# Supplementary Materials for "GREMI: an Explainable Framework for Enhanced Disease Prediction and Module Identification" by Hong Liang, Haoran Luo, Zhiling Sang, Miao Jia, Xiaohan Jiang, Zheng Wang, Xiaohui Yao, Shan Cong.

## 1 Supplementary Methods

### 1.1 Multi-omics datasets and preprocessing.

We conducted extensive experiments on eight public datasets: four benchmark datasets, three cancer in-house processed datasets, and one independent dataset for validation.

The benchmark datasets were obtained from Wang et al.[1], where ROSMAP and BRCA were downloaded from `https://github.com/txWang/MOGONET`, and the LGG and KIPAN were directly acquired from the authors. Detailed information regarding data acquisition and preprocessing were available in Wang et al.[1]. In brief, features with no signal (mean = 0) and low variances (standard deviation = 0.1 for mRNA, 0.001 for DNA methylation, and 0 for miRNA) were filtered out from each dataset. In addition, ANOVA tests were performed to further preselect features, aiming to decrease the negative effects of redundant features. Finally, every feature was scaled to [0,1] through a linear transformation. We also investigated how varying the number of features influenced model predictions on LGG and KIPAN datasets. Specifically, for each omics type, we extracted the top 1,000 (if available) and top 200 features based on the ANOVA $F$-value for comparison.

Besides four benchmark datasets, we extended the comparison using three cancer datasets (LUAD, THCA, and UCEC) to further demonstrate the stability and robustness of GREMI. To be specific, we downloaded raw multi-omics data for each disease from The Cancer Genome Atlas (TCGA, `https://portal.gdc.cancer.gov/`). Subsequently, we performed preprocessing for each dataset following the below criteria: (1) filter out features with no signal (mean = 0); (2) filter out features with low variances (standard deviation = 0.1 for mRNA, 0.001 for DNA methylation, and 0 for miRNA); (3) keep features exhibiting significant differences between classes (ANOVA FDR $P < 0.05$); (4) select top 200 features (i.e., features with the largest ANOVA $F$-values) for each omics type; (5) scale each feature into [0,1] interval via linear transformations.

We used an independent Chinese cohort to validate the predictive power of identified biomarkers. In detail, raw omics and clinical data of glioma patients were downloaded from the Chinese Glioma Genome Atlas (CGGA, http://www.cgga.org.cn/), including mRNAseq (batch 1) for a total of 693 samples, methylation microarray data for 159 samples, miRNA microarray data for 198 samples. Preprocessing was conducted to retain only the samples diagnosed with grades 2 and 3. Given that few methylation biomarkers and miRNA biomarkers identified from GREMI were available in CGGA data, we only kept the mRNA data in the LGG-V dataset and evaluated the performance of five mRNA biomarkers for CGGA LGG grade 2 vs. grade 3 classification.

## 2 Supplementary Results

Within the supplementary results section, our investigation encompassed the application of the interpretation method to seven distinct diseases. Initially, we provided a concise overview of representative studies related to the individual-level biomarkers of AD and BRCA. Subsequently, we performed the interpretation method for five other diseases: LGG, KIPAN, LUAD, THCA, and UCEC. For each disease dataset, the interpretation method was applied to three distinct omics data types. In the ensuing

**Table 1:** Summary of the interpretations across seven diseases by GREMI.

| Dataset | Omics | Number of the important subgraphs | Number of the consensus subgraphs |
|---|---|---|---|
| ROSMAP | mRNA | 3062 | 18 |
| | methy | 1 | 1 |
| | miRNA | 2 | 2 |
| BRCA | mRNA | 452 | 18 |
| | methy | 34 | 34 |
| | miRNA | 57 | 57 |
| LGG | mRNA | 10912 | 18 |
| | methy | 7135 | 18 |
| | miRNA | 10551 | 26 |
| KIPAN | mRNA | 5219 | 37 |
| | methy | 8255 | 20 |
| | miRNA | 178 | 19 |
| LUAD | mRNA | 203 | 201 |
| | methy | 5673 | 35 |
| | miRNA | 25 | 25 |
| THCA | mRNA | 4800 | 30 |
| | methy | 389 | 171 |
| | miRNA | 26 | 26 |
| UCEC | mRNA | 30 | 19 |
| | methy | 7 | 6 |
| | miRNA | 4 | 4 |

discussion, we briefly analyzed the significant biomarkers from the various omics data for each disease, supported by an extensive literature review. For the significant modules, one module from each omics data was selected, and functional annotation for this module was conducted using both GO (Gene Ontology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) databases[2]. The top ten significant pathways from GO and the top five significant pathways from KEGG of the selected module were then presented. Table 1 presents the details regarding the number of sample-wise important modules and consensus modules.

## 2.1 Top identified individual-level biomarkers of AD and BRCA.

Some of the top-identified individual biomarkers have shown relationships with AD and other neurodegenerative diseases. GWAS studies have reported the associations of *AC131056.3* and *MEIS3* with increased risk of AD[3,4]. In addition to AD, the *AC131056.3* has been identified to be associated with Parkinson's disease[5]. By integrating methylation and gene expression data from multiple brain regions, *ANKRD30B* exhibited differential methylation and differential expression between AD and controls[6]. Overexpression of miR-409-5p has been associated with impaired neurite outgrowth, reduced neuronal viability, and accelerated progression of $A\beta_{1-42}$-induced pathologies[7]. *HSPA6*, a member of the *HSP70* family, played a critical role in regulating protein misfolding, including tau levels and toxicity, within this pathological process associated with AD[8,9]. Physical activity has been shown to modulate miR-129-5p[10] and miR-132[11], both of which played important roles in alleviating cognitive impairment in AD and were considered to be potential therapeutic targets. Clinical studies have indicated that reduced levels of circulating miR-132 can function as a diagnostic biomarker for AD[12]. Furthermore, its downregulation has been implicated in the pathogenesis of AD in both in vivo and in vitro models[13].

The top individual biomarkers of BRCA also played important roles in the development and progression of various breast cancer subtypes. *C1orf106* has been recognized as a crucial regulator for basal-like/luminal progenitors and has been suggested for its potential as a therapeutic target for breast cancer[14]. A whole-transcriptome analysis has identified *CPA4* as a novel marker in breast cancer as well as a therapeutic target for triple-negative breast cancer (TNBC)[15]. *CLIC6*, a member of the chloride intracellular channel family, exhibited an altered expression profile in breast cancer[16]. A report suggested that polymorphisms in the *IGFBP3* genes may be linked to variations in survival outcomes

**Table 2:** Top identified individual-level biomarkers of AD and BRCA..

| Dataset | Omics | Significant Biomarker |
|---|---|---|
| ROSMAP | mRNA | AC131056.3, ANKRD30B, DENND3-AS1, MEIS3, PPDPF |
| | methy | C1orf83, C10orf99, C19orf54, HSPA6, PLEK |
| | miRNA | hsa-miR-129-3p, hsa-miR-129-5p, hsa-miR-132, hsa-miR-133b |
| BRCA | mRNA | C1orf106, CHAC2, CPA4, CX3CL1, SFRP1 |
| | methy | CLIC6, DCTN1, DNALI1, GPR37L1, IGFALS |
| | miRNA | hsa-mir-9-1, hsa-mir-187, hsa-mir-1301, hsa-mir-1304, hsa-mir-3934 |

among specific subgroups of breast cancer patients categorized by menopausal status[17]. Aberrant hypermethylation-induced epigenetic inactivation of the mir-9-1 gene was reported as a common and early event in breast cancer development[18]. By utilizing two independent cohorts, a breast cancer study[19] has indicated an association between high miR-187 expression and decreased breast cancer survival.

## 2.2 GREMI identified biomarkers related to LGG.

Table 3 shows the top five significant biomarkers of each type of omics related to the LGG. Table 4 presents the significant modules of each type of omics related to the LGG. For mRNA modules, nine were identified, all of which had the same normalized impact. Each of these mRNA modules passed the permutation test. Modules with two features exhibited a $P$-value of 3E-2, those with three features had a $P$-value of 5E-3, and modules with four features showed a $P$-value less than 1E-3. For methylation modules, three were identified, each having the same normalized impact. All of these methylation co-function modules were found to be significant, with a $P$-value of 2E-3. Regarding miRNA co-function modules, two were identified, both of which were significant with a $P$-value of 3E-3.

**Table 3:** Important omics biomarkers identified by GREMI in the LGG dataset.

| Omics | Significant Biomarker |
|---|---|
| mRNA | SFRP2, HMGCLL1, HPSE2, ALDOC, GLUD1 |
| methy | LOC339568, AZGP1, C14orf68, C20orf71, C3orf27 |
| miRNA | hsa-mir-491, hsa-mir-184, hsa-mir-383, hsa-mir-128-1, hsa-mir-1296 |

For significant biomarkers, secreted frizzled-related protein 2 (*SFRP2*) modulated Wnt signaling, acting either as an antagonist or agonist depending[20]. In mesenchymal stem cells, *SFRP2* overexpression diminished Wnt activity by reducing $\beta$-catenin levels[21]. *SFRP2* served as a tumor suppressor in various cancers, such as glioma, where its expression was reduced due to promoter hypermethylation[22]. *AZGP1*, showing significant amino-acid sequence similarity with tumor-derived lipid-mobilizing factor[23], was linked to cancer cachexia. In an AZGP1-producing tumor mouse model, it promoted adipocyte lipolysis, resulting in cachexia[24]. A result suggested that miR-491-5p and miR-491-3p played crucial roles as tumor suppressors in GBM, collectively targeting key oncogenes[25]. The miR-491-3p diminished glioma cell invasion, and the combined overexpression of both miRs impeded glioma cell proliferation and hinders glioma stem cell growth.

**Table 4:** Important omics modules identified by GREMI in the LGG dataset.

| Omics | Significant Module |
|---|---|
| mRNA | [GSG2, MND1], [GSG2, MYBL2], [MND1, MYBL2], [GSG2, MND1, MYBL2], [DEPDC1B, GSG2, MYBL2], [DEPDC1B, MND1, MYBL2], [DEPDC1B, GSG2, MND1], [DEPDC1B, MCM2, MND1, MYBL2], [DEPDC1B, GSG2, MND1, MYBL2] |
| methy | [OR10X1, OR2A4], [MYO7B, OR10X1], [MYO7B, OR2A4], |
| miRNA | [hsa-mir-491, hsa-mir-495] |

We performed functional annotations to the mRNA module [*DEPDC1B, MCM2, MND1, MYBL2*] and the methylation module [*OR10X1, OR2A4*]. Table 5 and Table 6 show the functional annotation results of the mRNA and methylation modules, respectively. Among the significant pathways presented in these tables, there were several pathways associated with the regulation of cell cycle, including GO:0090068 ($P$ = 3.48E-2), GO:0045787 ($P$ = 4.05E-2), and hsa04110 ($P$ = 3.71E-2). TUBA1C, a subtype of $\alpha$-tubulin, has been associated with the cell cycle pathways. It plays a crucial role in cellular mitosis and division[26]. Elevated expression of TUBA1C in LGG has been linked to a poor prognosis, suggesting its potential influence on tumor growth by modulating the tumor microenvironment[27]. For the methylation module, olfactory transduction was also identified in a previous study on glioblastoma[28]. In adult infiltrating glioma and GBM, losses at 9p21 were common[29–31]. Such deletions often resulted in the absence of the tumor suppressor CDKN2A[32]. Deletions in CDKN2A often coincided with BRAF p.V600E mutations, indicating its potential role as a molecular event that facilitates escaping from cell cycle regulation[33–35]. The above research findings directly or potentially confirmed the association between the modules and LGG.

**Table 5:** Significant pathways of the mRNA module of LGG.

| Database | ID | Description | P.adjust |
|---|---|---|---|
| GO | GO:0006310 | DNA recombination | 3.56E-02 |
| | GO:0000727 | double-strand break repair via break-induced replication | 3.56E-02 |
| | GO:0051095 | regulation of helicase activity | 3.56E-02 |
| | GO:1902969 | mitotic DNA replication | 3.56E-02 |
| | GO:0000280 | nuclear division | 3.56E-02 |
| | GO:0048285 | organelle fission | 3.56E-02 |
| | GO:0006268 | DNA unwinding involved in DNA replication | 3.56E-02 |
| | GO:0032780 | negative regulation of ATPase activity | 3.56E-02 |
| | GO:0071353 | cellular response to interleukin-4 | 4.10E-02 |
| | GO:0070670 | response to interleukin-4 | 4.10E-02 |
| KEGG | hsa03030 | DNA replication | 8.56E-03 |
| | hsa04218 | Cellular senescence | 3.68E-02 |
| | hsa04110 | Cell cycle | 3.71E-02 |

**Table 6:** Significant pathways of the methylation module of LGG.

| Database | ID | Description | P.adjust |
|---|---|---|---|
| GO | GO:0050911 | detection of chemical stimulus involved in sensory perception of smell | 2.58E-03 |
| | GO:0007608 | sensory perception of smell | 2.58E-03 |
| | GO:0050907 | detection of chemical stimulus involved in sensory perception | 2.58E-03 |
| | GO:0032467 | positive regulation of cytokinesis | 1.34E-02 |
| | GO:0051781 | positive regulation of cell division | 1.93E-02 |
| | GO:0032465 | regulation of cytokinesis | 1.93E-02 |
| | GO:0000910 | cytokinesis | 2.95E-02 |
| | GO:0051302 | regulation of cell division | 2.95E-02 |
| | GO:0090068 | positive regulation of cell cycle process | 3.48E-02 |
| | GO:0045787 | positive regulation of cell cycle | 4.05E-02 |
| KEGG | hsa04740 | Olfactory transduction | 2.73E-03 |

## 2.3 GREMI identified biomarkers related to KIPAN.

Table 7 shows the top five significant biomarkers of each type of omics related to the KIPAN. As shown in Table 8, all mRNA modules were found to be significant with a $P$-value of 2E-3. The methylation co-function modules were also significant, exhibiting a $P$-value of 6E-3. Both identified miRNA co-function modules were significant with a $P$-value of 2E-2.

**Table 7:** Important omics biomarkers identified by GREMI in the KIPAN dataset.

| Omics | Significant Biomarker |
|---|---|
| mRNA | AP1G2, C8orf74, COL4A4, EPHB2, ESPL1 |
| methy | CRLF3, LOC145814, ABHD10, ACOT11, ADM |
| miRNA | hsa-mir-100, hsa-mir-126, hsa-mir-1271, hsa-mir-210, hsa-mir-424 |

In human cellular biology, two isoforms of the $\gamma$ subunit were identified: *AP1G1* and *AP1G2*, sharing approximately 60% sequence identity. Downregulation of *AP1G1* has been observed in renal cancer tissues, correlating with reduced cell proliferation and migration[36]. It has been postulated that *AP1G2* may similarly exert influence on renal cancer pathogenesis[37]. *ACOT11*, a critical enzyme in fatty acid metabolism, has been identified as a diagnostic marker for clear cell renal cell carcinoma (ccRCC)[38]. The ccRCC was characterized by significant metabolic reprogramming across several pathways[39]. A prior study highlighted the role of miR-100 as a crucial prognostic indicator in RCC due to the correlation of its overexpression with advanced tumor stages and adverse patient outcomes[40]. Recent findings indicated a downregulation of miR-100 and an upregulation of *NOX4* in RCC tissues and cell lines[41]. *NOX4* has been confirmed as a target of miR-100. Elevated levels of miR-100 may enhance autophagy and reduce RCC cell invasion and migration by targeting *NOX4*, leading to inactivation of the mTOR pathway.

**Table 8:** Important omics modules identified by GREMI in the KIPAN dataset.

| Omics | Significant Module |
|---|---|
| mRNA | [C8orf74, MPV17L2], [COL4A4, MPV17L2], [EPHB2, MPV17L2], [GYG2, MYB] |
| methy | [C19orf26, COBRA1], [C18orf54, COBRA1] |
| miRNA | [hsa-mir-126, hsa-mir-143], [hsa-mir-126, hsa-mir-497] |

Functional annotations were conducted to the mRNA module containing [*C8orf74, MPV17L2*] and the methylation module containing [*C19orf26, COBRA1*]. Table 9 presents the functional annotation results for the mRNA module. However, the functional annotation for the methylation module was not found to be significant. As illustrated in Table 9, several pathways associated with mitochondrial processes were identified, including GO:0061668 ($P$ = 4.84E-3), GO:0070131 ($P$ = 4.84E-3), GO:0070129 ($P$ = 4.84E-3), GO:0062125 ($P$ = 4.84E-3), and so on. Mitochondria played a central role in cellular energy generation via oxidative phosphorylation to regulate calcium balance, and were crucial in the processes of apoptosis[42]. The mitochondrial respiratory system was the chief intracellular contributor of reactive oxygen species (ROS), pivotal for maintaining redox stability and cellular signal transduction[43]. Marquardt et al.[44] identified a unique histopathological subgroup in RCC using RNA-sequencing analysis. This subgroup markedly impacted the survival rates, decreasing them in ccRCC patients and increasing them in chRCC patients. In contrast, a majority of oncocytomas had malfunctioning mitochondria attributed to mutations in the first complex and obstructed mitochondrial clearance mechanisms[45,46]. Additionally, mutations in metabolic enzymes, notably fumarate hydratase (FH) and succinate dehydrogenase (SDH), underpinned the onset of FH-deficient RCC[47] and SDH-deficient RCC[48].

**Table 9:** Significant pathways of the mRNA module of KIPAN.

| Database | ID | Description | P.adjust |
|---|---|---|---|
| GO | GO:0061668 | mitochondrial ribosome assembly | 4.84E-03 |
| | GO:0070131 | positive regulation of mitochondrial translation | 4.84E-03 |
| | GO:0070129 | regulation of mitochondrial translation | 4.84E-03 |
| | GO:0062125 | regulation of mitochondrial gene expression | 4.84E-03 |
| | GO:0042255 | ribosome assembly | 8.30E-03 |
| | GO:0032543 | mitochondrial translation | 8.30E-03 |
| | GO:0140053 | mitochondrial gene expression | 1.03E-02 |
| | GO:0045727 | positive regulation of translation | 1.22E-02 |
| | GO:0034250 | positive regulation of cellular amide metabolic process | 1.28E-02 |
| | GO:0042254 | ribosome biogenesis | 2.10E-02 |
| KEGG | hsa04146 | Peroxisome | 9.77E-03 |

## 2.4 GREMI identified biomarkers related to LUAD.

Table 10 shows the top five significant biomarkers of each type of omics related to the LUAD. As detailed in Table 11, all 23 genetic factors within the mRNA modules exhibited significance with a $P$-value of 2E-3. Furthermore, all eight methylation co-function modules and all five miRNA co-function modules demonstrated high significance, each with a $P$-value less than 1E-3.

**Table 10:** Important omics biomarkers identified by GREMI in the LUAD dataset.

| Omics | Significant Biomarker |
|---|---|
| mRNA | PRKAR1A, SLC24A1, CRB3, GPR20, HFE |
| methy | A2ML1, AADACL3, AADACL4, ABAT, ABCC11 |
| miRNA | hsa-mir-1250, hsa-mir-1266, hsa-mir-129-1, hsa-mir-129-2, hsa-mir-3609 |

Significant biomarkers play crucial roles in understanding disease progression and therapeutic responses. Among these, Protein Kinase cAMP-Dependent Regulatory Type I Alpha (*PRKAR1A*) functioned as a tissue-specific modulator, exerting its effects through the phosphorylation of various target proteins[49].*PRKAR1A* deficiency has been identified in endocrine neoplasia and stromal cell tumors. Recent investigations have revealed a significant downregulation of *PRKAR1A* in patients with lung adenocarcinoma[50]. This reduced expression of *PRKAR1A* was associated with advanced tumor stages and diminished overall survival rates. Furthermore, reintroducing *PRKAR1A* in H1299 cell lines led to a marked decrease in both tumor cell proliferation and migration. Thus, *PRKAR1A* emerged as a critical suppressor, and targeting the PRKAR1A-ERK-Snail-E-cadherin pathway may offer therapeutic potential. *A2ML1*, a protease inhibitor, was a member of the alpha-macroglobulin superfamily[51,52]. This inhibitor exhibited a distinct trap mechanism, wherein a significant conformational shift occurred in *A2ML1* upon protease cleavage, effectively ensnaring the protease and preventing further substrate binding. Recent research has highlighted a correlation between the methylation of TRIM58 and the treatment of lung squamous cell carcinoma, with *A2ML1* being identified as a potential prognostic biomarker[53]. In the LUAD, methylation-mediated silencing has been observed to influence miR-1250-5p, leading to the upregulation of its direct target, WDR1[54]. Previous study observed an elevated expression of WDR1 in lung cancer, with a correlation to unfavorable prognosis[55]. In lung cancer cells, the oncogenic role of WDR1 manifested in its ability to modulate cellular proliferation. This modulation occured through dephosphorylation, enhancing the nuclear translocation of the YAP protein. The YAP protein was a key effector in the Hippo signaling pathway, which in turn activated genes that promoted cell proliferation.

We performed functional annotations to the mRNA module [*PLK1, TPX2*] and the methylation module [*C10orf120, CST4*]. Table 12 and Table 13 show the functional annotation results of the mRNA and methylation modules, respectively. As shown in Table 12, there were several enriched pathways associated with mitotic spindle, including GO:0060236 ($P$ = 4.91E-4), GO:0090224 ($P$ = 4.91E-4), GO:0090307 ($P$ = 8.50E-4), GO:0051225 ($P$ = 1.66E-3), GO:0007052 ($P$ = = 1.66E-3),

**Table 11:** Important omics modules identified by GREMI in the LUAD dataset.

| Omics | Significant Module |
|---|---|
| mRNA | [PLK1, TPX2], [PLK1, RAD54L], [RAD54L, TPX2], [CDCA5, PLK1], [KIF18B, PLK1], [CDCA5, TPX2], [KIF18B, TPX2], [CDCA5, RAD54L], [KIF18B, RAD54L], [KIF4A, TPX2], [KIF4A, PLK1], [CENPE, PLK1], [CENPE, TPX2], [KIF4A, RAD54L], [CENPE, RAD54L], [CDCA5, KIF18B], [CDCA5, PKMYT1], [KIF18B, PKMYT1], [CDCA5, KIF4A], [CDCA5, CENPE], [KIF18B, KIF4A], [CENPE, KIF18B], [CENPE, KIF4A] |
| methy | [C10orf120, CST4], [CST4, DCLK3], [C10orf120, CRTAM], [CST4, FOLR4], [CRTAM, CST4], [CST1, CST4], [AQP10, CST4], [CRTAM, CST1] |
| miRNA | [hsa-let-7a-2, hsa-let-7f-2], [hsa-let-7a-2, hsa-let-7a-3], [hsa-let-7a-1, hsa-let-7a-2], [hsa-let-7a-1, hsa-let-7a-3], [hsa-let-7a-3, hsa-let-7f-2] |

and so on. Chronic obstructive lung disease (COPD) was a persistent pulmonary condition, with 50%-80% of lung cancer patients exhibiting preexisting COPD[56]. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) contributed to tumor initiation by forming DNA adducts, leading to mutations in oncogenes and tumor suppressor genes[57]. Crucially, disruptions in the mitotic spindle apparatus significantly influenced genomic instability, primarily by facilitating chromosome mis-segregation and aneuploidy[58]. Recent studies indicated that NNK exacerbated chromosomal instability by interfering with spindle microtubule attachment to the kinetochore and altering spindle dynamics[59]. As for the hsa04068 ($P$ = 1.87E-2), Forkhead box O (FOXO) transcription factored orchestrate many cellular processes including development, metabolism, and stem cell homeostasis[60]. Their pivotal role in tumorigenesis was highlighted by the capacity of modulating gene expression. Specifically, the metastasis suppressor gene nm23-H1, implicated in attenuating the progression of malignancies such as non-small cell lung cancer (NSCLC), was positively regulated by FOXO1 in pulmonary neoplasms[61]. FOXO3 has been identified as a significant factor in the metastasis of many malignancies[62,63]. In addition, many pathways of the methylation module presented association with the sensory perception of taste. In a systematic scoping review on lung cancer[64], a noted prevalence ranged from 12% to 84% for self-reported taste disturbances among oncology patients[65]. A single-center study with 239 diverse cancer patients, including nine with lung cancer, indicated dysphagia in 54%, taste alterations in 62%, and olfactory changes in 35%[66]. The research results discussed above directly or potentially confirmed the relation between the modules and LUAD.

**Table 12:** Significant pathways of the mRNA module of LUAD.

| Database | ID | Description | P.adjust |
|---|---|---|---|
| GO | GO:0060236 | regulation of mitotic spindle organization | 4.91E-04 |
| | GO:0090224 | regulation of spindle organization | 4.91E-04 |
| | GO:0090307 | mitotic spindle assembly | 8.50E-04 |
| | GO:0051225 | spindle assembly | 1.66E-03 |
| | GO:0007052 | mitotic spindle organization | 1.66E-03 |
| | GO:1902850 | microtubule cytoskeleton organization involved in mitosis | 1.78E-03 |
| | GO:0070507 | regulation of microtubule cytoskeleton organization | 1.78E-03 |
| | GO:0007051 | spindle organization | 2.39E-03 |
| | GO:0032886 | regulation of microtubule-based process | 3.73E-03 |
| | GO:0140014 | mitotic nuclear division | 4.65E-03 |
| KEGG | hsa04914 | Progesterone-mediated oocyte maturation | 1.87E-02 |
| | hsa04068 | FoxO signaling pathway | 1.87E-02 |
| | hsa04114 | Oocyte meiosis | 1.87E-02 |
| | hsa04110 | Cell cycle | 1.87E-02 |

**Table 13:** Significant pathways of the methylation module of LUAD.

| Database | ID | Description | P.adjust |
|---|---|---|---|
| GO | GO:0001580 | detection of chemical stimulus involved in sensory perception of bitter taste | 1.07E-02 |
| | GO:0050913 | sensory perception of bitter taste | 1.07E-02 |
| | GO:0050912 | detection of chemical stimulus involved in sensory perception of taste | 1.07E-02 |
| | GO:0050909 | sensory perception of taste | 1.17E-02 |
| | GO:0001895 | retina homeostasis | 1.19E-02 |
| | GO:0010951 | negative regulation of endopeptidase activity | 2.51E-02 |
| | GO:0010466 | negative regulation of peptidase activity | 2.51E-02 |
| | GO:0001894 | tissue homeostasis | 2.51E-02 |
| | GO:0060249 | anatomical structure homeostasis | 2.51E-02 |
| | GO:0045861 | negative regulation of proteolysis | 2.51E-02 |
| KEGG | hsa04970 | Salivary secretion | 1.11E-02 |

## 2.5 GREMI identified biomarkers related to THCA.

Table 14 shows the top five significant biomarkers of each type of omics related to the THCA. As detailed in Table 15, both mRNA modules exhibited significance with a $P$-value of 2E-3. All five methylation co-function modules demonstrated high significance with a $P$-value less than 1E-3. Additionally, the miRNA co-function module was significant with a $P$-value of 2E-2.

For significant biomarkers, *FAM155B* stood out as a pivotal gene related to the B-type Raf (BRAF) kinase mutation in papillary thyroid cancer. Its expression varied significantly between the wild-type and its mutant counterpart[67]. In addition, Choi et al. formulated a 12-genes predictive model, with *FAM155B* being a key component, leveraging data from the TCGA THCA dataset to potentially forecast nodal metastasis in PTC[68]. Researchers have discovered an elevated expression of *GPR115* in thyroid carcinoma, with its methylation playing a significant role in lung cancer therapy[69]. This suggested that *GPR115* could be instrumental in driving tumor growth. Additionally, a study highlighted the potential of *GPR115* as a connecting factor between tumor advancement and survival prognosis, positioning it as a potential biomarker for LUAD treatment[70]. A study revealed that miR-618 was downregulated in thyroid cancer (TC)[71]. This downregulation was associated with a growth-suppressive effect in TC cells, largely attributed to its targeting of the PI3K/Akt signaling pathway. This finding emphasized the profound connection between miR-618 and TC.

**Table 14:** Important omics biomarkers identified by GREMI in the THCA dataset.

| Omics | Significant Biomarker |
|---|---|
| mRNA | FAM155B, ABHD10, BCAP29, BTBD11, LOC286002 |
| methy | C1orf180, CAPG, GPR115, KLF6, KRT13 |
| miRNA | hsa-mir-618, hsa-mir-1179, hsa-mir-144, hsa-mir-185, hsa-mir-190 |

**Table 15:** Important omics modules identified by GREMI in the THCA dataset.

| Omics | Significant Module |
|---|---|
| mRNA | [BTBD11, CYB5D1, GNA14], [ANKRD46, BTBD11, GNA14] |
| methy | [GPR115, MMP7], [KLF6, MMP7], [MMP7, SNHG3], [GPR115, KRT13], [CAPG, MMP7] |
| miRNA | [hsa-mir-1179, hsa-mir-7-2] |

We performed functional annotations to the mRNA module [*BTBD11, CYB5D1, GNA14*] and the methylation module [*GPR115, MMP7*]. Table 16 and Table 17 show the annotation results of the mRNA and methylation modules, respectively. SMAD protein signal transduction (GO:0060395, $P$ = 1.65E-2) was integral to SMAD family cellular processes, with SMAD3 being a central signaling molecule in the transforming growth factor-$\beta$ (TGF-$\beta$) pathway. This molecule has been implicated in apoptosis, metastasis, and tumor progression[72,73]. A recent study indicated the role of SMAD3 in regulating SPRY4 and SPRY4-IT1 as a transcriptional factor, suggesting its potential association with thyroid cancer predisposition[74]. In addition, calcium signaling pathway (hsa04020, $P$ = 2.86E-2) presented to be highly associated with thyroid cancer. A review highlighted the pivotal role of calcium pathways in thyroid function[75]. For example, proteins of the S100A category was related to multiple malignancies[76], including thyroid tumors. Specifically, proteins like S100A13[77] and S100A4[78] were instrumental in influencing the growth, infiltration, and spread of thyroid carcinoma cells. For the methylation module, Wnt signaling pathway (hsa04310, $P$ = 2.65E-2) was significant. A previous review[79] highlighted the role of Wnt signaling in thyroid physiology, including its development, equilibrium, and tumorigenesis[80]. Individuals with Familial Adenomatous Polyposis (FAP), Gardner's syndrome, or Turcot's syndrome possessing APC gene mutations exhibited heightened thyroid cancer susceptibility due to aberrant Wnt signaling[81,82]. Furthermore, Wnt signaling has been identified as a regulatory factor in Follicular thyroid carcinoma (FTC)[83]. Anaplastic thyroid carcinomas (ATC), recognized as highly aggressive malignancies, frequently exhibited reduced Wnt-5a expression, which was associated with enhanced malignancy[84]. The aforementioned research conclusions directly or potentially confirmed the association between the modules and THCA.

**Table 16:** Significant pathways of the mRNA module of THCA.

| Database | ID | Description | P.adjust |
|---|---|---|---|
| GO | GO:0007212 | dopamine receptor signaling pathway | 1.65E-02 |
| | GO:0060395 | SMAD protein signal transduction | 1.65E-02 |
| | GO:1903351 | cellular response to dopamine | 1.65E-02 |
| | GO:1903350 | response to dopamine | 1.65E-02 |
| | GO:0007200 | phospholipase C-activating G protein-coupled receptor signaling pathway | 1.65E-02 |
| | GO:0071868 | cellular response to monoamine stimulus | 1.65E-02 |
| | GO:0071870 | cellular response to catecholamine stimulus | 1.65E-02 |
| | GO:0071867 | response to monoamine | 1.65E-02 |
| | GO:0071869 | response to catecholamine | 1.65E-02 |
| | GO:0001508 | action potential | 1.97E-02 |
| KEGG | hsa05142 | Chagas disease | 1.82E-02 |
| | hsa05146 | Amoebiasis | 1.82E-02 |
| | hsa04020 | Calcium signaling pathway | 2.86E-02 |

**Table 17:** Significant pathways of the methylation module of THCA.

| Database | ID | Description | P.adjust |
|---|---|---|---|
| GO | GO:0031293 | membrane protein intracellular domain proteolysis | 5.85E-03 |
| | GO:0030574 | collagen catabolic process | 6.60E-03 |
| | GO:0006509 | membrane protein ectodomain proteolysis | 6.60E-03 |
| | GO:0033619 | membrane protein proteolysis | 6.60E-03 |
| | GO:0022617 | extracellular matrix disassembly | 6.60E-03 |
| | GO:0032963 | collagen metabolic process | 8.95E-03 |
| | GO:0030198 | extracellular matrix organization | 1.83E-02 |
| | GO:0043062 | extracellular structure organization | 1.83E-02 |
| | GO:0045229 | external encapsulating structure organization | 1.83E-02 |
| | GO:0022411 | cellular component disassembly | 2.45E-02 |
| KEGG | hsa04310 | Wnt signaling pathway | 2.65E-02 |
| | hsa05166 | Human T-cell leukemia virus 1 infection | 2.65E-02 |

## 2.6 GREMI identified biomarkers related to UCEC.

Table 18 shows the top five significant biomarkers of each type of omics related to the UCEC. As illustrated in Table 19, the mRNA co-function module exhibited significance with a $P$-value of 3E-2. The methylation co-function module demonstrated high significance, with a $P$-value less than 1E-3. All three miRNA co-function modules were significant, each with a $P$-value of 2E-2).

**Table 18:** Important omics biomarkers identified by GREMI in the UCEC dataset.

| Omics | Significant Biomarker |
|---|---|
| mRNA | AACS, C16orf89, ANKLE2, PIAS3, RICH2 |
| methy | CAMK2N1, PPP1R15A, C5orf62, LTBP3, SAP30BP |
| miRNA | hsa-mir-664, hsa-mir-20b, hsa-mir-144, hsa-mir-27a, hsa-mir-508 |

As for the significant biomarkers, endometrial cancer (EC) was the leading gynecologic malignancy in the US. A study revealed that the tumor suppressor gene *PIAS3* showed decreased expression in adipose and uterine tissues, revealing the mechanism of obesity-induced TMEM205 expression and exosome secretion in the pathogenesis of EC[85]. *PPP1R15A*, also termed *GADD34*, was a stress-responsive eIF2$\alpha$ phosphatase that could enhance cell death through increased protein synthesis and activation of death-associated pathways[86]. A recent study identified *PPP1R15A* as an ER stress-associated risk signature for predicting the prognosis of EC patients[87]. In addition, a study on MicroRNA signatures identified distinct patterns among uterine cancer tumor subtypes[88]. Specifically, carcinosarcomas showed a unique miRNA profile with an up-regulation of miR-20b.

**Table 19:** Important omics modules identified by GREMI in the UCEC dataset.

| Omics | Significant Module |
|---|---|
| mRNA | [SRPRB, WASF3] |
| methy | [APOL3, RCC1] |
| miRNA | [hsa-let-7i, hsa-mir-103-1], [hsa-mir-100, hsa-mir-103-1], [hsa-let-7i, hsa-mir-100] |

We performed functional annotations to the mRNA module [*SRPRB, WASF3*] and the methylation module [*APOL3, RCC1*]. Table 20 and Table 21 show the annotation results of the mRNA and methylation modules, respectively. For the mRNA module, there were several pathways associated with the regulation of actin nucleation, including GO:2000601 ($P$ = 1.52E-2), GO:0051127 ($P$ = 1.52E-2), GO:0034315 ($P$ = 1.57E-2), and GO:0051125 ($P$ = 1.60E-2). Arp2/3 complex-mediated actin nucleation (GO:2000601) was significantly influenced by ARPC5, which is a core component of the complex[89]. Deviations in ARPC5 expression can potentially affect the entire function of the complex. Multiple research findings have indicated that ARPC5 promotes tumor expansion and metastasis.[90,91]. Choline metabolism was also enriched. A research[92] suggested that EC exhibited disrupted choline phospholipid metabolism due to heightened expression of choline kinase alpha and an intensified deacylation pathway. This cancer presented marked lipid metabolism anomalies, with elevated phosphocholine levels as the primary lipid alteration. For the methylation module, both GO:0051225 and GO:0007052 were related to the organization and assembly of the spindle. Correct mitotic spindle orientation during cell division was crucial for determining cell fate, orchestrating tissue structure, and guiding development. Alterations in microtubule dynamics affecting the mitotic spindle can cause chromosomal instability, subsequently resulting in the production of tumorigenic cells[93,94]. Li et al. also identified the mitotic spindle from the result of gene set enrichment analysis[95]. They found that mitotic spindles played roles in DNA damage repair and cell cycle control. Disruptions in these pathways frequently correlated with tumor initiation and advancement. Previous research findings directly or potentially confirmed the association between the modules and UCEC.

**Table 20:** Significant pathways of the mRNA module of UCEC.

| Database | ID | Description | P.adjust |
|---|---|---|---|
| GO | GO:0098885 | modification of postsynaptic actin cytoskeleton | 1.52E-02 |
| | GO:2000601 | positive regulation of Arp2/3 complex-mediated actin nucleation | 1.52E-02 |
| | GO:0099010 | modification of postsynaptic structure | 1.52E-02 |
| | GO:0051127 | positive regulation of actin nucleation | 1.52E-02 |
| | GO:0031643 | positive regulation of myelination | 1.52E-02 |
| | GO:0099563 | modification of synaptic structure | 1.52E-02 |
| | GO:0034315 | regulation of Arp2/3 complex-mediated actin nucleation | 1.57E-02 |
| | GO:0051125 | regulation of actin nucleation | 1.60E-02 |
| | GO:0031646 | positive regulation of nervous system process | 1.60E-02 |
| | GO:0014003 | oligodendrocyte development | 1.60E-02 |
| KEGG | hsa03060 | Protein export | 3.29E-02 |
| | hsa04520 | Adherens junction | 3.48E-02 |
| | hsa04666 | Fc gamma R-mediated phagocytosis | 3.48E-02 |
| | hsa05231 | Choline metabolism in cancer | 3.48E-02 |

**Table 21:** Significant pathways of the methylation module of UCEC.

| Database | ID | Description | P.adjust |
|---|---|---|---|
| GO | GO:0007084 | mitotic nuclear membrane reassembly | 1.44E-02 |
| | GO:0101024 | mitotic nuclear membrane organization | 1.44E-02 |
| | GO:0031468 | nuclear membrane reassembly | 2.45E-02 |
| | GO:0071763 | nuclear membrane organization | 2.82E-02 |
| | GO:0006998 | nuclear envelope organization | 2.82E-02 |
| | GO:0071709 | membrane assembly | 2.82E-02 |
| | GO:0044091 | membrane biogenesis | 2.82E-02 |
| | GO:0007088 | regulation of mitotic nuclear division | 3.42E-02 |
| | GO:0051225 | spindle assembly | 3.42E-02 |
| | GO:0007052 | mitotic spindle organization | 3.42E-02 |

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