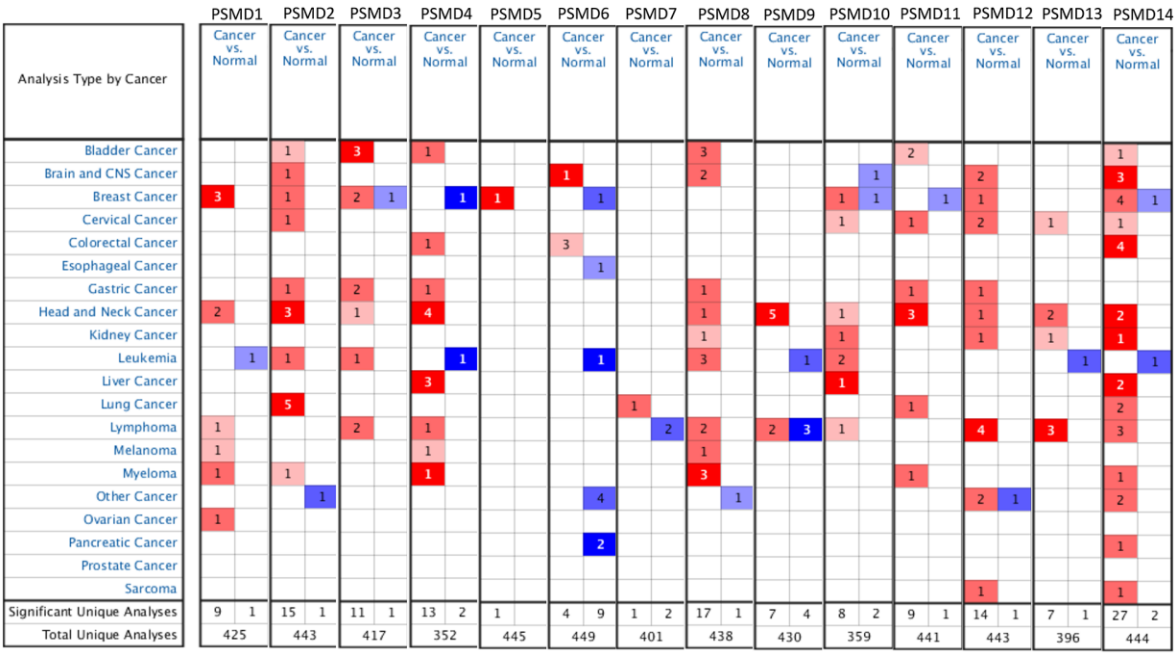

Figure 1. Systemic analysis of 26S proteasome delta subunit, non-ATPase (*PSMD*) family genes in 20 common types of cancer (Oncomine platform). Dysregulation of each *PSMD* individual gene in targeted cancer tissues as measured by the mRNA expression level

was compared to their normal counterparts using Students' *t*-test. The cutoff parameters were set as follows: $p<0.05$; multiple of change >2; and gene rank in the top 10%. The quantity of datasets which met those thresholds was represented as a number inside the table cells, while colors (red or blue) indicate the trend of gene expressions (up- or downregulation, respectively) and the intensity of colors indicates the degree of abnormal expression.

Associations of *PSMD* family gene interpretations in neoplastic cell lines with clinicopathological parameters of BRCA patients

After properly examining differences in *PSMD* family gene expressions between neoplastic and normal tissues using GEPIA2 datasets, we found that all mRNA levels of the former were upregulated compared to the latter, with the *q*-value cutoff set to <<0.001 (Figure 2). In addition, analysis performed on a Cancer Cell Line Encyclopedia (CCLE) dataset (https://www.broadinstitute.org/ccle) also indicated that PSMD mRNA levels were overexpressed in BRCA tissues (Figure 3).

Analysis of genes related to BRCA co-expressed with *PSMD* family genes

By leveraging the Oncomine online platform to perform a thorough analysis of the co-expression network of

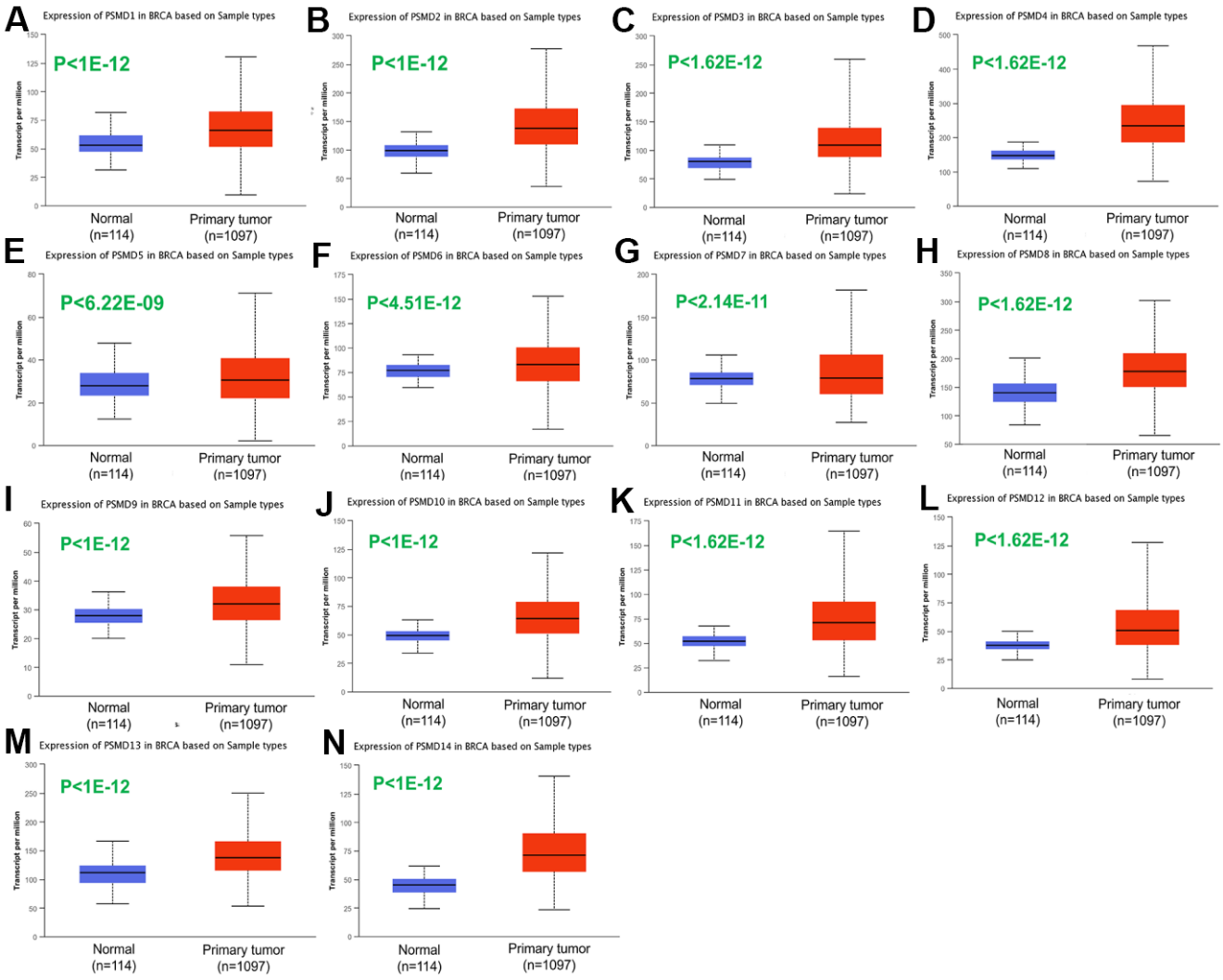

Figure 2. Transcriptional expression of 26S proteasome delta subunit, non-ATPase (PSMD) family members in breast cancer (BRCA) patients. (**A**–**N**) Transcriptome alterations observed in PSMD1~14. Boxplot of PSMD mRNA expression levels measured in BRCA specimens (red) compared to their normal counterparts (blue) obtained from the UALCAN database. Statistical analysis was performed using Student's *t*-test, and p<0.05 was considered statistically significant.

PSMD1, we found that *PSMD1* was positively correlated with *AGFG1*, *GPR107*, *PTH2R*, *TFPI*, *GUCY1A3*, *SLCO2Al*, *EIF5B*, *PAQR3*, and *ROD1*. As for genes which are supposedly co-expressed with *PSMD2*, we concluded that its expression was positively correlated with *EIF2S2*, *NUPL2*, *GLRX3*, *LSM5*, *CBX3*, *PAKIIP1*, *CCT6A*, *MRPS17*, *CHCHD2*, *PSMA2*, *SEC61G*, *NUDT1*, *POLD2*, *FSTL1*, *EIF3B*, *CYCS*, and *AIMP2*. As for genes co-expressed with *PSMD3*, there were positive correlations with *CASC3*, *MED24*, *MSL1*, *THRA*, *RAPGEFL1*, *RARA*, *WIPF2*, *SLC16A6*, *ACACA*, *PDESB*, *CST4*, *ABHD2*, *FRY*, and *POLG*. Similarly, genes co-expressed with *PSMD4* included *UBE2Q1*, *MRPL9*, *POGZ*, *SETDB1*, *P14KB*, *VPS72*, *SCNM1*, *P14KB*, *PRUNE*, *ADAR*, *APH1A*, *TDRKH*, *CLK2*, *PRPF3*, *UBAPZL*, and *DAP3*. Moreover, positive correlations with *PSMD5* were determined for *MEX3D*, *CATSPERB*, *SULT1E1*, *CEACAM7*, *CES1*, *MARCH6*, *GPD2*, *ATIC*, *GTF2H2*, *P4HAL*, *C2ORF54*, *GGCT*, *GUCY1A2*, *PPAP2B*, *MAP3K5*, *SMPDL3A*, and *SWAP70*. Similar to previous cases, *PSMD6* was found to be positively correlated with *GOLGA4*, *PDCD6IP*, *ARL8B*, *GHITM*, *NGLY1*, *OXSM*, *CYP51P2*, *CYP51A1*, *CLU*, *APOOL*, *MRS2*, *SLC25A46*, *RNF14*, *VDACIP3*, *CLINT1*, and *SEC24A*. We found that genes co-expressed with *PSMD7* included *NAE1*, *USP10*, *AP1G1*, *SETD6*, *NUP93*, *CBFB*, *BRD7*, *NFATC3*, *CNOTI*, *HNRNPD*, *CHMP1A*, *CFDP1*, *TAFIC*, *ZCCHC14*, *HSBP1*, *GOT2*, *CTCF*, *GPR56*, and *TMEM208*. Genes co-expressed with *PSMD8* included *PSMC4*, *MRPS12*, *EIF3K*, *EIF3K*, *RPS16*, *COX6B1*, *DGUOK*, *TPRKB*, *RNF7*, *COX7A2*, *METTL5*, *ATP5J*, *ATP50*, *TOR3A*, *SDHB*, *MBD2*, and *ATP5G3*. As for genes co-expressed with *PSMD9*, there were positive correlations with *ARPC3*, *GNS*, *POP5*, *WSB2*, *RFC5*, *NTAN1*, *EPB41L3*, *EPB41L3*, *GCA*, *HMGN3*, *ASNAI*, *ICAM3*, *RAB8A*, *UPF1*, *PPPICA*, *OTUBI*, *JARIDZ*, and *PGD*. Genes co-expressed with *PSMD10* included *UBEZN*, *C12orf29*, *TBC1D15*, *CCNT2*, *MAP4K3*, *MTX2*, *KDM6A*, *RNF13*, *C4orf43*, *UBE2K*, *PDS5A*, *CLIP1*, *CHD9*, *KIAA1033*, *PPPIR1ZA*, and *PPP1R12A*.

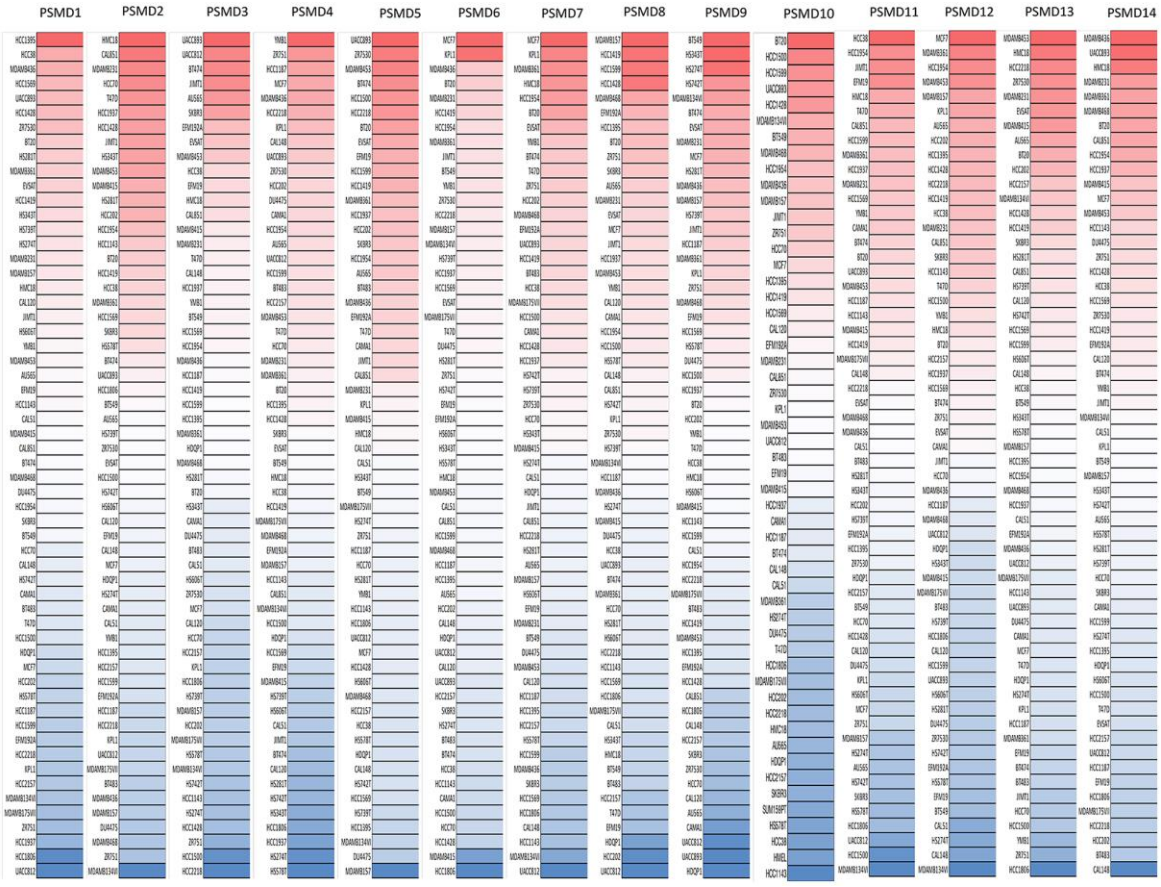

Figure 3. Expressions of 26S proteasome delta subunit, non-ATPase (*PSMD*) genes measured in common types of breast cancer (BRCA) cell lines. A CCLE database-built heatmap plot presents patterns of changes in expression levels of *PSMD* family genes among different BRCA cell lines. Shades of colors vary from red (overexpressed sample) to white (no change in gene expressions) and blue (under-expressed sample). The darker the colors are, the higher the gene expressions that were recorded.

Moreover, *PSMD11* was positively correlated with *SUMOZ*, *PSMD12*, *KPNA2*, *HN1*, *HSPH1*, *INTS8*, *LSM6*, *ANAPC10*, *ABCE1*, *ABCE1*, *SMARCA5*, *GRHL2*, *TUG1*, *EPB41L4B*, *RPRD1A*, and *HSPD1*. PSMD12 was found to be positively correlated with *HELZ*, *LOC220594*, *FASTKD3*, *PHB*, *CCDC47*, *TEX2*, *TEX14*, *RAD51C*, *BCAS3*, *SLC4A8*, *BPTF*, *AMZ2*, *NOL11*, *BPTF*, *SMARCD2*, *PSMC5*, *FTSJ3*, and *TACOI*. Genes co-expressed with *PSMD13* included *PSMC3*, *MRPL17*, *SPCS2*, *C7orf44*, *EWSR1*, *POLD3*, *ZNF84*, *ZNF140*, *ZNF268*, *NFYB*, *ZNF195*, *ANKLE2*, *GOLGA3*, *CHFR*, *NEK3*, *ELF1*, *ZC3H13*, *PHF11*, and *RCBTB1*. Finally, genes co-expressed with *PSMD14* were *ATP2C1*, *ATP2C1*, *HSPE1*, *PDE6D*, *CISD1*, *COQ2*, *ZMYND11*, *NUDT21*, *PKM2*, *HPS5*, *SLBP*, *EIF3J*, *ETF1*, *SMN1*, *GNAI3*, *MAPRE1*, *CLCC1*, *PSMA5*, *C2orf47*, and *NDUFS1* (Figure 4).

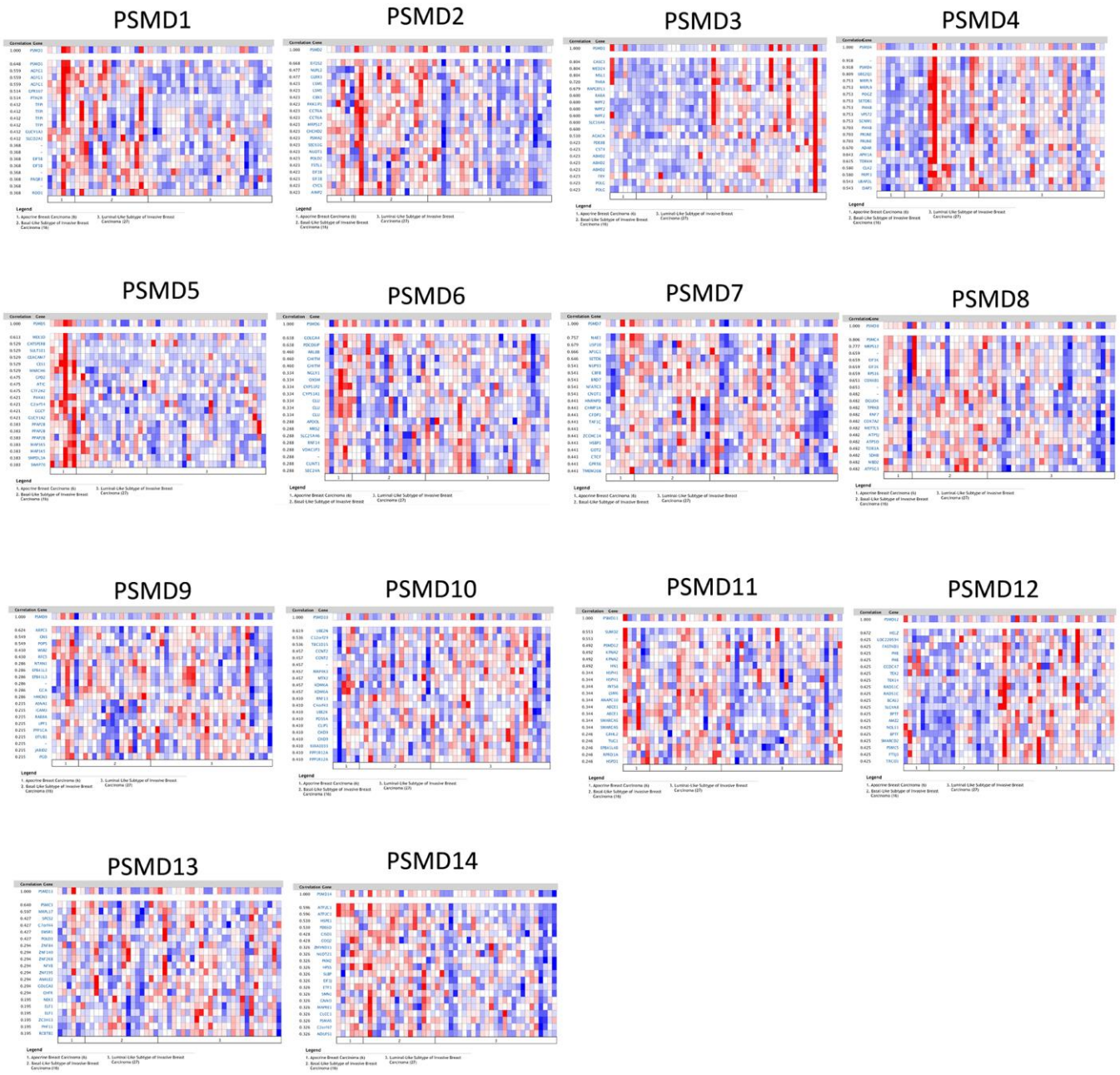

Figure 4. Heatmap co-expression profiles of 26S proteasome delta subunit, non -ATPase (PSMD) family members in breast cancer (BRCA). Genes co-expressed with each of the PSMD family members in term of BRCA patients are presented in a heatmap format (data extracted from the Oncomine database).

Relationships between disease prognostication and *PSMD* gene expression levels measured in tumor specimens

The Kaplan-Meier (KM) plotter database also indicated that most PSMD family members were associated with poor recurrence-free survival (RFS), except for PSMD9 and PSMD11. Higher expression levels of PSMD9 and PSMD11 were significantly associated with better survival rates of patients (Figure 5). We also validated these data from the NCBI GEO database (GSE21653) [54], and also obtained consistent data

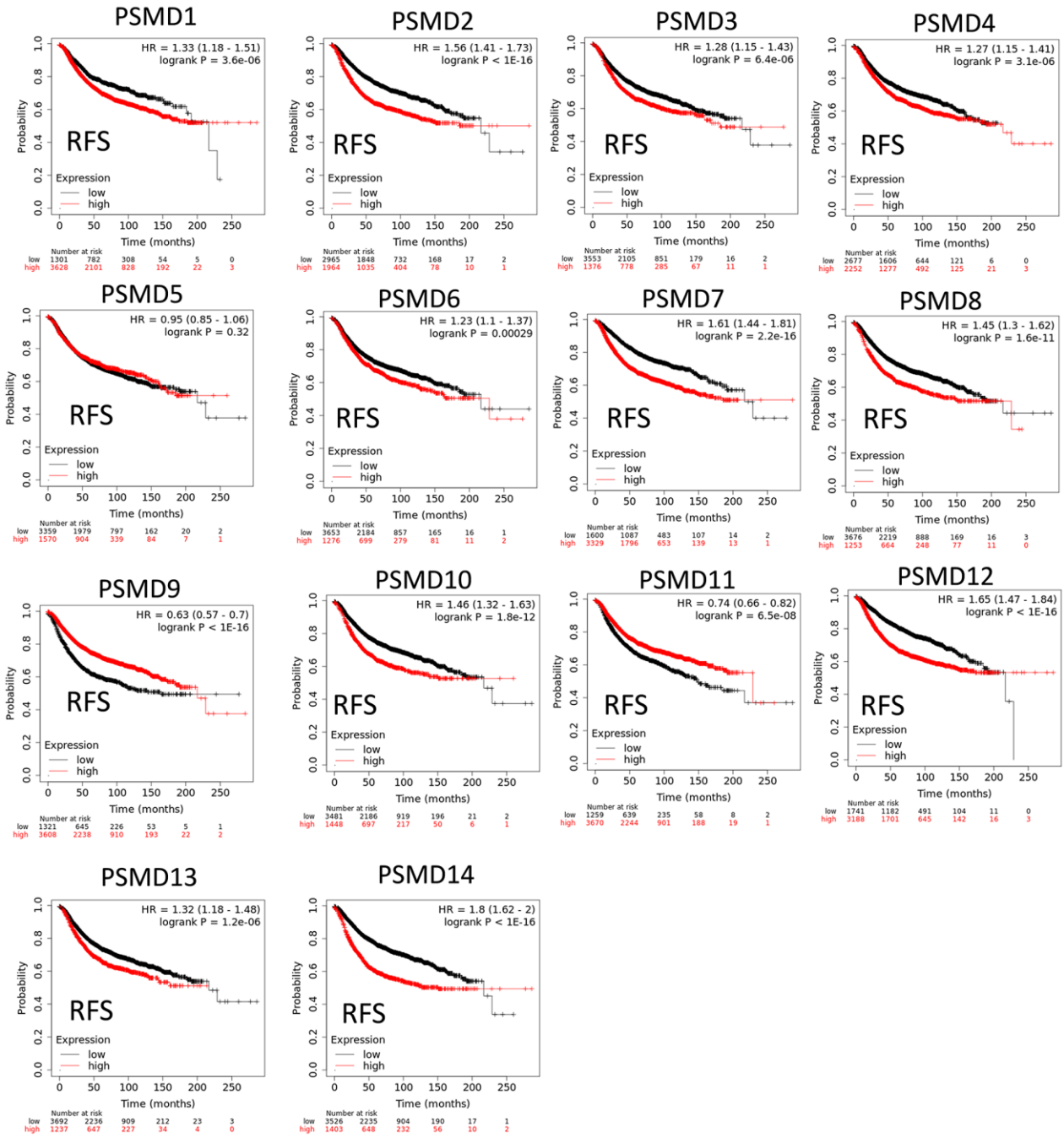

Figure 5. Significant correlations between mRNA levels of 26S proteasome delta subunit, non-ATPase (PSMD) family members and recurrence-free survival curve (RFS) of patients diagnosed with breast cancer (BRCA). The two survival curves respectively illustrate survival outcomes (including survival percentages and survival times) of BRCA patients with high (red) or low (black) expression levels of PSMD family members. Increased mRNA levels of target genes resulted in poor prognoses, while increasing levels of PSMD9 and PSMD11 were associated with favorable outcomes (p<0.05 was considered statistically significant).

(Supplementary Figure 1). In addition, high expression levels of PSMD1, PSMD2, PSMD3, PSMD7, PSMD10, PSMD12, and PSMD14 were linked with poor distant metastasis-free survival (DMFS), whereas others were not (Figure 6). The RFS and DMFS data implied that these genes have oncogenic roles in BRCA progression. Therefore, we chose PSMD1, PSMD2, PSMD3, PSMD7, PSMD10, PSMD12, and PSMD14 as objectives for further bioinformatics analyses. Due to the fact that samples from BRCA patients displayed distinctly different expressions of *PSMD* family genes, we continued to explore how these target genes participate in particular metabolic pathways prior to investigating their clinical relevance. Therefore, the intensities of antibodies represented in clinical BRCA specimens were extracted from the Human Protein Atlas (HPA) for further

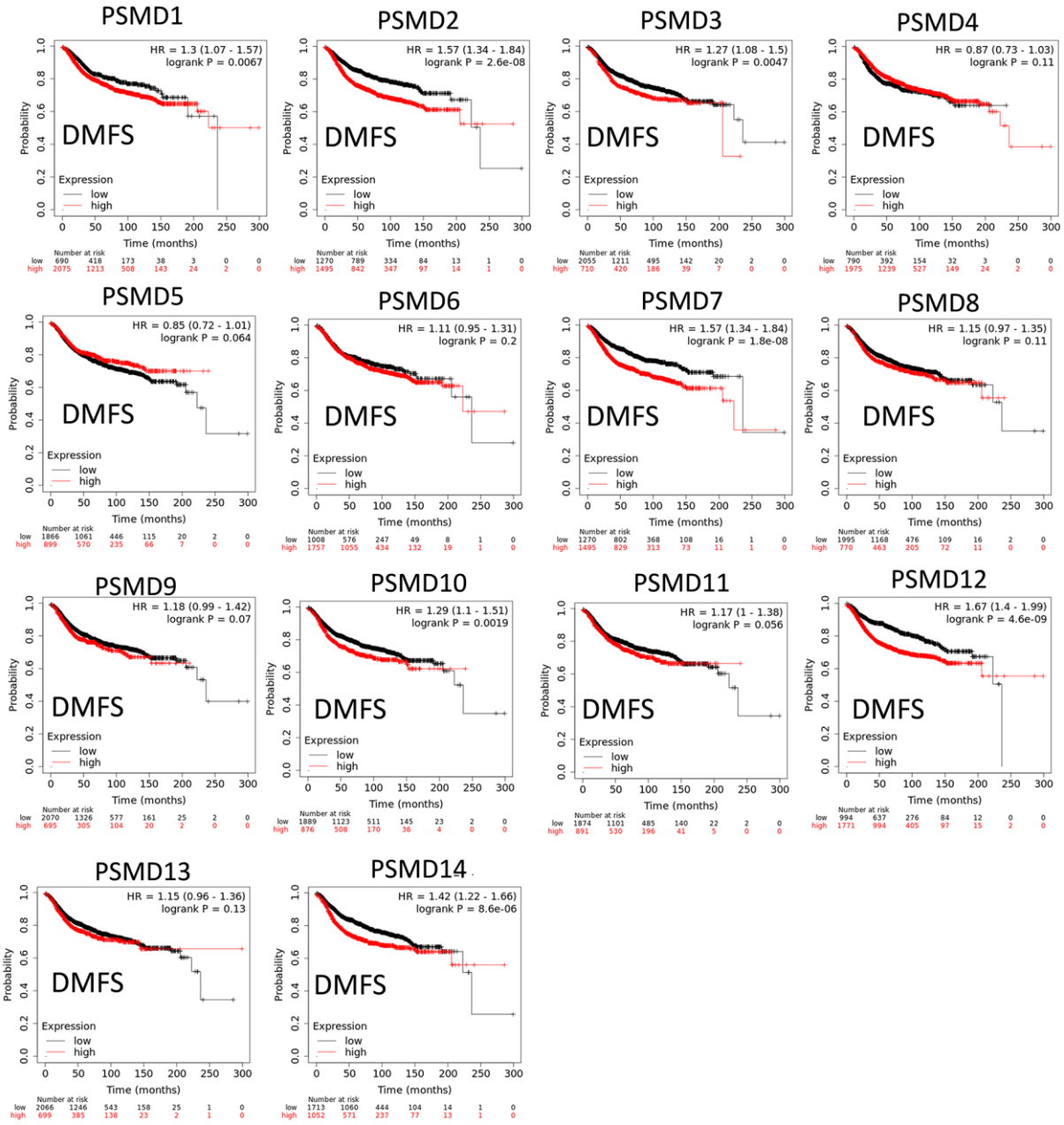

Figure 6. Significant correlations between mRNA levels of 26S proteasome delta subunit, non-ATPase (PSMD) family members, and distant metastasis-free survival (DMFS) curve of patients diagnosed with breast cancer (BRCA). The two survival curves respectively illustrate survival outcomes (including survival percentages and survival times) of BRCA patients with high (red) and low (black) expression levels of PSMD family members. Increased mRNA levels of target genes resulted in poor prognoses, except for PSMD4, PSMD5, PSMD6, PSMD8, PSMD9, PSMD11, and PSMD13 (p<0.05 was considered statistically significant).

analysis. Immunohistochemical (IHC) images revealed dense distributions of PSMD2 and PSMD4, while the other PSMDs, including PSMD1, PSMD2, PSMD3, PSMD7, PSMD12, and PSMD14, were moderately distributed in breast tumor samples (Figure 7).

In addition, when we performed the required analysis using the Tumor Immune Estimation Resource (TIMER) database (available at: http://timer.cistrome.org/), *PSMD* member genes also showed relevance to immune infiltration profiles of BRCA, and the expression of

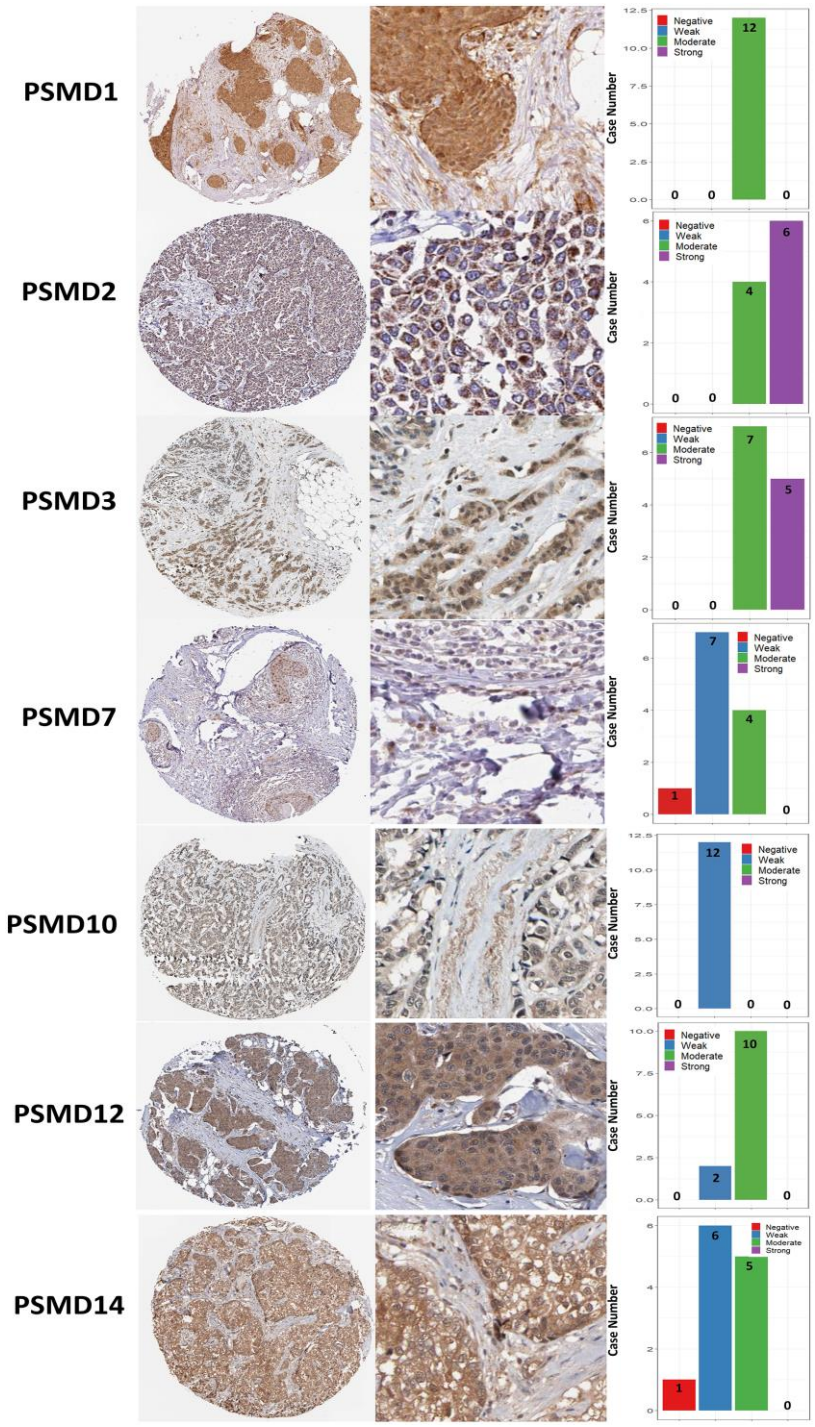

Figure 7. Immunohistochemical staining of 26S proteasome delta subunit, non-ATPase (PSMD) family members in normal tissues and breast cancer (BRCA) tissues represented in IHC staining images and bar chart. The images illustrate intensities of antibodies in both BRCA and adjacent normal tissues while the bar charts of IHC staining show intensities of PSMD family members in BRCA.

each individual was related to tumor purity and markers of six tumor-infiltrating immune cell types which belonged to two separate groups: a lymphoid lineage (B cells, cluster of differentiation 4-positive ($CD4^+$) T cells, and cluster of differentiation 8-positivie (CD8+) T cells) and myeloid lineage (neutrophils, macrophages, and dendritic cells) (Figure 8).

Pathway and network analysis of *PSMD* family genes

Since some potential information for refining the full picture of regulated pathways available to *PSMD* family genes is still missing, GeneGo Metacore software was launched to extensively explore downstream networks linked to the aforementioned co-expression patterns of

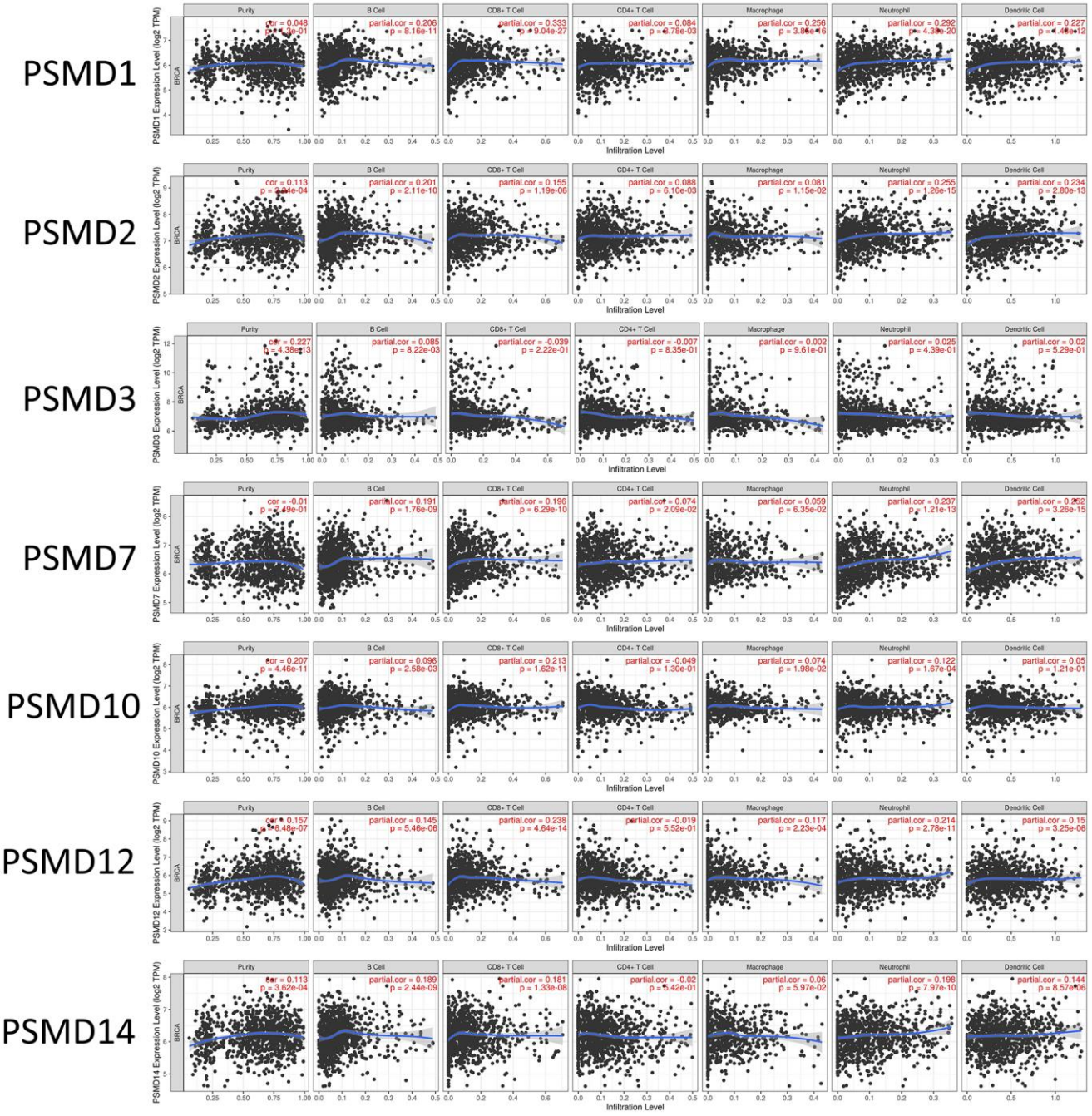

Figure 8. Correlations between expressions of 26S proteasome delta subunit, non-ATPase (PSMD) family members and immune infiltration profiles of breast cancer via the TIMER database. The figure shows correlations between each abnormally expressed gene of the *PSMD* family and levels of several tumor-infiltrating immune cell markers, such as B cells, cluster of differentiation 8-positive ($CD8^+$) T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells.

PSMD family genes. We obtained PSMD1 coexpression profiles of BRCA from available datasets from both METABRIC and TCGA. As a result, annotations of biological processes obtained from GeneGo Metacore showed that genes co-expressed with PSMD1 participated in several networks and cell cycle-related pathways such as "Cell cycle_Role of APC in cell cycle regulation", "Cell cycle_The metaphase checkpoint", "Cell cycle_Spindle assembly and chromosome separation", "DNA damage_Intra S-phase checkpoint", and "Cell cycle_Start of DNA replication in early S phase" (Figure 9 and Supplementary Table 2). PSMD2 was associated with "Cell cycle_Cell cycle (generic schema) Cell cycle_Start of DNA replication in early S phase", "Cell cycle_Chromosome condensation in prometaphase", "DNA damage_Intra S-phase checkpoint", "Cell cycle_Role of SCF complex in cell cycle regulation", and "Reproduction_Progesterone-mediated oocyte maturation" (Figure 10 and Supplementary Table 3). PSMD3 was involved in "Cell cycle_Role of Nek in cell cycle regulation", "Transcription_Negative regulation of HIF1A function", "DNA damage_Intra S-phase checkpoint", "DNA damage_ATM/ATR regulation of G2/M checkpoint: cytoplasmic signaling", "Cytoskeleton remodeling_Keratin filaments", and "Regulation of degradation of deltaF508-CFTR in CF" (Figure 11 and Supplementary Table 4). PSMD7 was involved in "Cell cycle_ESR1 regulation of G1/S transition", "The role of aberrations in CDKN2 locus and CDK4 in familial melanoma", "Putative role of estrogen receptor and androgen receptor signaling in the progression of lung cancer", "Signal transduction_Adenosine A3 receptor signaling pathway", and "Transport_RAN regulation pathway" (Figure 12 and Supplementary Table 5). PSMD10 was involved in "DNA damage_Nucleotide excision repair", "CFTR folding and maturation (normal and CF)", "Immune response_Antigen presentation by MHC class II", "Regulation of degradation of deltaF508-CFTR in CF", "Cell cycle_Role of SCF complex in cell cycle regulation", and "Immune response_BAFF-induced non-canonical NF-kB signaling" (Figure 13 and Supplementary Table 6). PSMD12 was involved in "DNA damage_ATM/ATR regulation of G_2/M checkpoint: nuclear signaling", "Cell cycle_Initiation of mitosis", "Cell cycle_ESR1 regulation of G_1/S transition", "Cell cycle_Nucleocytoplasmic transport of CDK/cyclins", and "Mitogenic action of estradiol/ESR1 (nuclear) in breast

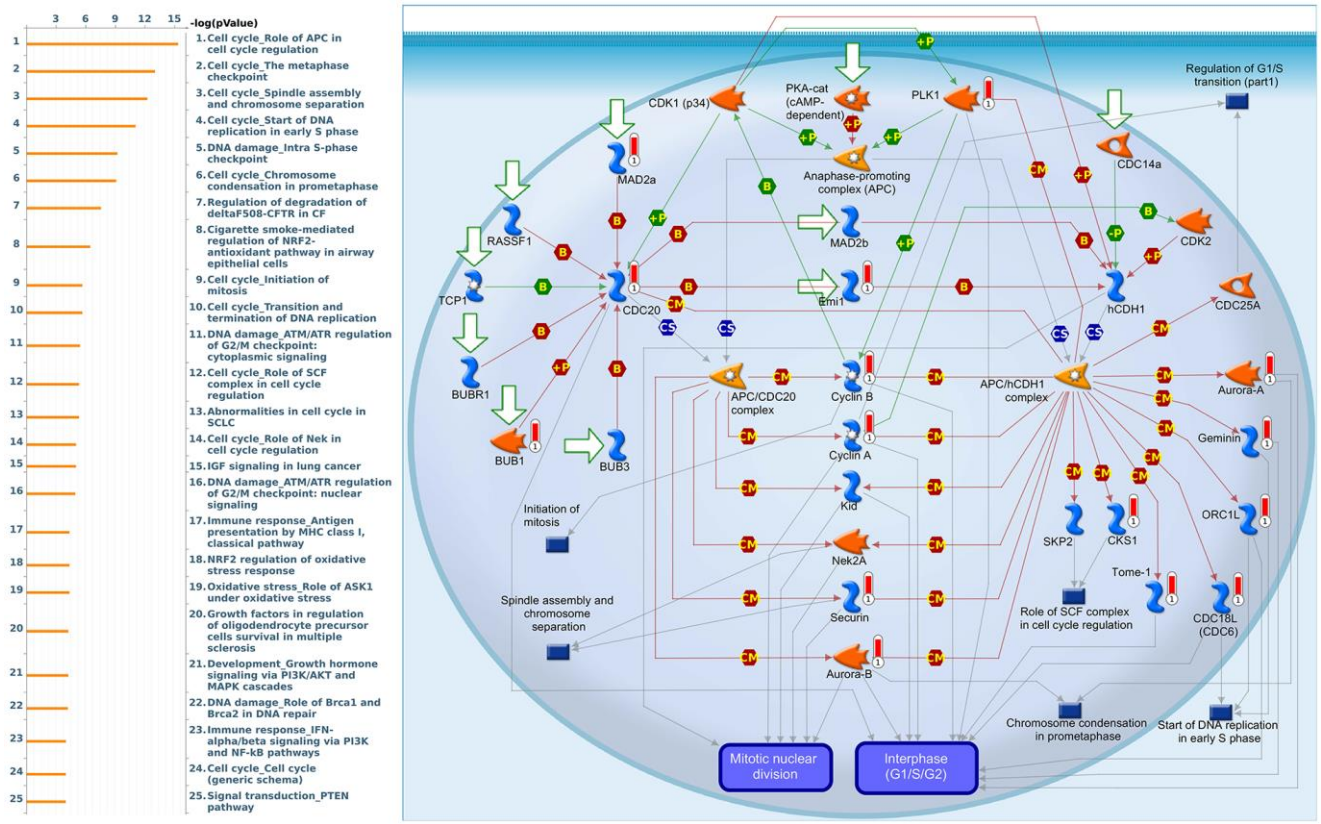

Figure 9. Cell cycle-related networks correlated with the 26S proteasome delta subunit, non-ATPase 1 (*PSMD1*) family gene in breast cancer (BRCA). MetaCore pathway analysis of biological processes revealed that pathways related to "Cell cycle_Role of APC in cell cycle regulation" were correlated with BRCA development.

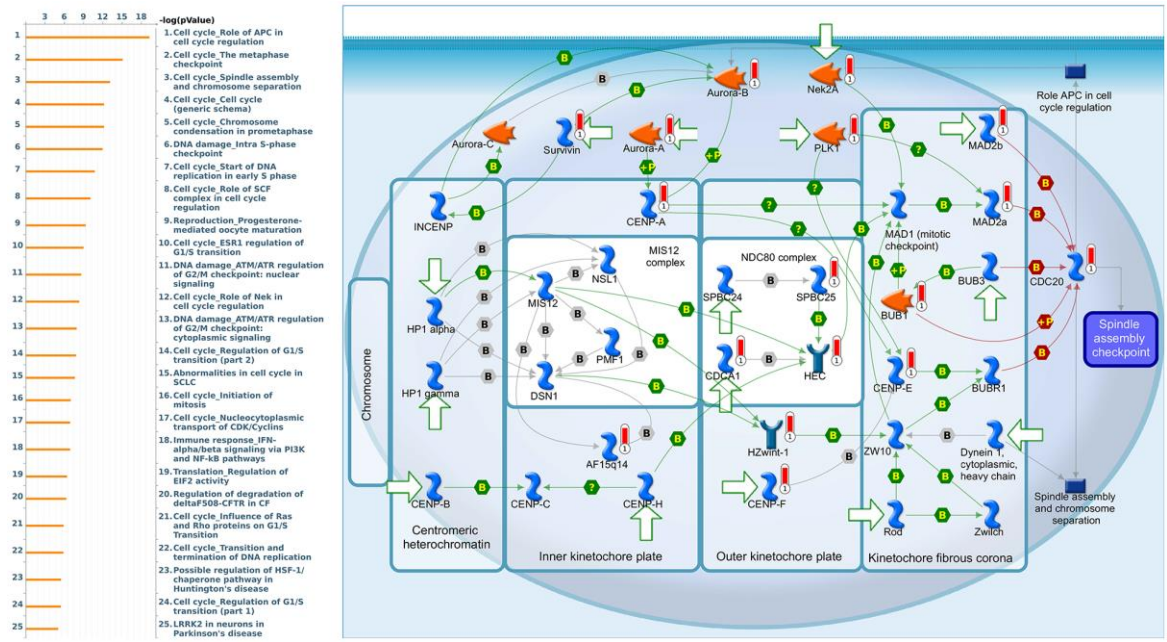

Figure 10. Cell cycle-related networks correlated with the 26S proteasome delta subunit, non-ATPase 2 (*PSMD2*) family gene in breast cancer (BRCA). MetaCore pathway analysis of biological processes revealed that pathways related to "Cell cycle_The metaphase checkpoint" were significantly associated with BRCA development.

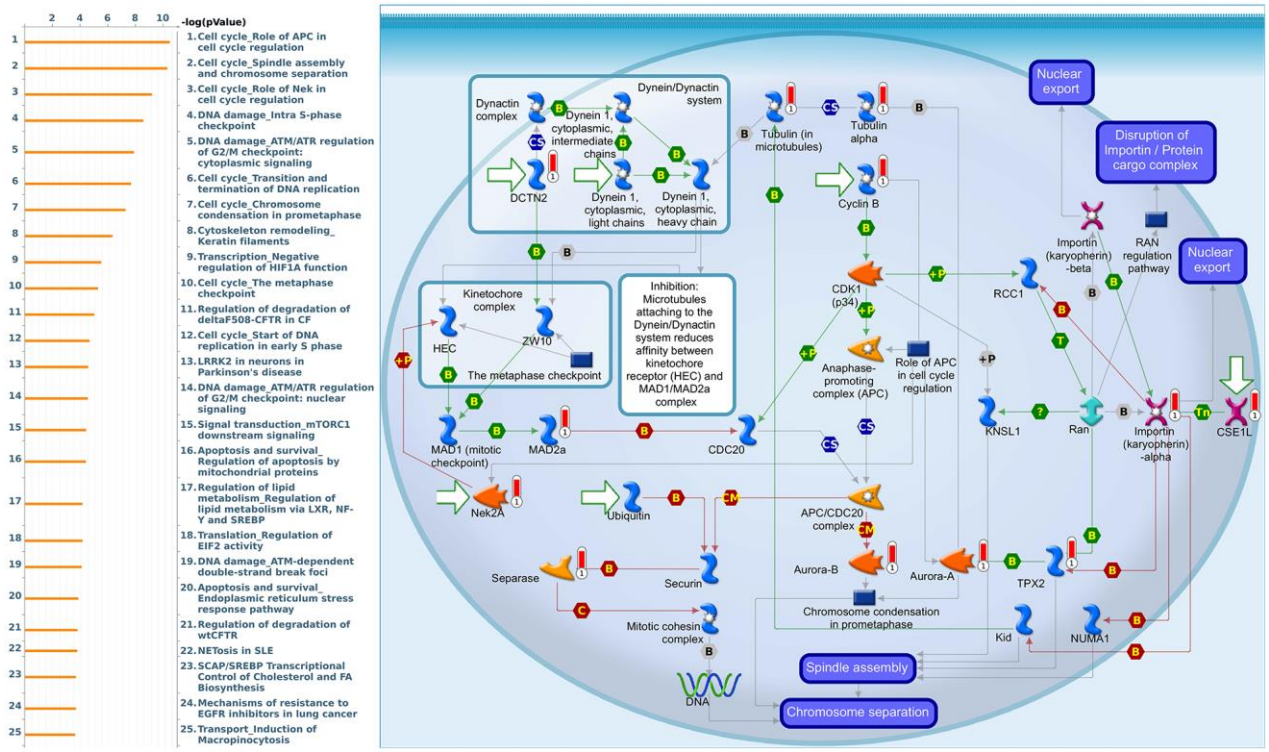

Figure 11. Cell cycle-related networks correlated with the 26S proteasome delta subunit, non-ATPase 3 (*PSMD3*) family gene in breast cancer (BRCA). MetaCore pathway analysis of biological processes revealed that pathways related to "Cell cycle_Spindle assembly and chromosome separation" were significantly associated with BRCA development.

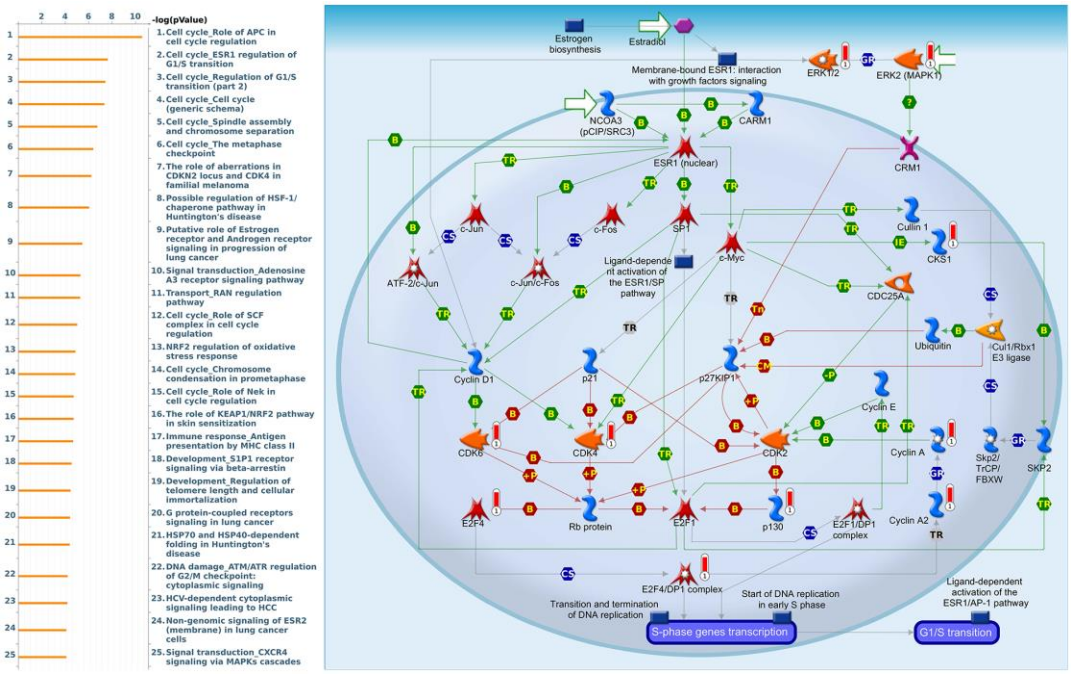

Figure 12. Cell cycle-related networks correlated with the 26S proteasome delta subunit, non-ATPase 7 (*PSMD7*) family gene in breast cancer (BRCA). MetaCore pathway analysis of biological processes revealed that pathways related to "Cell cycle_ESR1 regulation of G1S transition" were significantly associated with BRCA development.

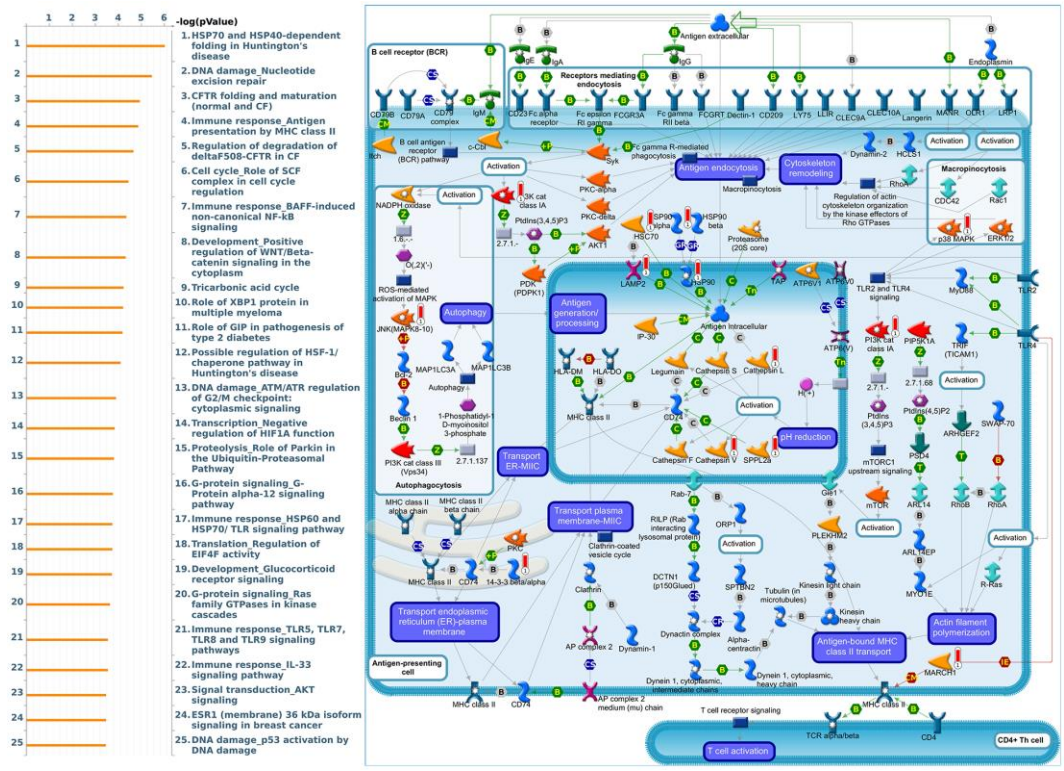

Figure 13. Cell cycle-related networks correlated with the 26S proteasome delta subunit, non-ATPase 10 (*PSMD10*) family gene in breast cancer (BRCA). MetaCore pathway analysis of biological processes revealed that pathways related to "Immune response_Antigen presentation by MHC class II" were significantly associated with BRCA development.

cancer" (Figure 14 and Supplementary Table 7). PSMD14 was involved in "Cell cycle_The metaphase checkpoint", "Regulation of degradation of deltaF508-CFTR in CF", "Cell cycle_Sister chromatid cohesion", "Oxidative stress_Role of ASK1 under oxidative stress", and "Transport_RAN regulation pathway" (Figure 15 and Supplementary Table 8). Meanwhile, we obtained similar results from the cBioPortal and the Cytoscape and METABRIC databases, which revealed that these PSMD members were correlated with metabolic pathways and the cancer development-related genes (Supplementary Figure 2).

DISCUSSION

Recent epidemiologic studies indicated that BRCA has been displaced lung cancer in term of the most frequently diagnosed cases among women globally. Despite some improvements having been made in medical and surgical treatments of BRCA, a shortage of detection methods for early screening or diagnosis, accompanied by high risks of metastasis, chemoresistance, endocrine-resistance, and recurrence has resulted in a top ranking in overall mortality for this disease, which still needs to be fully investigated. Therefore, identifying specific key molecular pathways and highly sensitive, reliable biomarkers is urgently needed [48–53]. In recent times, the rapid growth of microarray and high-throughput sequencing data has provided convenient and comprehensive online platforms to elucidate the pathogenesis of tumors, which has allowed us to properly monitor tumor progression and prognoses [22–26].

Based on the results of this study, it suggested that most of the PSMD family are generally dysregulated in hundreds of distinctive types of cancers. On the other hand, expression profiles indicated that this family's genes not only accompany tumor multi-stage progression but are also involved in other tumor-related issues. For instance, upregulation of the PSMD1 gene was mainly enriched alongside a rise in tamoxifen resistance displayed by BRCA cells [55]. The autophagic degradation of 19S proteasomal subunits of both PSMD1 and PSMD2 were mediated by ATG16 [56]. PSMD3 is believed to be involved in stabilizing HER2, a growth-promoting protein on the exterior of all breast cells, from degradation [57]. Upregulation of the PSMD4 gene by hypoxic conditions in prostate cancer cells suggests a novel therapy for treatment [58]. PSMD7 was significantly linked to earlier stimulation of prostate cancer [59]. PSMD10 overexpression was

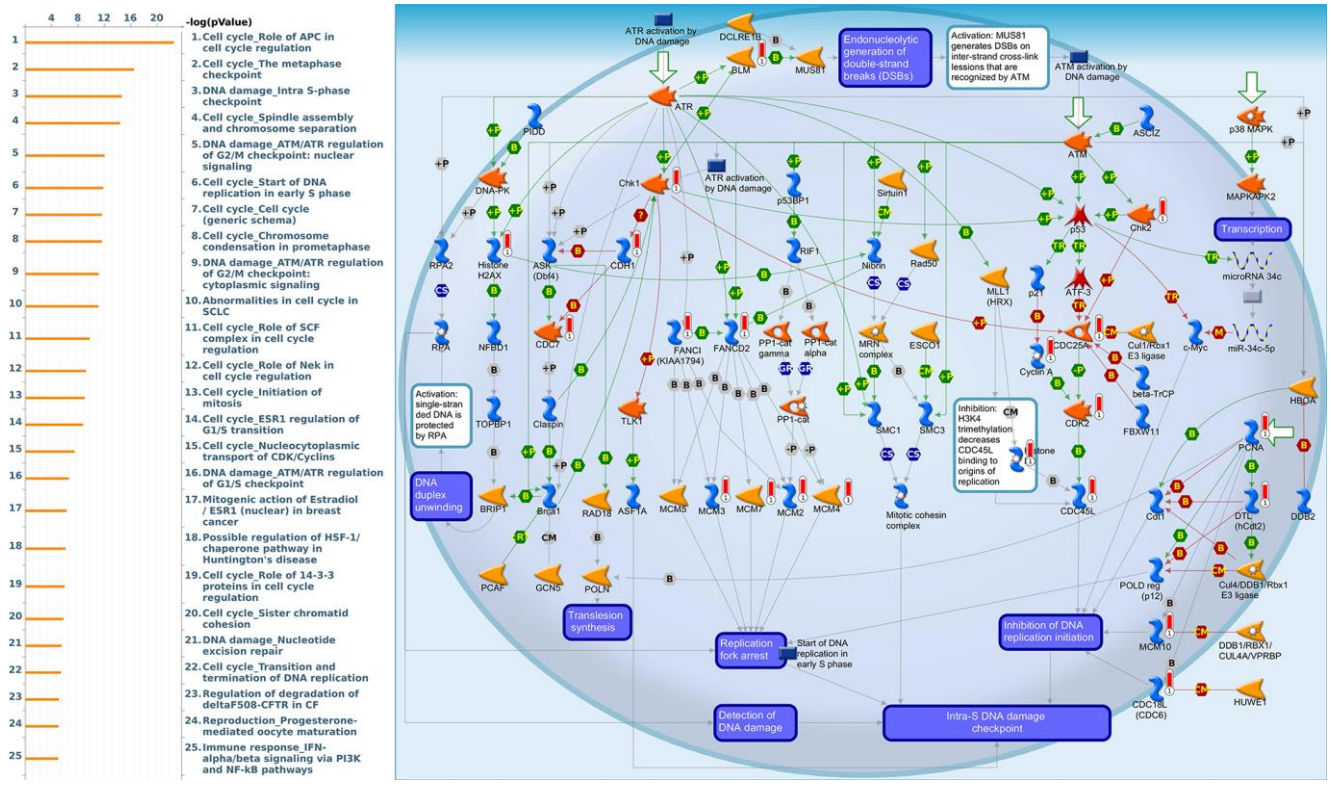

Figure 14. Cell cycle-related networks correlated with the 26S proteasome delta subunit, non-ATPase 12 (*PSMD12*) family gene in breast cancer (BRCA). MetaCore pathway analysis of biological processes revealed that pathways related to "DNA damage_Intra S-phase checkpoint" were significantly associated with BRCA development.

supposed to substantially contribute to the onset of tumors as observed in various cancer types [60]. PSMD11 is a novel biomarker of pancreatic cancer progression [61]. High levels of PSMD12 enhanced both the proliferation and invasion of BRCA and gliomas, one of the fastest-growing and most aggressive brain neoplasms, by upregulating nuclear factor erythroid 2-related factor 2 (Nrf2) [62]. In the case of proteasomal degradation, consistently high levels of PSMD14, which regulates the de-ubiquitination substrate, may lead to a worse prognosis of lung adenocarcinomas [63]. The recent literature indicated that PSMDs play important roles in various cancers, and may represent possible biomarkers for predicting clinical out-comes and precise diagnoses, which provides promising molecular targets for the research and development of drugs and targeted therapies.

Despite extensive efforts having been made to properly understand the roles of each PSMD family member in various clinical diseases and cancer development, there is still limited evidence regarding relationships between all PSMD family genes and BRCA. We therefore conducted this study using available public databases to analyze possible biological regulation of PSMD family genes along with the occurrence and the development of BRCA. The data revealed that higher mRNA and protein levels of PSMD1, PSMD2, PSMD3, PSMD7, PSMD10, PSMD12, and PSMD14 lead to worse prognoses in terms of both DMFS and RFS. Therefore, we chose these PSMD family genes for further bioinformatics analyses. Moreover, the coexpression and pathway analysis also revealed the involvement of these family genes together with cell metabolism, immune responses, cyclin-dependent kinases (CDKs), and other cell-cycle pathways and signaling networks. The current study was consistent with the previous literature; these results credibly suggest that some specific genes of the PSMD family act as oncogenes, whose differential expressions may serve as potential molecular biomarkers in terms of diagnosis, classification, and prognosis for developing BRCA treatments.

Figure 15. Cell cycle-related networks correlated with the 26S proteasome delta subunit, non-ATPase 14 (*PSMD14*) family gene in breast cancer (BRCA). MetaCore pathway analysis of biological processes revealed that pathways related to "DNA damage_ATMATR regulation of G_2M checkpoint cytoplasmic signaling" were significantly associated with BRCA development.

Based on our knowledge, this is the first ever report on PSMD family genes expression in relation to patient survival prediction in BRCA. Most of all, since various types of high-throughput databases were integrated and some underlying biological mechanism were revealed that PSMD genes show prognostic and predictive value in BRCA, hence they may possibly serve as novel biomarkers in malignancy screening and/or potential prognosticators in assessing BRCA severity and prognosis.

MATERIALS AND METHODS

Oncomine and UALCAN analysis

Oncomine, available at (https://www.oncomine.org), is generally recognized as a bioinformatics analytical tool for gene expression microarrays among PSMD family members [64]. Differences in expression between normal tissues and 20 types of cancer counterparts were comprehensively evaluated, under conditions that thresholds of three parameters were adjusted to a multiple of change >2; $p<0.0001$; and gene ranked in the top 10%; with data type as "all". Numbers of significant unique analyses that met the selection criteria in BRCA are presented as digits, while overexpressed and under-expressed genes are displayed in red and blue gradients, respectively, in descending order of the gene rank percentile. In the subsequent stage, the ggpubr package in R environment was run to obtain plots of BRCA subtypes as we previously described [65–68].

Transcriptomic expressions of PSMD family members were analyzed in BRCA sample using the UALCAN (http://ualcan.path.uab.edu/) platform. UALCAN collected TCGA level 3 RNA-Seq and clinical data from different cancer types. With genes of interest, UALCAN allows users to perform biomarkers identification to verify gene expressions with multiple clinical factors. A boxplot was drawn of PSMD mRNA expression levels measured in BRCA specimens (red) compared to their normal counterparts (blue) obtained from the UALCAN database. Statistical analysis was performed using Student's t-test, and $p<0.05$ was considered statistically significant [69].

Evaluation of differential PSMD expressions in cancer cell lines by a cancer cell line encyclopedia (CCLE) analysis

To further search for individual expression levels of *PSMD* family genes on a larger scale, the CCLE project (available at https://portals.broadinstitute.org/ccle) was launched [70]. 1000 This web-based tool offers public access to both genetic and pharmacologic characterizations of numerous human cancer models, including over human cancer cell lines and over 130,000 unique datasets. Moreover, the integrated RNA-Seq Aligned Reads tool was applied to 60 independent BRCA cell lines prior to plotting expressions of *PSMD* family members one at a time [71–73].

Kaplan-Meier (KM) overall survival analysis

The KM database (https://kmplot.com/), an integrated online database well-known for assessing target genes of survivors among 21 cancer types, was subsequently leveraged to further expand some prognosis-related issues. By concurrently integrating mRNA expression levels and clinical data obtained from target genes, the independent prognostic values of PSMD target genes on patients diagnosed with BRCA, including both distant metastasis-free survival (DMFS) and relapse-free survival (RFS), were represented as KM survival plots of two distinct groups of patients. Comparisons of the two patient cohorts were performed with 95% confidence intervals of hazard ratios (HRs) and fixed log-rank *p* values [74].

Analysis of protein expressions in clinical human specimens

The Human Protein Atlas (HPA, https://www.proteinatlas.org) provides a wealth of information on sequences, pathology, expressions, and distributions in various cancer tissues. The first version of this database contained more than 400,000 high-resolution images corresponding to more than 700 antibodies to human proteins [75]. This study analyzed the differential status of protein expressions and the localization of select PSMD family protein expression in breast tissue.

Functional enrichment analysis of *PSMD* target genes

To visualize genomics datasets on a large scale, particularly TCGA and METABRIC databases (available at the cBioPortal platform), the InteractiVenn tool (http://www.interactivenn.net/) was chosen to draw a one-way Venn diagram which illustrates the overlap and numbers of genes associated with expressions of *PSMD* target genes across the two given datasets [76]. The intersection between the two sets was subsequently analyzed for related pathways and involved networks using the online MetaCore platform (https://portal.genego.com/), with p-value of <0.05, as we previously described [77–82].

Tumor immune estimation resource (TIMER) database analysis

TIMER vers. 2.0 (available at http://timer.comp-genomics.org/) is generally known as a trustworthy

resource for systematic analysis of host immune infiltrates across multiple cancer types and related diseases. In other words, this webserver can help estimate abundances of six given immune cell types which belong to two separate groups: the lymphoid lineage (B cells, cluster of differentiation 4-positivie ($CD4^+$) T cells, and cluster of differentiation 8-positivie ($CD8^+$) T cells) and myeloid lineage (neutrophils, macrophages, and dendritic cells) in the tumor microenvironment, under the DiffExp module with default parameters. Finally, correlations were illustrated as a scatterplot, while *PSMD* gene expression levels were represented on the x-axis and related tumor-infiltrating immune cell markers were represented on the y-axis [83, 84].

AUTHOR CONTRIBUTIONS

Conceptualization, D.T.M.X. and C.C.W.; methodology, D.T.M.X.; software, T.J. K. and M.A.; validation, T.J. K.; formal analysis, H.D.K.T and G.A.; investigation, J.Y.C. and C.C.W.; resources, C.C.C. and V.A.; data curation, Y.F.W. and K.H.L.; writing—original draft preparation, D.T.M.X. and C.C.W.; writing—review and editing, C.Y.W. and J.Y.C.; visualization, H.D.K.T and G.A.; supervision, C.Y.W. and J.Y.C.; project administration, C.Y.W. and J.Y.C.; funding acquisition, J.Y.C. and C.C.W. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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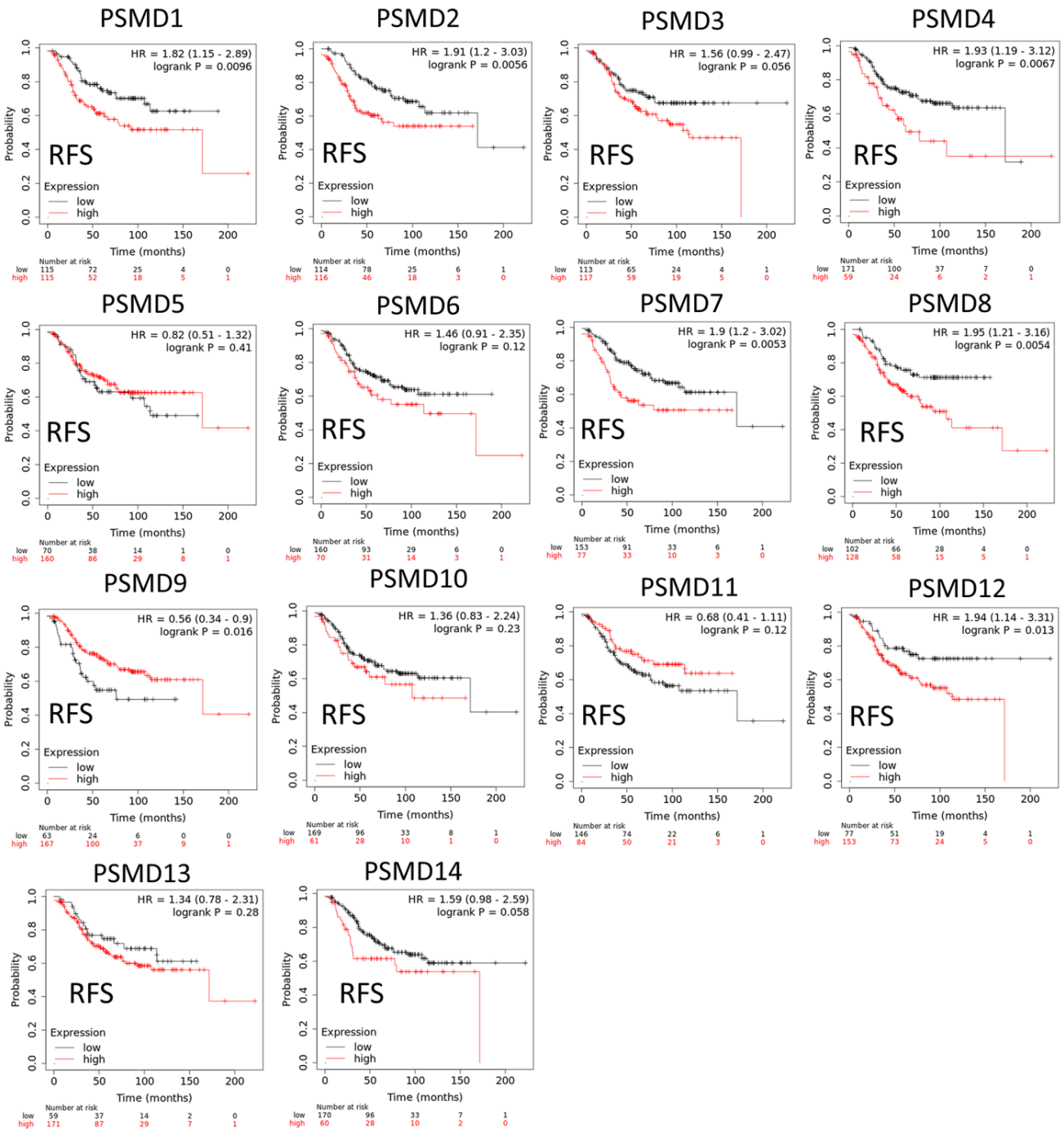
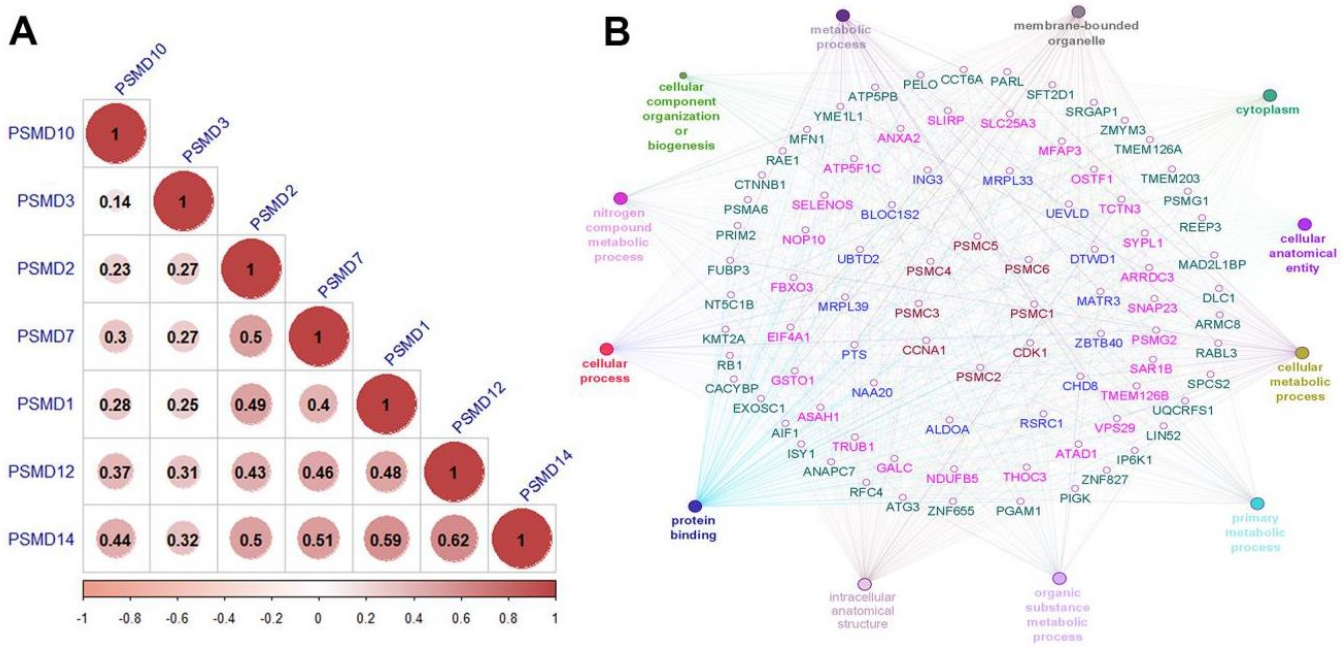
SUPPLEMENTARY MATERIALS

Supplementary Figures



Supplementary Figure 1. Prognostic values of 26S proteasome delta subunit, non-ATPase (PSDM) family genes in breast cancer (BRCA) patients (GSE21653 database). A recurrence metastasis-free sur-vival (RFS) dataset was used for the analysis. An auto-cutoff strategy was set in this analysis to differentiate patients into two groups based on the value of PSMDs mRNAs. The two survival curves respectively illustrate survival outcomes (including survival per-centages and survival times) of BRCA patients with high (red) or low (black) expression levels of PSMD family members. Increased mRNA levels of most PSMD family genes resulted in poor prognoses, while an increasing level of PSMD9 was associated with favorable outcomes ($p<0.05$ was considered statistically significant).



Supplementary Figure 2. Correlations among different 26S proteasome delta subunit, non-ATPase (PSMD) family members in breast cancer (BRCA). (**A**) Correlations between PSMD family members and cell-cycle-related genes in BRCA patients from the METABRIC database, and in-significant correlations are marked by crosses. (**B**) Through a Cytoscape analysis, high correlations between PSMD members and cancer development-related pathways were observed.

Supplementary Tables

Supplementary Table 1. Univariate and multivariate Cox proportional hazards regression analysis of breast cancer (BRCA) overall survival (OS) outcomes.

Variables	Patient number	Univariate		Multivariate	
		HR (95% CI)	p value	HR (95% CI)	p value
Age (year)					
< 60	533	reference	0.0001	reference	0.000165 ***
> 60	461	1.97 (1.40 – 2.77)		1.966 (1.383 – 2.795)	
Gender					
Male	11	reference	0.956		
Female	983	0.945 (0.132 – 6.78)			
Tumor stage					
Stage I/II	740	reference	1.2e-08 ***	reference	0.000116 ***
Stage III/IV	236	2.791 (1.96 – 3.97)	0.0189 *	3.4 (1.825 – 6.34)	0.055078
Stage X	18	2.56 (1.17 – 5.6)		3.503 (0.97 – 12.61)	
T					
T1/T2	841	reference	0.0019*	reference	0.496934
T3/T4	150	1.85 (1.25 – 2.73)	0.527	0.834 (0.494 – 1.4)	0.039511 *
TX	3	0.527 (0.072 – 3.84)		0.098 (0.01 – 0.89)	
N					
N0/N1	799	reference	4.75e-05 ***	reference	0.407585
N2/N3	176	2.32 (1.547 – 3.484)	3.73e-05 ***	0.784 (0.44 – 1.39)	0.022777 *
NX	19	3.97 (2.06 – 7.65)		2.79 (1.154 – 6.76)	
M					
M0	834	reference	1.08e-09 ***	reference	0.62
M1	20	5.296 (3.09 – 9.05)	0.262	1.2 (0.5 – 2.6)	
MX	140	1.396 (0.778 – 2.5)			
PSMD1 expression					
Low	497	reference	0.064		
High	497	1.4 (0.98 – 2)			
PSMD2 expression					
Low	497	reference	0.457		
High	497	1.137 (0.81 – 1.59)			
PSMD3 expression					
Low	497	reference	0.421		
High	497	1.149 (0.81 – 1.61)			
PSMD7 expression					
Low	497	reference	0.343		
High	497	1.178 (0.84 – 1.7)			
PSMD10 expression					
Low	497	reference	0.0035 **	reference	0.001508 **
High	497	1.68 (1.188 – 2.396)		1.798 (1.251 – 2.585)	
PSMD12 expression					
Low	497	reference	0.168		
High	497	1.27 (0.9 – 1.792)			
PSMD14 expression					
Low	497	reference	0.127		
High	497	1.3 (0.93 – 1.836)			

Factors showing significant relationships with OS from a univariate analysis were then used for a multi-variate analysis. HR, hazard ratio; CI, confidence interval; * p<0.05.

Supplementary Table 2. Pathway analysis of genes co-expressed with 26S proteasome delta subunit, non-ATPase 1 (PSMD1) from public breast cancer (BRCA) databases using the MetaCore platform (with p<0.01 set as the cutoff value).

No.	Map	*p*-Value	Network objects from active data
1	Cell cycle_Role of APC in cell cycle regulation	4.58E-16	BUB1, CDC18L (CDC6), Tome-1, Geminin, Emi1, Cyclin A, Aurora-A, PLK1, Aurora-B, CDC20, Cyclin B, MAD2a, Securin, ORC1L, CKS1
2	Cell cycle_The metaphase checkpoint	1.10E-13	BUB1, SPBC25, CENP-A, Aurora-A, PLK1, Aurora-B, HEC, CDC20, HZwint-1, CENP-F, MAD2a, Survivin, CENP-E, AF15q14
3	Cell cycle_Spindle assembly and chromosome separation	6.96E-13	Importin (karyopherin)-alpha, TPX2, CSE1L, Aurora-A, KNSL1, Aurora-B, HEC, CDC20, Tubulin alpha, Cyclin B, MAD2a, Separase, Securin
4	Cell cycle_Start of DNA replication in early S phase	1.10E-11	CDC18L (CDC6), Geminin, DP1, MCM4, MCM3, Cyclin E, MCM10, ORC6L, MCM4/6/7 complex, MCM2, ORC1L, CDC45L
5	DNA damage_Intra S-phase checkpoint	8.17E-10	PCNA, CDC18L (CDC6), BLM, FANCD2, DTL (hCdt2), Histone H2AX, MCM4, MCM3, Cyclin A, Chk1, MCM7, MCM10, MCM2, Histone H3, CDC45L
6	Cell cycle_Chromosome condensation in prometaphase	1.08E-09	CAP-C, Cyclin A, CAP-G/G2, Aurora-A, Aurora-B, CAP-E, Cyclin B, TOP2, Histone H3
7	Regulation of degradation of deltaF508-CFTR in CF	3.98E-08	Csp, HSP70, RNF4, UFD1, SUMO-2, Derlin1, UCHL1, Hdj-2, SUMO-3, HSC70
8	Cigarette smoke-mediated regulation of NRF2-antioxidant pathway in airway epithelial cells	5.08E-07	PRDX1, TXNRD1, NRF2, SRX1, GCL reg, ME1, TALDO, DJ-1
9	Cell cycle_Initiation of mitosis	3.22E-06	Nucleolin, PLK1, KNSL1, Cyclin B2, FOXM1, Kinase MYT1, Histone H3
10	Cell cycle_Transition and termination of DNA replication	3.22E-06	TOP2 alpha, PCNA, Bard1, Cyclin A, MCM2, TOP2, FEN1
11	DNA damage_ATM/ATR regulation of G2/M checkpoint: cytoplasmic signaling	5.62E-06	UBE2C, JAB1, Chk1, Aurora-A, PLK1, Aurora-B, DCK, Histone H3, 14-3-3
12	Cell cycle_Role of SCF complex in cell cycle regulation	7.15E-06	Emi1, Cyclin E, Chk1, PLK1, RING-box protein 1, NEDD8, CKS1
13	Abnormalities in cell cycle in SCLC	7.15E-06	PCNA, Cyclin A, Cyclin E, Aurora-B, Histone H3, Cyclin E2, CKS1
14	Cell cycle_Role of Nek in cell cycle regulation	1.44E-05	TPX2, Aurora-A, PI3K cat class IA, HEC, Tubulin alpha, MAD2a, Histone H3
15	IGF signaling in lung cancer	1.49E-05	4E-BP1, Histone H2AX, PI3K cat class IA, SOS, RHEB2, Survivin, mTOR, GRB2
16	DNA damage_ATM/ATR regulation of G2/M checkpoint: nuclear signaling	1.78E-05	CDC18L (CDC6), Histone H2AX, Cyclin A, Chk1, PLK1, Cyclin B, Cyclin B2, TTK
17	Immune response_Antigen presentation by MHC class I, classical pathway	7.00E-05	PSMB5, HSP70, TAP1 (PSF1), IDE, Nardilysin, TAP, PSMB2, TAP2 (PSF2)
18	NRF2 regulation of oxidative stress response	7.00E-05	Thioredoxin, PRDX1, TXNRD1, NRF2, GCL reg, PI3K cat class IA, SOD1, DJ-1
19	Oxidative stress_Role of ASK1 under oxidative stress	7.00E-05	HPK38, UNRIP, Thioredoxin, PRDX1, MT-TRX, 14-3-3 zeta/delta, SOD1, 14-3-3
20	Growth factors in regulation of oligodendrocyte precursor cells survival in multiple sclerosis	9.25E-05	4E-BP1, 14-3-3 beta/alpha, CD80, PI3K cat class IA, 14-3-3 zeta/delta, Caspase-3, mTOR
21	Development_Growth hormone signaling via PI3K/AKT and MAPK cascades	9.25E-05	4E-BP1, ATF-2, Elk-4, SOS, RHEB2, mTOR, GRB2
22	DNA damage_Role of Brca1 and Brca2 in DNA repair	1.03E-04	PCNA, FANCD2, Histone H2AX, Rad51, MSH6, Bard1
23	Immune response_IFN-alpha/beta signaling via PI3K and NF-κB pathways	1.60E-04	PCNA, 4E-BP1, Cyclin A, Cyclin E, GBP1, p19, PI3K cat class IA, DHFR, RSAD2, ISG15
24	Cell cycle_Cell cycle (generic schema)	1.66E-04	E2F5, DP1, Cyclin A, Cyclin E, Cyclin B
25	Signal transduction_PTEN pathway	1.68E-04	PCNA, PI3K cat class IA, SOS, Caspase-3, RHEB2, mTOR, GRB2

Supplementary Table 3. Pathway analysis of genes co-expressed with 26S proteasome delta subunit, non-ATPase 2 (PSMD2) from public breast cancer databases using the MetaCore platform (with p<0.01 set as the cutoff value).

No.	Map	*p*-Value	Network objects from active data
1	Cell cycle_Role of APC in cell cycle regulation	5.61E-20	Nek2A, BUB1, MAD2b, CDC18L (CDC6), Tome-1, Emi1, Cyclin A, Aurora-A, PLK1, Aurora-B, CDC25A, CDC20, SKP2, Cyclin B, MAD2a, Securin, ORC1L, CDK2, CKS1
2	Cell cycle_The metaphase checkpoint	9.51E-16	Nek2A, BUB1, MAD2b, SPBC25, CENP-A, Aurora-A, PLK1, Aurora-B, HEC, CDCA1, CDC20, HZwint-1, CENP-F, MAD2a, Survivin, CENP-E, AF15q14
3	Cell cycle_Spindle assembly and chromosome separation	9.84E-14	Nek2A, Importin (karyopherin)-alpha, TPX2, CSE1L, Aurora-A, KNSL1, Aurora-B, HEC, CDC20, Tubulin alpha, Cyclin B, MAD2a, Separase, Securin, Tubulin (in microtubules)
4	Cell cycle_Cell cycle (generic schema)	8.83E-13	CDC25C, CDK4, DP1, p107, Cyclin A, Cyclin E, CDC25A, Cyclin B, E2F2, CDC25B, E2F4, CDK2
5	Cell cycle_Chromosome condensation in prometaphase	8.83E-13	CAP-H/H2, Condensin, CAP-C, Cyclin A, CNAP1, CAP-G/G2, Aurora-A, CAP-D2/D3, Aurora-B, CAP-E, Cyclin B, TOP2
6	DNA damage_Intra S-phase checkpoint	1.45E-12	TOPBP1, CDC18L (CDC6), BLM, FANCD2, DTL (hCdt2), Chk2, MCM4, MCM3, Cyclin A, Chk1, FANCI (KIAA1794), PP1-cat, CDC25A, MCM7, MCM10, PP1-cat alpha, CDC7, MCM2, CDK2, CDC45L
7	Cell cycle_Start of DNA replication in early S phase	2.63E-11	CDC18L (CDC6), DP1, MCM4, MCM3, Cyclin E, MCM10, ORC6L, MCM4/6/7 complex, CDC7, MCM2, ORC1L, CDK2, CDC45L
8	Cell cycle_Role of SCF complex in cell cycle regulation	1.2E-10	Cullin 1, CDK4, Emi1, Cyclin E, Skp2/TrCP/FBXW, Chk1, PLK1, CDC25A, SKP2, NEDD8, CDK2, CKS1
9	Reproduction_Progesterone-mediated oocyte maturation	6.99E-10	CDC25C, BUB1, MEK1(MAP2K1), Cyclin B1, Aurora-A, PLK1, c-Raf-1, GSK3 beta, Adenylate cyclase, CDC20, SOS, CDC25B, Kinase MYT1
10	Cell cycle_ESR1 regulation of G1/S transition	1.58E-09	Cullin 1, CDK4, Cyclin A2, E2F4/DP1 complex, Cyclin A, Cyclin E, Skp2/TrCP/FBXW, CDC25A, SKP2, E2F4, CDK2, CKS1
11	DNA damage_ATM/ATR regulation of G2/M checkpoint: nuclear signaling	3.6E-09	CDC25C, CDC18L (CDC6), Cyclin B1, Chk2, Cyclin A, DNMT1, Chk1, PLK1, GTSE1, Cyclin B, Cyclin B2, TTK, CDK2
12	Cell cycle_Role of Nek in cell cycle regulation	7.47E-09	Nek2A, Tubulin beta, Tubulin gamma, Cyclin B1, TPX2, Aurora-A, PI3K cat class IA, HEC, Tubulin alpha, MAD2a, Tubulin (in microtubules)
13	DNA damage_ATM/ATR regulation of G2/M checkpoint: cytoplasmic signaling	1.93E-08	CDC25C, UBE2C, Cyclin B1, Chk2, PP2A regulatory, Chk1, Aurora-A, PLK1, PP1-cat, Aurora-B, CDC25A, CDC25B, 14-3-3
14	Cell cycle_Regulation of G1/S transition (part 2)	2.39E-08	CDK4, Cyclin A2, E2F4/DP1 complex, DP1, p107, Cyclin A, Cyclin E, GSK3 beta, E2F4, CDK2
15	Abnormalities in cell cycle in SCLC	3.53E-08	CDK4, Cyclin B1, Cyclin A, Cyclin E, Aurora-B, SKP2, E2F2, Cyclin E2, CDK2, CKS1
16	Cell cycle_Initiation of mitosis	1.68E-07	CDC25C, Lamin B, Cyclin B1, PLK1, KNSL1, Cyclin B2, CDC25B, FOXM1, Kinase MYT1
17	Cell cycle_Nucleocytoplasmic transport of CDK/Cyclins	2.04E-07	CDK4, Importin (karyopherin)-alpha, Cyclin B1, Cyclin A, Cyclin E, GSK3 beta, CDK2
18	Immune response_IFN-alpha/beta signaling via PI3K and NF-κB pathways	2.07E-07	CDK4, I-κB, MEK1/2, I-TAC, p107, Cyclin A, p70 S6 kinases, Cyclin E, PI3K cat class IA, c-Raf-1, GSK3 beta, p107/E2F4, CDC25A, eIF4G1/3, E2F4, CDK2
19	Translation_Regulation of EIF2 activity	6.24E-07	GSK3 alpha/beta, Casein kinase II, beta chain (Phosvitin), MEK1/2, Casein kinase I, PP1-cat, PI3K cat class IA, c-Raf-1, SOS, PP1-cat alpha, eIF2B5
20	Regulation of degradation of deltaF508-CFTR in CF	8.12E-07	HSP90, Csp, Sti1, HSP70, Aha1, SAE1, SUMO-2, NPL4, VCP, SUMO-3
21	Cell cycle_Influence of Ras and Rho proteins on G1/S Transition	2.23E-06	CDK4, MEK1(MAP2K1), Cyclin A2, DIA1, Cyclin E, PI3K cat class IA, c-Raf-1, GSK3 beta, SKP2, LIMK2, CDK2
22	Cell cycle_Transition and termination of DNA replication	2.31E-06	TOP2 alpha, Ribonuclease H1, Cyclin A, MCM2, TOP2, POLD reg (p50), FEN1, CDK2
23	Possible regulation of HSF-1/ chaperone pathway in Huntington's disease	5.55E-06	HSP90, GSK3 alpha/beta, PLA2, HSP70, PLK1, SUMO-2, HSP90 beta
24	Cell cycle_Regulation of G1/S transition (part 1)	5.95E-06	CDK4, Chk2, PP2A regulatory, Cyclin A, Cyclin E, Skp2/TrCP/FBXW, GSK3 beta, CDC25A, CDK2
25	LRRK2 in neurons in Parkinson's disease	1.65E-05	AP-2 alpha subunits, HSP90, MEK1/2, GSK3 beta, MARK2, AP2A1, Tubulin (in microtubules), 14-3-3

Supplementary Table 4. Pathway analysis of genes co-expressed with 26S proteasome delta subunit, non-ATPase 3 (*PSMD3*) from public breast cancer databases using the MetaCore platform (with *p*<0.01 set as the cutoff value).

No.	Map	*p*-Value	Network objects from active data
1	Cell cycle_Role of APC in cell cycle regulation	3.21E-11	Nek2A, CDC18L (CDC6), CDH1, Tome-1, Aurora-A, PLK1, Aurora-B, CDC25A, Cyclin B, MAD2a, ORC1L, CDK2
2	Cell cycle_Spindle assembly and chromosome separation	4.92E-11	Nek2A, Importin (karyopherin)-alpha, TPX2, CSE1L, DCTN2, Aurora-A, Aurora-B, Tubulin alpha, Cyclin B, MAD2a, Separase, Tubulin (in microtubules)
3	Cell cycle_Role of Nek in cell cycle regulation	6.49E-10	Nek2A, Tubulin beta, Tubulin gamma, Cyclin B1, TPX2, Aurora-A, Tubulin alpha, MAD2a, Histone H1, Histone H3, Tubulin (in microtubules)
4	DNA damage_Intra S-phase checkpoint	2.89E-09	CDC18L (CDC6), CDH1, DTL (hCdt2), Chk2, MCM4, PP1-cat, CDC25A, MCM7, Brca1, PP1-cat alpha, MCM2, Histone H3, CDK2, GCN5, CDC45L
5	DNA damage_ATM/ATR regulation of G2/M checkpoint: cytoplasmic signaling	1.39E-08	UBE2C, Cyclin B1, Chk2, PP2A regulatory, Aurora-A, PLK1, PP1-cat, Aurora-B, CDC25A, Brca1, Histone H3, 14-3-3
6	Cell cycle_Transition and termination of DNA replication	2.28E-08	TOP2 alpha, Brca1, TOP1, MCM2, TOP2, POLD reg (p50), FEN1, DNA ligase I, CDK2
7	Cell cycle_Chromosome condensation in prometaphase	5.90E-08	CAP-H/H2, Aurora-A, Aurora-B, TOP1, Cyclin B, TOP2, Histone H1, Histone H3
8	Cytoskeleton remodeling_Keratin filaments	5.33E-07	Tubulin beta, Keratin 8, Tubulin gamma 1, Keratin 18, Keratin 19, Tubulin alpha, Keratin 8/18, GRB2, Tubulin (in microtubules)
9	Transcription_Negative regulation of HIF1A function	3.57E-06	HSP90, Calpain 1(mu), HSP70, RUVBL2, Casein kinase I delta, Sirtuin7, HSP90 beta, MCM7, VCP, MCM2, PSMA7
10	Cell cycle_The metaphase checkpoint	6.04E-06	Nek2A, Aurora-A, PLK1, Aurora-B, HZwint-1, MAD2a, Survivin, CENP-E
11	Regulation of degradation of deltaF508-CFTR in CF	1.14E-05	HSP90, Csp, Sti1, HSP70, Aha1, NPL4, Derlin1, VCP
12	Cell cycle_Start of DNA replication in early S phase	2.61E-05	CDC18L (CDC6), MCM4, MCM2, ORC1L, Histone H1, CDK2, CDC45L
13	LRRK2 in neurons in Parkinson's disease	3.23E-05	AP-2 alpha subunits, HSP90, MARK2, AP2A1, Tubulin (in microtubules), Beta-adaptin 2, 14-3-3
14	DNA damage_ATM/ATR regulation of G2/M checkpoint: nuclear signaling	3.44E-05	CDC18L (CDC6), Cyclin B1, CDH1, Chk2, PLK1, Brca1, Cyclin B, CDK2
15	Signal transduction_mTORC1 downstream signaling	4.58E-05	SCD, p70 S6 kinase2, MVK, p70 S6 kinases, UBF, SIN1, MAF1, ATG13, ULK1
16	Apoptosis and survival_Regulation of apoptosis by mitochondrial proteins	4.71E-05	Calpain 1(mu), PKC-delta, Metaxin 1, Smac/Diablo, RAD9A, 14-3-3 zeta/delta, PP1-cat alpha, PP2C, LETM1, RAD9, SOD1, CDK2
17	Regulation of lipid metabolism_Regulation of lipid metabolism via LXR, NF-Y and SREBP	8.45E-05	AMPK gamma subunit, SCD, FASN, LDLR, ACACA, ACLY, RARalpha
18	Translation_Regulation of EIF2 activity	8.45E-05	PKR, Casein kinase I, PP1-cat, H-Ras, PP1-cat alpha, eIF2AK1, GRB2
19	DNA damage_ATM-dependent double-strand break foci	9.86E-05	STARING, PRMT1, NPL4, Histone H2A, Brca1, VCP, BRG1, Histone H3, GCN5
20	Apoptosis and survival_Endoplasmic reticulum stress response pathway	1.72E-04	Calpain 1(mu), I-κB, TRAF2, PP1-cat, Derlin1, GRP78, PP1-cat alpha, ERP5
21	Regulation of degradation of wtCFTR	1.99E-04	HSP90, Csp, NPL4, Derlin1, VCP
22	NETosis in SLE	2.06E-04	DNase I, Histone H2, Histone H2A, PKC, Histone H1, Histone H3
23	SCAP/SREBP Transcriptional Control of Cholesterol and FA Biosynthesis	2.56E-04	ELOVL1, SCD, FASN, ERG1, MVK, ACACA, ACLY
24	Mechanisms of resistance to EGFR inhibitors in lung cancer	2.56E-04	HSP90, E-cadherin, H-Ras, Claudin-7, ErbB2, Survivin, GRB2
25	Transport_Induction of Macropinocytosis	2.96E-04	HSP90, ARF1, BAIAP2, SHIP2, H-Ras, 14-3-3 zeta/delta, PDGF-B, PKC, RhoGDI alpha

Supplementary Table 5. Pathway analysis of genes co-expressed with 26S proteasome delta subunit, non-ATPase 7 (*PSMD7*) from public breast cancer databases using the MetaCore platform (with $p<0.01$ set as the cutoff value).

No.	Map	*p*-Value	Network objects from active data
1	Cell cycle_Role of APC in cell cycle regulation	2.73E-11	BUB1, CDH1, Geminin, Emi1, Cyclin A, Aurora-A, PLK1, PKA-cat (cAMP-dependent), Cyclin B, MAD2a, Securin, CKS1
2	Cell cycle_ESR1 regulation of G1/S transition	2.64E-08	CDK4, Cyclin A2, E2F4/DP1 complex, p130, Cyclin A, ERK1/2, E2F4, ERK2 (MAPK1), CKS1, CDK6
3	Cell cycle_Regulation of G1/S transition (part 2)	4.24E-08	CDK4, Cyclin A2, E2F4/DP1 complex, p130, DP1, Cyclin A, ERK1/2, E2F4, CDK6
4	Cell cycle_Cell cycle (generic schema)	5.29E-08	CDK4, E2F5, p130, DP1, Cyclin A, Cyclin B, E2F4, CDK6
5	Cell cycle_Spindle assembly and chromosome separation	2.09E-07	Importin (karyopherin)-alpha, Aurora-A, HEC, Tubulin alpha, Cyclin B, MAD2a, Securin, Ran, Tubulin (in microtubules)
6	Cell cycle_The metaphase checkpoint	4.73E-07	BUB1, SPBC25, CENP-A, Aurora-A, PLK1, HEC, HZwint-1, MAD2a, CENP-E
7	The role of aberrations in CDKN2 locus and CDK4 in familial melanoma	6.81E-07	CDK4, E2F4/DP1 complex, E2F5, p130, DP1, E2F5/DP1 complex, E2F4, CDK6
8	Possible regulation of HSF-1/ chaperone pathway in Huntington's disease	1.08E-06	HSP90, PLA2, HSP70, HSP90 alpha, PLK1, ERK1 (MAPK3), p23 co-chaperone
9	Putative role of Estrogen receptor and Androgen receptor signaling in progression of lung cancer	4.23E-06	MEK1(MAP2K1), E-cadherin, p38 MAPK, ERK1 (MAPK3), G-protein alpha-i family, Caspase-3, ERK1/2, ERK2 (MAPK1), SRD5A1, 14-3-3
10	Signal transduction_Adenosine A3 receptor signaling pathway	6.26E-06	HIF1A, MEK1/2, p38 MAPK, G-protein alpha-i family, G-protein alpha-i3, G-protein alpha-i2, ERK1/2, PKC, G-protein alpha-q/11
11	Transport_RAN regulation pathway	6.57E-06	NTF2, NUP54, Importin (karyopherin)-alpha, RanBP1, NUP153, Ran
12	Cell cycle_Role of SCF complex in cell cycle regulation	1.19E-05	CDK4, p130, Emi1, Chk1, PLK1, NEDD8, CKS1
13	NRF2 regulation of oxidative stress response	1.71E-05	Casein kinase II, alpha chains, MEK1(MAP2K1), Thioredoxin, PRDX1, TXNRD1, GCL reg, ERK1 (MAPK3), PKC, ERK2 (MAPK1)
14	Cell cycle_Chromosome condensation in prometaphase	1.79E-05	CAP-C, Cyclin A, CAP-G/G2, Aurora-A, CAP-E, Cyclin B
15	Cell cycle_Role of Nek in cell cycle regulation	2.39E-05	Tubulin beta, Aurora-A, HEC, Tubulin alpha, MAD2a, Ran, Tubulin (in microtubules)
16	The role of KEAP1/NRF2 pathway in skin sensitization	2.39E-05	HSP70, Thioredoxin, E-cadherin, TXNRD1, ERK1 (MAPK3), ERK1/2, ERK2 (MAPK1)
17	Immune response_Antigen presentation by MHC class II	2.64E-05	HSP90, Cathepsin L, Dectin-1, HSP90 alpha, Cathepsin V, p38 MAPK, Legumain, MARCH1, ERK1/2, HSC70, PKC, MAP1LC3B, Tubulin (in microtubules)
18	Development_S1P1 receptor signaling via beta-arrestin	3.63E-05	MEK1(MAP2K1), ERK1 (MAPK3), G-protein alpha-i family, G-protein alpha-i3, G-protein alpha-i2, ERK1/2, ERK2 (MAPK1)
19	Development_Regulation of telomere length and cellular immortalization	4.43E-05	HSP90, hnRNP C, TRF2, PTOP, hRap1, Staufen, p23 co-chaperone
20	G protein-coupled receptors signaling in lung cancer	4.94E-05	PGE2R4, Galpha(i)-specific peptide GPCRs, G-protein alpha-i family, TGF-alpha, PKA-cat (cAMP-dependent), Galanin, Galpha(q)-specific peptide GPCRs, CXCR4, ERK1/2, G-protein alpha-q/11
21	HSP70 and HSP40-dependent folding in Huntington's disease	5.30E-05	HSP90, HSP70, HSP90 alpha, PSMD1, Hdj-2, HSC70
22	DNA damage_ATM/ATR regulation of G2/M checkpoint: cytoplasmic signaling	7.93E-05	p38alpha (MAPK14), Chk1, Aurora-A, PLK1, p38 MAPK, DCK, ERK2 (MAPK1), 14-3-3
23	HCV-dependent cytoplasmic signaling leading to HCC	8.45E-05	MEK1(MAP2K1), p38 MAPK, PKA-cat (cAMP-dependent), ERK1/2, PKC, ERK2 (MAPK1)
24	Non-genomic signaling of ESR2 (membrane) in lung cancer cells	1.05E-04	MEK1(MAP2K1), ERK1 (MAPK3), N-Ras, G-protein alpha-i family, TGF-alpha, PKA-cat (cAMP-dependent), ERK1/2, ERK2 (MAPK1)
25	Signal transduction_CXCR4 signaling via MAPKs cascades	1.05E-04	MEK1(MAP2K1), MEK1/2, p38 MAPK, N-Ras, G-protein alpha-i family, G-protein alpha-i2, CXCR4, ERK1/2

Supplementary Table 6. Pathway analysis of genes co-expressed with 26S proteasome delta subunit, non-ATPase 10 (*PSMD10*) from public breast cancer databases using the MetaCore platform (with $p<0.01$ set as the cutoff value).

No.	Map	p-Value	Network objects from active data
1	HSP70 and HSP40-dependent folding in Huntington's disease	9.52E-07	HSP90, Ubiquitin, HSP70, HSP90 alpha, PSMD1, Hdj-2, HSC70
2	DNA damage_Nucleotide excision repair	3.58E-06	ERCC8, ERCC6, PCNA, HMG14, Centrin-2, TFIIS, Histone H2A, E2N(UBC13), NEDD4, NEDD8
3	CFTR folding and maturation (normal and CF)	1.21E-05	HSP70, Calnexin, HSP105, HSP90 alpha, Hdj-2, p23 co-chaperone
4	Immune response_Antigen presentation by MHC class II	1.43E-05	HSP90, Cathepsin L, 14-3-3 beta/alpha, HSP90 alpha, Cathepsin V, PI3K cat class IA, JNK(MAPK8-10), p38 MAPK, LAMP2, MARCH1, HSC70, SPPL2a
5	Regulation of degradation of deltaF508-CFTR in CF	2.32E-05	HSP90, Ubiquitin, HSP70, RNF4, HSP105, Hdj-2, HSC70
6	Cell cycle_Role of SCF complex in cell cycle regulation	3.89E-05	Ubiquitin, p130, Emi1, Skp2/TrCP/FBXW, Wee1, NEDD8
7	Immune response_BAFF-induced non-canonical NF-kB signaling	4.77E-05	Ubiquitin, SUMO-1, UBE1C, Skp2/TrCP/FBXW, E2N(UBC13), NEDD8
8	Development_Positive regulation of WNT/Beta-catenin signaling in the cytoplasm	5.15E-05	PP2C alpha, GSKIP, SIAH1, HSP105, JNK(MAPK8-10), SMAD4, PP2A catalytic, RNF146, 14-3-3
9	Tricarbonic acid cycle	6.45E-05	SDHA, SUCLG1, SDHB, CISY, SUCB1, IDH3B, DLDH, SCS-A
10	Role of XBP1 protein in multiple myeloma	6.70E-05	SERP1, DnaJB9, PSMA6, GRP78, ERP5
11	Role of GIP in pathogenesis of type 2 diabetes	7.06E-05	Ubiquitin, RAP-1A, p38alpha (MAPK14), MEK1/2, JNK(MAPK8-10), p38 MAPK, PP2A catalytic
12	Possible regulation of HSF-1/ chaperone pathway in Huntington's disease	8.63E-05	HSP90, HSP70, HSP90 alpha, JNK(MAPK8-10), p23 co-chaperone
13	DNA damage_ATM/ATR regulation of G2/M checkpoint: cytoplasmic signaling	1.39E-04	JAB1, p38alpha (MAPK14), p38 MAPK, JNK2(MAPK9), DCK, PP2A catalytic, 14-3-3
14	Transcription_Negative regulation of HIF1A function	1.57E-04	HSP90, PRDX4, Ubiquitin, HSP70, FBXW7, LAMP2, Elongin C, HSC70
15	Proteolysis_Role of Parkin in the Ubiquitin-Proteasomal Pathway	1.70E-04	SIAH1, HSP70, FBXW7, UBC7, Tubulin alpha
16	G-protein signaling_G-Protein alpha-12 signaling pathway	1.90E-04	MEK1(MAP2K1), RAP-1A, 14-3-3 beta/alpha, PI3K cat class IA, JNK(MAPK8-10), p38 MAPK
17	Immune response_HSP60 and HSP70/ TLR signaling pathway	2.00E-04	Ubiquitin, HSP70, I-kB, MEK1/2, JNK(MAPK8-10), p38 MAPK, E2N(UBC13)
18	Translation_Regulation of EIF4F activity	2.00E-04	MEK1(MAP2K1), eIF4H, PI3K cat class IA, p38 MAPK, PP2A catalytic, RHEB2, eIF4E
19	Development_Glucocorticoid receptor signaling	2.09E-04	HSP90, SUMO-1, HSP70, NCOA2 (GRIP1/TIF2), p23 co-chaperone
20	G-protein signaling_Ras family GTPases in kinase cascades	2.54E-04	MEK1(MAP2K1), RAP-1A, p38alpha (MAPK14), JNK(MAPK8-10), p38 MAPK
21	Immune response_TLR5, TLR7, TLR8 and TLR9 signaling pathways	3.15E-04	Ubiquitin, I-kB, MEK1/2, PI3K cat class IA, JNK(MAPK8-10), p38 MAPK, E2N(UBC13)
22	Immune response_IL-33 signaling pathway	3.15E-04	Ubiquitin, p38alpha (MAPK14), I-kB, MEK1/2, PI3K cat class IA, Histone H2A, JNK(MAPK8-10)
23	Signal transduction_AKT signaling	3.83E-04	HSP90, PCNA, I-kB, PI3K cat class IA, PP2A catalytic, RHEB2
24	ESR1 (membrane) 36 kDa isoform signaling in breast cancer	3.83E-04	HSP90, E-cadherin, MEK1/2, PI3K cat class IA, JNK(MAPK8-10), CXCR4
25	DNA damage_p53 activation by DNA damage	3.89E-04	TTC5 (Strap), p38alpha (MAPK14), 14-3-3 theta, JNK(MAPK8-10), p38 MAPK, PP2A catalytic, 14-3-3

Supplementary Table 7. Pathway analysis of genes co-expressed with 26S proteasome delta subunit, non-ATPase 12 (*PSMD12*) from public breast cancer databases using the MetaCore platform (with $p<0.01$ set as the cutoff value).

No.	Map	*p*-Value	Network objects from active data
1	Cell cycle_Role of APC in cell cycle regulation	2.62E-23	Nek2A, BUB1, CDC18L (CDC6), CDH1, Tome-1, Geminin, Emi1, Cyclin A, Aurora-A, PLK1, Aurora-B, CDC25A, CDC20, SKP2, Cyclin B, MAD2a, Securin, ORC1L, CDK2, CKS1
2	Cell cycle_The metaphase checkpoint	3.68E-17	Nek2A, INCENP, BUB1, SPBC25, CENP-A, Aurora-A, PLK1, Aurora-B, HEC, CDCA1, CDC20, HZwint-1, CENP-F, MAD2a, Survivin, CENP-E, AF15q14
3	DNA damage_Intra S-phase checkpoint	2.96E-15	PCNA, CDC18L (CDC6), BLM, CDH1, FANCD2, DTL (hCdt2), Histone H2AX, Chk2, MCM4, MCM3, Cyclin A, Chk1, FANCI (KIAA1794), CDC25A, MCM7, MCM10, CDC7, MCM2, Histone H3, CDK2, CDC45L
4	Cell cycle_Spindle assembly and chromosome separation	5.66E-15	Nek2A, Importin (karyopherin)-alpha, TPX2, CSE1L, Aurora-A, KNSL1, Aurora-B, HEC, CDC20, Tubulin alpha, Cyclin B, MAD2a, Separase, Securin, Tubulin (in microtubules)
5	DNA damage_ATM/ATR regulation of G2/M checkpoint: nuclear signaling	1.36E-12	CDC25C, WDHD1, CDC18L (CDC6), Cyclin B1, CDH1, HSF1, Histone H2AX, Chk2, Cyclin A, Chk1, PLK1, Cyclin B, Cyclin B2, TTK, CDK2
6	Cell cycle_Start of DNA replication in early S phase	2.27E-12	CDC18L (CDC6), Geminin, MCM4, MCM3, Cyclin E, MCM10, ORC6L, MCM4/6/7 complex, CDC7, MCM2, ORC1L, CDK2, CDC45L
7	Cell cycle_Cell cycle (generic schema)	3.57E-12	CDC25C, CDK4, E2F5, p107, Cyclin A, Cyclin E, CDC25A, Cyclin B, E2F2, CDC25B, CDK2
8	Cell cycle_Chromosome condensation in prometaphase	3.57E-12	INCENP, CAP-C, Cyclin A, CNAP1, CAP-G/G2, Aurora-A, CAP-D2/D3, Aurora-B, Cyclin B, TOP2, Histone H3
9	DNA damage_ATM/ATR regulation of G2/M checkpoint: cytoplasmic signaling	1.07E-11	CDC25C, UBE2C, Cyclin B1, JAB1, BORA, Chk2, Chk1, Aurora-A, PLK1, Aurora-B, CDC25A, DCK, CDC25B, Histone H3, 14-3-3
10	Abnormalities in cell cycle in SCLC	1.25E-11	CDK4, PCNA, Cyclin B1, Cyclin A, Cyclin E, Aurora-B, SKP2, E2F2, Histone H3, Cyclin E2, CDK2, CKS1
11	Cell cycle_Role of SCF complex in cell cycle regulation	2.83E-10	CDK4, Emi1, Cyclin E, Skp2/TrCP/FBXW, Chk1, PLK1, CDC25A, SKP2, NEDD8, CDK2, CKS1
12	Cell cycle_Role of Nek in cell cycle regulation	9.73E-10	Nek2A, Tubulin beta, Tubulin gamma, Cyclin B1, TPX2, Aurora-A, HEC, Tubulin alpha, MAD2a, Histone H3, Tubulin (in microtubules)
13	Cell cycle_Initiation of mitosis	1.59E-09	CDC25C, Lamin B, Cyclin B1, PLK1, KNSL1, Cyclin B2, CDC25B, FOXM1, Kinase MYT1, Histone H3
14	Cell cycle_ESR1 regulation of G1/S transition	2.91E-09	CDK4, Cyclin A2, NCOA3 (pCIP/SRC3), Cyclin A, Cyclin E, Skp2/TrCP/FBXW, CDC25A, SKP2, CRM1, CDK2, CKS1
15	Cell cycle_Nucleocytoplasmic transport of CDK/Cyclins	5.40E-08	CDK4, Importin (karyopherin)-alpha, Cyclin B1, Cyclin A, Cyclin E, CRM1, CDK2
16	DNA damage_ATM/ATR regulation of G1/S checkpoint	4.62E-07	CDK4, PCNA, Histone H2AX, Chk2, Cyclin A, Cyclin E, Chk1, CDC25A, CDK2, RFWD3
17	Mitogenic action of Estradiol / ESR1 (nuclear) in breast cancer	1.01E-06	CDK4, NCOA3 (pCIP/SRC3), WIP1, Cyclin E, SGOL2, CDC25A, Cyclin E2, CDK2
18	Possible regulation of HSF-1/ chaperone pathway in Huntington's disease	1.53E-06	HSP90, PLA2, HSP70, HSF1, HSP90 alpha, PLK1, p23 co-chaperone
19	Cell cycle_Role of 14-3-3 proteins in cell cycle regulation	2.18E-06	CDC25C, Chk2, 14-3-3 theta, Chk1, CDC25A, 14-3-3 zeta/delta, CDC25B
20	Cell cycle_Sister chromatid cohesion	3.06E-06	PCNA, Rad21, Cyclin B, DCC1, Separase, Securin, Histone H3
21	DNA damage_Nucleotide excision repair	5.95E-06	ERCC6, PCNA, DTL (hCdt2), EZH2, UFD1, Histone H2A, DNA polymerase kappa, Histone H2B, NEDD8, Histone H4, Histone H3
22	Cell cycle_Transition and termination of DNA replication	7.60E-06	TOP2 alpha, PCNA, Cyclin A, MCM2, TOP2, FEN1, CDK2
23	Regulation of degradation of deltaF508-CFTR in CF	1.50E-05	HSP90, Csp, Sti1, HSP70, SAE1, HSP105, UFD1, Derlin1
24	Reproduction_Progesterone-mediated oocyte maturation	1.83E-05	CDC25C, BUB1, Cyclin B1, Aurora-A, PLK1, CDC20, CDC25B, Kinase MYT1
25	Immune response_IFN-alpha/beta signaling via PI3K and NF-kB pathways	2.03E-05	CDK4, PCNA, 4E-BP1, p107, Cyclin A, Cyclin E, p19, DHFR, CDC25A, eIF4E, CDK2, ISG15

Supplementary Table 8. Pathway analysis of genes co-expressed with 26S proteasome delta subunit, non-ATPase 14 (PSMD14) from public breast cancer databases using the MetaCore platform (with p<0.01 set as the cutoff value).

No.	Map	*p*-Value	Network objects from active data
1	Cell cycle_The metaphase checkpoint	4.46E-14	Nek2A, BUB1, SPBC25, CENP-A, Aurora-A, PLK1, Aurora-B, HEC, CDCA1, HZwint-1, MAD2a, Survivin, CENP-H, CENP-E, AF15q14
2	Cell cycle_Role of APC in cell cycle regulation	3.39E-12	Nek2A, BUB1, Tome-1, Geminin, Emi1, Cyclin A, Aurora-A, PLK1, Aurora-B, Cyclin B, MAD2a, Securin, CKS1
3	Cell cycle_Spindle assembly and chromosome separation	5.44E-12	Nek2A, Importin (karyopherin)-alpha, TPX2, CSE1L, Aurora-A, KNSL1, Aurora-B, HEC, Tubulin alpha, Cyclin B, MAD2a, Securin, Tubulin (in microtubules)
4	DNA damage_ATM/ATR regulation of G2/M checkpoint: cytoplasmic signaling	1.68E-11	UBE2C, Cyclin B1, JAB1, 14-3-3 gamma, BORA, Chk2, Chk1, Aurora-A, PLK1, PP1-cat, Aurora-B, DCK, Nucleolysin TIAR, Histone H3, 14-3-3
5	Cell cycle_Role of Nek in cell cycle regulation	2.23E-08	Nek2A, Tubulin beta, Cyclin B1, TPX2, Aurora-A, HEC, Tubulin alpha, MAD2a, Histone H3, Tubulin (in microtubules)
6	DNA damage_Intra S-phase checkpoint	5.98E-08	PCNA, DTL (hCdt2), Chk2, PP1-cat gamma, Cyclin A, RIF1, Claspin, Chk1, FANCI (KIAA1794), PP1-cat, MCM10, CDC7, Histone H3, CDC45L
7	Cell cycle_Chromosome condensation in prometaphase	1.01E-07	Cyclin A, CAP-G/G2, Aurora-A, Aurora-B, CAP-E, Cyclin B, TOP2, Histone H3
8	DNA damage_G2 checkpoint in response to DNA mismatches	1.71E-07	PCNA, MutSalpha complex, Chk2, MSH6, PMS1, Claspin, Chk1, EXO1, MSH2
9	DNA damage_ATM/ATR regulation of G2/M checkpoint: nuclear signaling	7.73E-07	Cyclin B1, Chk2, Ku70, Cyclin A, Claspin, Chk1, PLK1, Cyclin B, Cyclin B2, TTK
10	Regulation of degradation of deltaF508-CFTR in CF	1.98E-06	Csp, HSP70, Aha1, HSP105, SUMO-2, Derlin1, UCHL1, Hdj-2, HSC70
11	Cell cycle_Sister chromatid cohesion	3.77E-06	PCNA, Rad21, Cyclin B, DCC1, RFC3, Securin, Histone H3
12	Oxidative stress_Role of ASK1 under oxidative stress	4.54E-06	HPK38, SOD2, UNRIP, 14-3-3 gamma, Thioredoxin, PRDX1, MT-TRX, Glutaredoxin, SOD1, 14-3-3
13	Cell cycle_Initiation of mitosis	9.36E-06	Cyclin B1, Nucleolin, PLK1, KNSL1, Cyclin B2, FOXM1, Histone H3
14	Transport_RAN regulation pathway	1.06E-05	NUP54, SUMO-1, Importin (karyopherin)-alpha, NUP58, RanBP1, CRM1
15	Abnormalities in cell cycle in SCLC	2.05E-05	PCNA, Cyclin B1, Cyclin A, Aurora-B, Histone H3, Cyclin E2, CKS1
16	Possible regulation of HSF-1/ chaperone pathway in Huntington's disease	2.87E-05	PLA2, HSP70, PLK1, SUMO-2, Calmodulin, p23 co-chaperone
17	Microsatellite instability in gastric cancer	3.85E-05	PCNA, MutSalpha complex, MSH6, PMS1, EXO1, MSH2
18	CFTR folding and maturation (normal and CF)	6.59E-05	Csp, HSP70, Aha1, HSP105, Hdj-2, p23 co-chaperone
19	Release of pro-inflammatory mediators and elastolytic enzymes by alveolar macrophages in COPD	1.66E-04	MMP-12, Cathepsin L, MMP-1, IL-8, IP10, HDAC2
20	Reproduction_Progesterone-mediated oocyte maturation	1.83E-04	BUB1, MEK1(MAP2K1), Cyclin B1, Aurora-A, PLK1, PKA-reg (cAMP-dependent), G-protein alpha-i family
21	Cell cycle_Role of SCF complex in cell cycle regulation	2.04E-04	Emi1, Chk1, PLK1, RING-box protein 1, NEDD8, CKS1
22	Apoptosis and survival_Granzyme A signaling	2.49E-04	Ku70/80, NDPK A, Ku80, HMGB2, Ku70, Histone H3
23	DNA damage_Mismatch repair	3.61E-04	PCNA, MutSalpha complex, MSH6, EXO1, MSH2, Histone H3
24	Signal transduction_MIF signaling pathway	5.04E-04	MEK1/2, PRDX1, SFK, IL-8, GCL reg, G-protein alpha-i family, CXCR4, SPPL2a
25	Microsatellite instability in colorectal cancer	5.09E-04	PCNA, MutSalpha complex, Beta-2-microglobulin, MSH6, EXO1, MSH2