

# geneDRAGGN Supplementary Material

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## 1 Literature-based Validation of Top Prioritized Genes

Table 1: A detailed literature analysis of some of the top predicted genes associated with LUAD from the SGConv model. \* indicates that the result was predicted with the MLP model.

| Rank | Gene  | Gene functional description and Literature review   |
|------|-------|---|
| 2    | CDC42 | This gene encodes a member of the Rho subfamily of small GTP-binding proteins and plays a key role in cancer cell migration and metastasis. [1, 2] found decreased levels of StarD13, a suppressor of CDC42, in lung tumor tissue and A549 cells subsequently leading to increased CDC42 activation thus increasing formation of invadopodia, a unique hallmark of cancer, and matrix degradation.  |
| 3    | PTPRC | This gene encodes a tyrosine-protein phosphatase required for T-cell activation. Upon T-cell activation, PTPRC recruits and dephosphorylates FYN which has been shown to be correlated with LUAD by [1]. [3] directly supports PTPRC association with LUAD by demonstrating that PTPRC was a key gene in affecting the immune state of the tumor microenvironment and was ultimately correlated with a variety of tumor-infiltrating immune cells.  |
| 4    | LRRK2 | In an analysis of TCGA LUAD RNA-seq data, [4] identified that decreased LRRK2 expression is associated with LUAD. In [5], reduced LRRK2 expression was found to promote LUAD tumorigenesis and was associated with poor survival outcomes. This study also found overactivity in LRRK2 contributes to Parkinson’s disease, which suggests pathological links between neurodegenerative disease and cancer are emerging.   |
| 5    | CREB1 | This gene encodes a phosphorylation-dependent transcription factor that stimulates transcription upon binding to DNA cAMP response element (CRE) [1]. [6] used protein expression assays to understand the underlying mechanism of ferroptosis, a new form of regulated cell death associated with cancer, in LUAD. They found that CREB was highly expressed in LUAD and knockdown of CREB inhibited cell viability and growth by promoting apoptosis- and ferroptosis-like cell death.  |
| 8    | ISG15 | ISG15 acts as a cytokine, modulating immune responses, and can delay tumor cell growth by inhibiting tumor cell proliferation and angiogenesis. [7] found that high expression of ISG15 serves as a positive prognostic marker for long-term survival in LUAD patients. ISG15 has a broad network of protein targets, and [8] concludes that covalent ISG15 conjugation enhances the tumor-suppressive activity of the carboxyl terminus of Hsp70-interacting protein (CHIP), thereby showing an antitumor effect of Type 1 interferon. |

|        |       |  |
|--------|-------|--|
| 9      | FYN   | FYN encodes a tyrosine-protein kinase essential in cell motility and adhesion and plays an important role in the PI3K/AKT pathway responsible for regulating the cell cycle [1]. [9] demonstrated that overexpression of FYN accelerated cell apoptosis and reduced both angiogenesis capacity and PI3K/AKT expression levels in lung carcinoma A549 cells. Conversely, FYN expression was shown to be correlated with LUAD prognosis as FYN expression levels were shown to be down-regulated in LUAD tissues and cells .   |
| 10     | ITGB1 | ITGB1 encodes the Integrin beta-1 subunit which when associated with Integrin alpha-3 provides a docking site for FAP, a serine protease involved in extracellular matrix degradation and tumor growth, at invadopodia plasma membranes. Hence ITGB1 may participate in formation of invadopodia, matrix degradation, and can promote cell invasion [1]. Immune infiltration analysis revealed that the ITGB1-DT/ARNTL2 axis may effect the progression of LUAD and the immune microenvironment. ITGB1-DT/ARTL2 [10]   |
| 4800*  | FTL   | A study published in 2021 demonstrated a negative correlation between high expression of FTL or LUAD malignancy and a decrease in lipid peroxidation and labile. [11] In an RNA-sequencing study, FTL and FTH1 expression levels were significantly positively correlated with tumor infiltration by tumor-associated macrophages and T regulatory cells. [12] Ferritin light chain (FTL) and ferritin heavy chain (FTH1) were compared and FTL subunits had higher expression levels for LUAD than its heavy chain iron counterpart. FTL also had higher expression for tumorous tissues in most types of cancer, and LUAD showed higher levels of expression and tumor tissue (in comparison to other subtypes of cancer) for the FTL experiment [12]  |
| 12626* | TFF3  | It is involved in the maintenance and repair of the intestinal mucosa. It also promotes the mobility of epithelial cells during healing [1] The highest classified gene from the MLP node-only model is TFF3. This gene was excluded from the training set because it had a GDA score of 0.01, but an association has already been detected by DisGeNet. In 2021, for the first time it was shown that TFF3 was associated with sub diseases of LUAD and was specifically associated with LUAD invasiveness [13]. In 2019, TFF3 was identified as a biomarker to be able to distinguish between LUAD and lung squamous-cell carcinoma (SCC) [14]. In [14], over 90% of LUAD was observed to be TFF3 positive, whereas no TFF3 expression was observed in cases of SCC, suggesting TFF3 is an insightful biomarker that enables experts to distinguish and diagnose subtypes of non-small cell lung cancer (NSCLC). |

## 2 Functional Enrichment Analysis

Table 2: Functional Enrichment Top 10 genes

| Category         | Term  | Count | P-value              |
|------------------|---|-------|----------------------|
| GOTERM_MF_DIRECT | Identical protein binding                                     | 6     | $1.8 \times 10^{-5}$ |
| GOTERM_BP_DIRECT | vascular endothelial growth factor receptor signaling pathway | 3     | $6.4 \times 10^{-4}$ |
| GOTERM_CC_DIRECT | plasma membrane   | 8     | $7.0 \times 10^{-4}$ |
| GOTERM_CC_DIRECT | focal adhesion  | 4     | $7.5 \times 10^{-4}$ |
| GOTERM_BP_DIRECT | ephrin receptor signaling pathway                             | 3     | $9.1 \times 10^{-4}$ |
| GOTERM_BP_DIRECT | Fc-gamma receptor signaling pathway involved in phagocytosis  | 3     | $2.0 \times 10^{-3}$ |
| GOTERM_BP_DIRECT | negative regulation of gene expression                        | 3     | $2.3 \times 10^{-3}$ |
| GOTERM_BP_DIRECT | positive regulation of GTPase activity                        | 4     | $2.7 \times 10^{-3}$ |
| GOTERM_BP_DIRECT | axon guidance   | 3     | $3.1 \times 10^{-3}$ |
| GOTERM_CC_DIRECT | membrane raft   | 3     | $4.3 \times 10^{-3}$ |
| GOTERM_CC_DIRECT | external side of plasma membrane                              | 3     | $4.6 \times 10^{-3}$ |
| GOTERM_CC_DIRECT | extracellular exosome   | 6     | $6.4 \times 10^{-3}$ |
| GOTERM_BP_DIRECT | MAPK cascade  | 3     | $8.1 \times 10^{-3}$ |
| GOTERM_BP_DIRECT | cellular response to platelet-derived growth factor stimulus  | 2     | $9.6 \times 10^{-3}$ |
| GOTERM_CC_DIRECT | cytosol   | 6     | $1.3 \times 10^{-2}$ |
| GOTERM_BP_DIRECT | sarcomere organization  | 2     | $1.5 \times 10^{-2}$ |
| GOTERM_CC_DIRECT | membrane  | 5     | $1.6 \times 10^{-2}$ |

Table 3: Functional Enrichment Top Decile genes

| Category         | Term                              | Count | P-value                |
|------------------|-----------------------------------|-------|------------------------|
| GOTERM_MF_DIRECT | protein binding                   | 1076  | $1.7 \times 10^{-102}$ |
| GOTERM_CC_DIRECT | cytosol                           | 562   | $1.3 \times 10^{-94}$  |
| GOTERM_CC_DIRECT | extracellular exosome             | 451   | $5.5 \times 10^{-64}$  |
| GOTERM_CC_DIRECT | nucleoplasm                       | 410   | $7.5 \times 10^{-47}$  |
| GOTERM_CC_DIRECT | extracellular matrix              | 104   | $1.6 \times 10^{-42}$  |
| GOTERM_BP_DIRECT | T cell receptor signaling pathway | 71    | $2.7 \times 10^{-37}$  |
| GOTERM_CC_DIRECT | membrane                          | 320   | $3.8 \times 10^{-34}$  |
| GOTERM_CC_DIRECT | cell surface                      | 131   | $4.7 \times 10^{-34}$  |
| GOTERM_BP_DIRECT | inflammatory response             | 111   | $5.9 \times 10^{-34}$  |
| GOTERM_BP_DIRECT | NIK/NF-kappaB signaling           | 46    | $6.4 \times 10^{-34}$  |

Table 4: Functional Enrichment MLP

| Category         | Term                                   | Count | Percent | P-value               |
|------------------|--|-------|---------|-----------------------|
| GOTERM_CC_DIRECT | intracellular ferritin complex         | 2     | 20      | $9.87 \times 10^{-4}$ |
| GOTERM_CC_DIRECT | cell                                   | 3     | 30      | 0.001 047             |
| GOTERM_MF_DIRECT | iron ion binding                       | 3     | 30      | 0.002 205             |
| GOTERM_BP_DIRECT | intracellular sequestering of iron ion | 2     | 20      | 0.003 212             |
| GOTERM_CC_DIRECT | autolysosome                           | 2     | 20      | 0.003 945             |
| GOTERM_MF_DIRECT | ferric iron binding                    | 2     | 20      | 0.004 73              |
| GOTERM_CC_DIRECT | extracellular region                   | 5     | 50      | 0.005 32              |
| GOTERM_BP_DIRECT | iron ion transport                     | 2     | 20      | 0.006 415             |
| GOTERM_CC_DIRECT | endocytic vesicle lumen                | 2     | 20      | 0.007 876             |
| GOTERM_BP_DIRECT | translational elongation               | 2     | 20      | 0.009 608             |
| GOTERM_CC_DIRECT | cytosol                                | 6     | 60      | 0.013 053             |
| GOTERM_BP_DIRECT | cellular iron ion homeostasis          | 2     | 20      | 0.023 342             |
| GOTERM_MF_DIRECT | protein binding                        | 8     | 80      | 0.045 004             |
| GOTERM_BP_DIRECT | platelet degranulation                 | 2     | 20      | 0.053 882             |
| GOTERM_CC_DIRECT | blood microparticle                    | 2     | 20      | 0.072 625             |
| GOTERM_CC_DIRECT | cytoplasm                              | 6     | 60      | 0.083 113             |
| GOTERM_BP_DIRECT | receptor-mediated endocytosis          | 2     | 20      | 0.095 407             |

### 3 KEGG Pathway Enrichment

Table 5: KEGG Pathway Enrichment Top 10

| Category     | path                                   | Count | p-value              |
|--------------|--|-------|----------------------|
| KEGG_PATHWAY | Pathogenic Escherichia coli infection  | 4     | $3.1 \times 10^{-5}$ |
| KEGG_PATHWAY | Focal adhesion                         | 4     | $1.9 \times 10^{-3}$ |
| KEGG_PATHWAY | Shigellosis                            | 3     | $2.9 \times 10^{-3}$ |
| KEGG_PATHWAY | Adherens junction                      | 3     | $3.6 \times 10^{-3}$ |
| KEGG_PATHWAY | Bacterial invasion of epithelial cells | 3     | $4.3 \times 10^{-3}$ |
| KEGG_PATHWAY | Salmonella infection                   | 3     | $4.9 \times 10^{-3}$ |
| KEGG_PATHWAY | T cell receptor signaling pathway      | 3     | $7.0 \times 10^{-3}$ |
| KEGG_PATHWAY | Leukocyte transendothelial migration   | 3     | $9.2 \times 10^{-3}$ |
| KEGG_PATHWAY | Axon guidance                          | 3     | $1.1 \times 10^{-2}$ |
| KEGG_PATHWAY | Platelet activation                    | 3     | $1.2 \times 10^{-2}$ |

Table 6: KEGG Pathway Enrichment Top Decile

| Category     | path                                      | Count | p-value               |
|--------------|---|-------|-----------------------|
| KEGG_PATHWAY | Epstein-Barr virus infection              | 58    | $2.2 \times 10^{-17}$ |
| KEGG_PATHWAY | Pathways in cancer                        | 120   | $6.4 \times 10^{-16}$ |
| KEGG_PATHWAY | Measles                                   | 59    | $6.8 \times 10^{-16}$ |
| KEGG_PATHWAY | PI3K-Akt signaling pathway                | 106   | $2.8 \times 10^{-14}$ |
| KEGG_PATHWAY | Osteoclast differentiation                | 56    | $3.0 \times 10^{-14}$ |
| KEGG_PATHWAY | Toxoplasmosis                             | 49    | $2.3 \times 10^{-13}$ |
| KEGG_PATHWAY | TNF signaling pathway                     | 48    | $3.1 \times 10^{-13}$ |
| KEGG_PATHWAY | Proteasome                                | 28    | $1.7 \times 10^{-12}$ |
| KEGG_PATHWAY | Chagas disease (American trypanosomiasis) | 44    | $3.7 \times 10^{-11}$ |
| KEGG_PATHWAY | HTLV-I infection                          | 79    | $4.5 \times 10^{-11}$ |

### 4 Model Parameters

The MLPs used a simple architecture with 2 hidden layers of 128 units each and ReLU activation, implemented with PyTorch [15]. The number of estimators of the random forests was set to 100. The K-Nearest Neighbors classifier used  $k=5$  and the standard euclidean metric. The Support Vector Machine classifier used the Radial Basis Function kernel. Random Forests, K-Nearest Neighbours, and Support Vector Machine classifiers were implemented with Sci-Kit Learn [16].

Our implementations used the ‘PyTorch Geometric’ library [15]. First, we converted LS-fGIN to a format readable by PyTorch Geometric by mapping our Ensembl gene identifiers to a 0-based indexing system and creating an edge list of shape `[2, n_edges]`. The edge features, which are not used by all our models, are represented by `[n_edges, n_edge_feats]` tensors. The Adam optimizer is used [17] with the cross-entropy loss and models are trained for 250 epochs. Throughout the training process, the model is evaluated on the training and validation sets, and model checkpoints are saved along the way. At the end of the 250 epochs, the model with the highest validation accuracy is restored and evaluated on the test set. This completes one trial.

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