**“Beyond Differential Expression: Deep Neural Profiling Reveals RAP1GAP2 as a Latent Regulator of Tumor Invasion in Oropharyngeal Carcinoma”**

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**A dissertation submitted to the Shahjalal University of Science and Technology in partial fulfillment of the requirements for the Bachelor of Science (BSc) Degree in Biochemistry and Molecular Biology**

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**Dedicated To,**

**My Beloved Parents**

**My Respected Teachers**

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Foremost, I want to express my gratitude to Almighty Allah for the wisdom, strength, peace of mind, and good health. He bestowed upon me to complete my dissertation.

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**Joy Prokash Debnath**

7th July 2025

**To Whom It May Concern**

I hereby certify that in accordance with the laws of Shahjalal University of Science and Technology, Sylhet-3114, Bangladesh, the project work entitled **“Beyond Differential Expression: Deep Neural Profiling Reveals RAP1GAP2 as a Latent Regulator of Tumor Invasion in Oropharyngeal Carcinoma”**described here is entirely own work of **Joy Prokash Debnath** bearing Registration No. **2019433077**, **Session:** 2019-2020. This project does not contain any materials which were previously published or written by another person, except duly referred. The work was conducted under my supervision and was enrolled in the degree of Bachelor of Science in Biochemistry and Molecular Biology at the Shahjalal University of Science and Technology, Sylhet-3114, Bangladesh. All information provided in the project paper has been obtained and presented following academic rules and ethical guidelines.

I hereby endorse his project to be submitted for evaluation.

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**Abbreviations**

|  |  |
| --- | --- |
| Abbreviation | Full Form |
| OC | **Oropharyngeal Carcinoma** |
| DGE | **Differential Gene Expression** |
| PCA | **Principal Component Analysis** |
| PEM | **Probabilistic Embedding Model** |
| SBS | **Sensitivity-Based Scoring** |
| GSEA | **Gene Set Enrichment Analysis** |
| IG | **Integrated Gradients** |
| GEO | **Gene Expression Omnibus** |
| NES | **Normalized Enrichment Score** |
| AUROC | **Area Under the Receiver Operating Characteristic curve** |
| AUPRC | **Area Under the Precision–Recall Curve** |
| KEGG | **Kyoto Encyclopedia of Genes and Genomes** |
| GO | **Gene Ontology** |

# **Abstract**

**Background:** Traditional differential gene expression analysis doesn't fully capture the complex molecular changes that drive the progression of oropharyngeal carcinoma (OC). Probabilistic Embedding Models (PEMs) are a deep learning method that can find hidden patterns in high-dimensional transcriptomic data. This could help find molecular drivers of cancer that other methods miss.

**Methods:** We combined gene expression datasets from multiple cohorts and trained a PEM to compress the data into a small, hidden space. We used Integrated Gradients, an explainable AI attribution method, to figure out how much each gene added to each latent feature. Genes that consistently had high attribution scores across all latent dimensions were chosen as potential regulators. We used pathway enrichment and classification analyses to learn more about the biological importance of these genes.

**Results:** The PEM learned latent features that are biologically important, and Integrated Gradients showed a group of genes that have a big impact on these features. RAP1GAP2 was consistently one of the top contributors across all 50 latent variables, which is a big deal. RAP1GAP2 had the highest latent-space importance and strong discriminative power for telling OC apart, with an area under the precision–recall curve of 0.769. This was even though it didn't show any significant differential expression in tumors compared to normal samples. Biological interpretation suggests that RAP1GAP2, a protein that activates Rap1 GTPase, may help tumors invade by turning off Rap1 and changing MAPK signaling and Golgi-mediated secretion.

**Conclusion:** Our deep learning framework found RAP1GAP2 to be a hidden driver in oropharyngeal carcinoma. This shows how PEMs and Integrated Gradients can find molecular regulators that other methods miss. This method gives us new information about the biology of OC tumors that could help with future research and treatment.

**Keywords:** Oropharyngeal carcinoma; transcriptomics; deep learning; latent features; RAP1GAP2; Rap1 signaling; MAPK pathway; Golgi secretion

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**Chapter One**

# **Introduction**

## **1.1 Significance of Oropharyngeal Carcinoma**

One type of head and neck cancer that has significant clinical significance is oropharyngeal carcinoma (OC). Human papillomavirus (HPV) infection has contributed to the increase in its incidence in recent decades, making HPV-positive oropharyngeal squamous cell carcinoma one of the cancers that is growing the fastest in many high-income nations (Lechner et al. 2022). Because of its subtle early symptoms, OC frequently manifests at advanced stages, leading to substantial morbidity and mortality. Therefore, a deeper comprehension of the molecular foundations of OC is urgently needed to facilitate earlier detection, better patient stratification, and more successful precision therapies (Sabbatini and Manganaro 2023). Results for advanced OC are still uncertain despite advancements in systemic treatments, radiation therapy, and surgery. Gaining a better understanding of the transcriptome landscape of the tumor may help identify new molecular drivers that could enhance patient care.

## **1.2 Complexity of Cancer Biology and Analytical Gaps**

The biology of cancer is extraordinarily complex, involving non-linear interactions among genes and pathways that drive tumor behavior. Traditional differential gene expression (DGE) analysis – which typically relies on linear models or statistical tests to find genes individually up- or down-regulated in tumors – has clear limitations when faced with this complexity. DGE methods excel at identifying genes with large average expression changes, but they may overlook hidden drivers that exert their effects through subtle or combinatorial patterns.

In other words, patient subgroups or tumor phenotypes could be determined by gene sets that do not show obvious one-at-a-time differences and thus remain “invisible” to linear DGE approaches (Rampášek et al. 2019). Indeed, recent work has cautioned that when nonlinear machine learning models identify patient groupings, the defining gene signatures might be missed by conventional DGE due to its linear nature (Rampášek et al. 2019).

Such underappreciated genes or gene interactions may be crucial for the development of cancer, making this gap problematic. Analytical techniques that can capture the nonlinear dependencies in gene expression data and go beyond linear assumptions are required. One potential remedy is explainable algorithms (machine learning), which can reveal multivariate gene patterns that would otherwise go unnoticed by applying interpretability techniques to complex models (Abbas and El-Manzalawy 2020; Way et al. 2020). In conclusion, techniques that can model and explain the complex, nonlinear relationships that define cancer biology are necessary to overcome the shortcomings of DGE.

## **1.3 Deep Learning for Latent Feature Discovery**

We use deep learning—more especially, unsupervised deep neural networks—to learn biologically significant latent variables from transcriptomic data in order to overcome these difficulties. A class of deep generative models that are ideal for this task are Probabilistic Embedding Models (PEMs). A PEM preserves as much information as possible while compressing high-dimensional gene expression profiles into a lower-dimensional latent space. Complex gene expression patterns can be reduced by this method to a collection of latent features that capture patient variability and underlying biological signals. Large-scale gene expression datasets have seen the successful application of PEMs and related autoencoder techniques, which have shown promise in modeling non-linear gene interactions and enhancing outcome predictions (Sundararajan et al. 2017). To illustrate the ability of deep learning to capture subtle transcriptomic effects of treatment, Rampášek et al. demonstrated that a PEM-based model ("Dr.PEM") could learn latent representations of cancer cell line expression data that improve drug response prediction (Zhang et al. 2006). Similar to this, Way et al. used PEM to compress pan cancer gene-expression data and discovered that different biological signals (like pathway activities and mutational status) emerged when the latent dimensionality was varied. This suggests that deep compression can learn complementary aspects of tumor biology that are not possible with a single linear compression or DGE analysis (Way et al. 2020). These studies demonstrate how deep neural networks can identify patterns in gene expression data that conventional methods might miss by extracting non-linear features.

However, a known drawback of deep learning models is their limited interpretability – the latent features or learned representations are “black boxes” without clear biological meaning. In the context of cancer transcriptomics, it is not enough to discover latent variables; we also need to understand which genes those variables represent or how they relate to known biology. Simply compressing data with a PEM might yield abstract features that correlate with disease, but without interpretation we cannot translate those features into testable biological insights. This motivates integrating explainable AI techniques into our deep learning pipeline.

## **1.4 Gene Attribution with Integrated Gradients**

To interpret the latent space and connect it back to gene-level biology, we employ integrated gradients, a robust feature attribution method for neural networks. Integrated gradients provide a way to quantify the contribution of each input feature (in this case, each gene’s expression) to a given output or latent variable in the model (Janizek et al. 2023). Formally, integrated gradients work by integrating the gradients of the model’s output with respect to inputs along a path from a baseline to the actual input, yielding an attribution score for every feature that satisfies desirable axioms of fairness and sensitivity (Janizek et al. 2023). Introduced by Sundararajan et al. in 2017, this method has become a popular tool for explaining deep learning predictions in various domains (Janizek et al. 2023). In our study, we harness integrated gradients to attribute genes to latent variables learned by the PEM and to any downstream predictive outputs. This approach effectively “opens the black box” of the autoencoder by highlighting which genes most strongly influence each latent dimension of the model.

Notably, earlier studies have shown how useful it is to combine feature attribution and deep generative models in genomics. For instance, Dincer et al. identified the top contributing genes for each latent dimension by applying integrated gradients to the latent features of a PEM trained on cancer gene expression data (Janizek et al., 2023). Researchers can anchor abstract features in concrete biology by using this post hoc interpretation of latent space. For example, based on the genes with the highest attributions, a latent dimension may end up representing a pathway or cell cycle signature. Building on these concepts, we derive gene-level importance scores for the learned latent factors by combining our PEM with integrated gradients. By doing this, we can identify the genes that are most important for differentiating oropharyngeal tumors from controls (or other tumor subtypes) and that drive the variations recorded in the latent space. In addition to maintaining interpretability, this combination of unsupervised deep learning and explainability techniques enables us to find biologically significant patterns that would be missed by linear analysis alone.

## **1.5 Revealing Hidden Drivers: The Case of *RAP1GAP2***

By using this deep learning framework on OC transcriptomic data, new understandings of the molecular causes of the disease are revealed. Integrated gradients identify the genes that define the latent variables that the variational autoencoder extracts and that summarize gene expression patterns across tumors. Our analysis reveals that RAP1GAP2 is a crucial latent driver gene in oropharyngeal carcinoma, which is intriguing. The GTPase-activating protein encoded by RAP1GAP2 controls the small GTPase Rap1, a signaling molecule implicated in adhesion and cell proliferation. With a high attribution score, RAP1GAP2 stands out in our model as one of the main contributors to a latent feature that is very predictive of the presence of OC. This finding is noteworthy because, according to standard differential expression analysis, RAP1GAP2 was not identified as significant; that is, its average expression levels between tumor and normal do not differ sufficiently to meet standard statistical thresholds. RAP1GAP2 would have been completely overlooked by traditional DGE, but our deep learning method revealed it to be a significant participant with a nonlinear contribution to the tumor transcriptome. The impact of RAP1GAP2 only becomes apparent when taking into account intricate interactions recorded in the latent space, demonstrating how deep learning can uncover "hidden" drivers that elude linear analysis. This finding emphasizes the benefit of employing a non-linear model.

From a biological standpoint, the implication of RAP1GAP2 in OC is plausible and generates new hypotheses. Although RAP1GAP2 itself has not been well-studied in oropharyngeal cancer, it belongs to the same family as Rap1GAP (also known as RAP1GAP1), which has been reported to act as a tumor suppressor in squamous cell carcinoma. In fact, restoring Rap1GAP expression in OC cell lines was shown to reduce active Rap1 signaling and significantly slow tumor growth in vivo (Zhang et al. 2006). This prior evidence of the Rap1 pathway’s involvement in head and neck cancer provides context for our findings: it suggests that downregulation or dysregulation of Rap1-inhibitory proteins (like Rap1GAP or RAP1GAP2) could contribute to oncogenic processes in the oropharynx. Our discovery of RAP1GAP2 as a latent driver, despite its subtle expression changes, underscores how deep learning-based analysis can pinpoint functionally relevant genes that conventional analyses deem insignificant. Such genes might represent early changes or context specific vulnerabilities that are missed when focusing only on large fold-changes. Identifying RAP1GAP2 as highly predictive of OC opens the door to further experimental validation and investigation into its potential role in tumor suppression or as a biomarker for disease presence.

## **1.6 Hypothesis and Objective**

Given the aforementioned factors, we postulate that latent transcriptomic characteristics and gene drivers of oropharyngeal carcinoma that are not discernible using conventional linear techniques can be revealed by deep neural network models. These models have the potential to uncover biological signals that are essential to the pathophysiology of OC by capturing nonlinear combinations of gene expression changes. Our study's goal is to find new gene-level drivers of oropharyngeal carcinoma by combining supervised gene attribution and unsupervised latent space modeling. In particular, we use integrated gradients to assign genes to the learned latent features (and to any predictive model based on them) after using a variational autoencoder to learn a compressed representation of OC transcriptomic data. Our goal is to use deep learning to enhance our molecular understanding of oropharyngeal cancer beyond the scope of differential expression analysis by identifying hitherto unknown genes and pathways that cause the disease.

**Chapter Two**

# **Material and Methods**

## **2.1 Overview of the Study**

The design of the overall study is illustrated in **Figure 2.1**

A diagram of a computer

AI-generated content may be incorrect.**Figure 2.1 Overview of the study pipeline.** PCA-transformed multi-dataset gene expression is encoded via PEM to latent space, followed by Integrated Gradients-based gene attribution and supervised learning to identify molecular drivers and extract biological insights of the latent spaces.

## **2.2 Datasets Retrieval**

Publicly available gene-expression datasets of oral carcinoma (OC) generated using different platforms—including [HG-U133\_Plus\_2] Affymetrix Human Genome U133 Plus 2.0 Array, [HG-U133A] Affymetrix Human Genome U133A Array, Illumina NextSeq 500 (Homo sapiens)—were downloaded. A total of 19 datasets were parsed from the National Center for Biotechnology Information (NCBI) (<https://www.ncbi.nlm.nih.gov/>) Gene Expression Omnibus (GEO) (<https://www.ncbi.nlm.nih.gov/geo/>) database for Oral Cancer types, where a python library **GEOparse v2.0.0** (<https://github.com/guma44/GEOparse>) was incorporated to extract the sequencing data with their phenotype data from the database server. All information about the datasets including sample size mentioned in **Table 2.1.**

# **Table 2.1 Expression Profiling Datasets for OC**

|  |  |  |  |
| --- | --- | --- | --- |
| **GEO\_Accession** | **Samples** | **Platform** | **Study\_Type** |
| GSE37991 | 80 (40 tumor + 40 normal) | GPL6883 (Illumina HumanRef‑8) | Expression profiling by array |
| GSE23558 | 31 (27 tumor + 4 normal) | GPL6480 (Agilent 44K) | Expression profiling by array |
| GSE25099 | 79 (57 tumor + 22 normal) | GPL5175 (Affymetrix Exon ST) | Expression profiling by array |
| GSE10121 | 41 (35 tumor + 6 normal) | Operon Oligoset 4.0 | Expression profiling by array |
| GSE31853 | 11 (8 tumor cell lines + 3 normal) | GPL96/570 (Affymetrix) | Expression profiling by array |
| GSE131182 | 12 (6 paired tumor + normal) | GPL20301 (Illumina HiSeq) | Expression profiling by RNA‑seq |
| GSE145272 | 10 (5 metastatic + 5 non-metastatic) | HiSeq 2500 RNA‑seq | Expression profiling by RNA‑seq |
| GSE217142 | 6 (primary + recurrent tumors) | NovaSeq 6000 RNA‑seq | Expression profiling by RNA‑seq |
| GSE85195 | 49 (34 OSCC + 15 OPL) | GPL6480 (Agilent 44K) | Expression profiling by array |
| GSE168227 | 6 paired tumor-normal samples | Agilent lncRNA microarray | Expression profiling by array |
| GSE84805 | 6 paired tumor-normal samples | Agilent lncRNA array | Expression profiling by array |
| GSE30784 | 229 total (167 tumor + others) | GPL570 (Affymetrix U133 Plus 2.0) | Expression profiling by array |
| GSE2280 | 32 (27 non-metastatic + 5 metastatic) | GPL96 (Affymetrix U133A) | Expression profiling by array |
| GSE3524 | 20 (16 tumor + 4 normal) | GPL96 (Affymetrix U133A) | Expression profiling by array |
| GSE6791 | 154 (119 tumor + 35 controls) | Affymetrix U133 Plus 2.0 | Expression profiling by array |
| GSE41442 | 55 (45 tumor + 10 normal) | GPL570 (Affymetrix) | Expression profiling by array |
| GSE37371 | 100 (50 tumor + 50 normal) | GPL96 (Affymetrix) | Expression profiling by array |
| GSE23030 | 30 metastatic tongue OSCC | GPL5175 (Affymetrix Exon ST) | Expression profiling by array |
| GSE29000 | 50 (40 tumor + 10 normal) | GPL570 (Affymetrix) | Expression profiling by array |

Extracted results according to the supplied GEO accession ids filtered out based on the treatment and condition of the samples. We got a total of 1001 samples from all the datasets combined, where sample number with OC positive was 754. Samples treated with radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy and drugs were excluded from the study manually.

## **2.3 Data Integration, Batch Effect Removal and Preprocessing**

To amalgamate data from different platforms, a python data analysis library pandas v1.5.3 (McKinney 2011) was incorporated. Data imputation was conducted by missForest v0.9 (Stekhoven and Bühlmann 2012) package in R to avoid the NA values in the datasets. For concatenating multiple datasets from multiple platforms with different techniques, a batch effect correction method based on python library was applied on the integrated data to combat the platform specific biases. A function called “ComBat” from python library pyComBat v0.3.2 (Behdenna et al. 2023) was used to remove the technical biases that arose by the integration process. Expression data of merged dataset was log-transformed, Z-standardized on each gene to ensure that all features are on the same scale.

## **2.4 Training Deep Neural Network Models**

### **2.4.1 Datasets Merging and Standardization**

After manual selection and preprocessing, we had 663 cancer-positive samples, each containing 11020 genes—common in all datasets. Despite the high dimensional gene expression matrix, which was complex to interpret the samples with their condition, a principal component analysis was conducted with 500 PCs (n\_components=500) while preserving all important data and variance among the samples. PCA was performed in R using the following packages: stats v4.2.3, factoextra v1.0.7 (Kassambara and Mundt 2020) for extraction and display of PCA results, and dplyr v1.1.4 (Hadley Wickham et al. 2020) for data manipulation.

### **2.4.2 Traditional Deep Learning Model**

A probabilistic latent variable model was built on reduced PC data to learn a compact, non-linear delineation of the high-dimensional gene expression data. This is a type of neural network that contains an encoder and a decoder network with an entropy-limited latent mapping with *D* latent variables (here, *D* *≪* *M*, where *M=500PC*,represents the number of features) in the middle. This process generates an embedding *Z*, which preserves the whole information of the input (*500PC*) into a lower dimensional space (Bro and Smilde 2014). Categorically, the encoder network, defined as , maps from the input space to latent embedding . Similarly, the decoder network, defined as maps the embedding Z back to input space. The main objective of the model is to minimize the anticipated squared Euclidean (L2) norm (Tian et al. 2017) between the input and its reconstruction:

Here, and are the parameters of the encoder and decoder, respectively, and represents the reconstructed input for every sample. Where, L2 loss denoted by , captures the total reconstruction error across all dimensions of the input. Overtly, this corresponds to:

### **2.4.3 Additional Sample Distribution**

Unlike conventional approach, we used probabilistic embedding model (PEM), which encodes each sample as a probability distribution—captures uncertainty and biological variability inherent in gene expression profiles. Samples with 500 principal components (PCs) were used to construct the input matrix , where is the number of samples and is the number of features. This matrix was passed to an encoder , which outputs a mean vector and a variance vector :

**.**

A decoder reconstructs the input from the sampled latent vector . The model is trained to minimize the following loss:

The first term ensures accurate reconstruction, while the KL divergence regularizes the latent space by encouraging it to resemble a standard (Pan et al. 2020). After training, the learned latent variables were used for gene importance analysis using Integrated Gradients, followed by pathway enrichment.

## **2.5 Neural Network Design and Hyperparameter Optimization**

### **2.5.1 Train Model with Adam Optimizer**

PEM models were trained to unite the PCs from the OC gene expression matrix as inputs. Three-layer encoder and decoder networks were designed as a mirror of each other. The model was trained in batches of 50 samples by using (Wang et al. 2022), with a learning rate of 0.0005, with weight initialized randomly using the Glorot uniform method.

### **2.5.2 Cross validate and Extract Best Latent Dimension**

To determine the best fitted latent space as per my study, we deliberately selected a set of sizes: 5, 10, 25, 50, 75, and 100. This comprehensive selection was made to give our models a broad scope to capture a wide range of information from the datasets. Hyperparameter tuning was performed to fine-tune hyperparameters including the dropout rate and the number of neurons per layer using 5-fold cross-validation, guided by validation reconstruction error (Elgeldawi et al. 2021). We tested dropout values including 0, 0.2, 0.4, and 0.6. For hidden layer configurations, we explored multiple settings such as (50, 5), (100, 25), (250, 50), (250, 100), and (300, 150), where the first and second values indicate the number of neurons in the first and second hidden layers, respectively. The model was implemented in Python using Keras v2.2.4 (Chollet 2015) and TensorFlow v1.12.0 (Filus and Domańska 2023).

## **2.6 Learning Robust Latent Representations**

To find out the stable and fruitful biological representation of the data, PEMs were trained with different random initializations and latent dimensionalities. For each latent size, training across multiple random seeds was repeated, resulting in a large collection of embeddings. To aggregate latent variables generated across multiple folds of different models, k-means clustering was applied to group (*I*) similar latent features togethe (Sinaga and Yang 2020). To obtain the final ensemble latent dimension , G-means clustering was implemented, resulting in a fixed latent size *L*=50, which was used across all samples for downstream analysis. The final latent embedding for each sample was constructed by averaging all latent variables within each cluster (Ri and Kim 2020).

## **2.7 Gene Attribution and Pathway Analysis**

### **2.7.1 Sensitivity-Based Scoring (SBS) for Gene-to-Latent Attribution**

To determine which gene contributed to what latent variables, a custom sensitivity-based scoring (SBS) approach was applied. SBS was first integrated into the method to calculate the importance of each PC for every latent variable. Then these attributions were scaled to gene level with the PC level weights, resulting in gene-level importance scores and by averaging we got global gene attributions for each latent.

### **2.7.2 Pathway Enrichment Analysis of Latent Variable-Associated Genes**

To interpret the biological representation, top-ranked genes derived from every ensemble latent variable, we performed pathway enrichment analysis using the g:Profiler tool via the gprofiler2 v2.34 (Peterson et al. 2020) R package. Gene sets with the highest attribution scores were input into the gost() function, which maps genes to known functional categories including Gene Ontology (GO) terms (Biological Process, Molecular Function, Cellular Component), KEGG pathways, and Reactome pathways (Carbon et al. 2017; Jassal et al. 2020; Kanehisa et al. 2023). We used the default settings for the organism (Homo sapiens), applied multiple testing correction via the Benjamini–Hochberg method (FDR < 0.05), and excluded electronic GO annotations to improve specificity (Ferreira and Zwinderman 2006). The results were visualized and ranked by adjusted p-values and term size to highlight the most enriched biological functions associated with each latent variable.

### **2.7.3 Gene Set Enrichment Analysis (GSEA)**

To uncover the biological functions associated with each latent variable, we performed Gene Set Enrichment Analysis (GSEA) using pre-ranked gene lists derived from latent variable attributions (Balagopalan et al. 2009). The enrichment results were obtained using a standardized pipeline and summarized across all latent variables. Pathways with a false discovery rate (FDR) < 0.05 were considered statistically significant. We calculated the normalized enrichment score (NES) for each term-latent pair and constructed a matrix of NES values. To focus on the most variable biological patterns, we selected the top 50 pathways based on the highest variance across latent variables. These were visualized as a heatmap using the seaborn v0.11.5 (Waskom 2021)library in Python, highlighting pathway–latent associations that may represent underlying biological signals.

## **2.8 Supervised Deep Learning Model Training**

### **2.8.1 Gene Selection and Data Collection**

To identify important driver genes for oropharyngeal carcinoma (OC), we analyzed gene attribution scores generated by the Deep model across 50 latent variables. Based on this analysis, we selected 20 genes that consistently ranked among the top contributors across multiple latent dimensions. These candidate driver genes were validated using an independent dataset, which included both OC and non-tumor control samples profiled on Illumina HiSeq 4000 and NovaSeq 6000 sequencing platforms.

### **2.8.2 Normalization and Batch Correction**

To address potential batch effects and platform-specific variability, we applied gene-wise Z-score normalization within each batch. Following normalization, batch correction was carried out using the empirical Bayes method implemented in the pycombat v0.3.5. All data manipulation and preprocessing were performed using the pandas v2.2.1 and numpy (v1.24.4) libraries, with additional support from scanpy v1.9.6 (Wolf et al. 2018) for annotation and matrix handling.

### **2.8.3 Model Development and Training**

We developed and trained three types of deep learning models to classify samples into OC or control groups based on the expression of the 20 selected genes. These models were implemented using TensorFlow 2.12.0 with the Keras backend. Hyperparameter tuning was conducted using the kerastuner library (v1.3.5), and model performance was assessed through five-fold stratified cross-validation (Wazery et al. 2023). The optimal MLP architecture consisted of two hidden layers with 128 and 64 neurons respectively, each followed by ReLU activation and dropout layers with a rate of 0.2. A final sigmoid-activated output layer was used for binary classification (Tolstikhin et al. 2021). All models were trained using the Adam optimizer (Wang et al. 2022) (learning rate = 1e-4), binary cross-entropy loss, a batch size of 32, and early stopping based on validation loss with a patience of 10 epochs.

### **2.8.4 Evaluation and Visualization**

Model performance was evaluated using two key metrics: area under the precision–recall curve (AUPRC) and area under the receiver operating characteristic curve (AUROC). Visualizations of model predictions, ROC curves, and PR curves were generated using matplotlib (v3.8.0) and seaborn (v0.13.2). All experiments were conducted in a s Linux-based computing environment.

## **2.9 Differential Gene Expression analysis**

Expression data were analyzed using ***DESeq2 v1.40.2***. Low-expression entries were removed before normalization. Variance-stabilizing transformation was applied for visualization. Differential expression analysis was performed using negative binomial distribution, and significance was defined as adjusted p-value < 0.05 and absolute log₂ fold change > 1. Volcano plots were generated using EnhancedVolcano v1.20.0 (Blighe et al. 2021).

**Chapter Three**

# **Result**

## **3.1 Data Preprocessing and Quality Assessment**

Highly expressive models such as deep neural networks tend to overfit when the sample size is small, we collected 19 available expression datasets from different platforms for human Oropharyngeal Cancer (OC). To remove the platform-specific biases, we preprocessed the datasets **(Figure 3.1A)**, manually excluded samples that did not satisfy the requirements, and finalized 643 samples for PCA, with 11020 genes common across all datasets. Standardized gene expression values were visualized using a boxplot **(Figure 3.1A)** among all the samples, showing consistent distribution across samples and confirming effective scalability. PCA was performed on the 643 samples expression to reduce the dimension of the features in 500 PCs for model training, where scatterplot **(Figure 3.1B)** showed no ostensible clustering or batch effect, indicating appropriateness for unsupervised modeling. The scree plot **(Figure 3.1C)** of the first 50 PCs shows uniformly low variance,confirmedthat the components are evenly distributed. Other 450 PCs are similarly contained the same proportion of variance around 0.002. A minor drop in ratio in PC9 was observed, which likely reflects numerical or structural variance fluctuations other than biological interpretation. Overall, all PCs supported further processing, used as inputs to train deep neural networks.

## **3.2 Latent Space Extraction Using Deep Neural Network**

An unsupervised neural network, PEM, was introduced to the 500 PCs to train the models. A unique methodology implied to extract the optimal latent dimension, as this unswervingly affects the model’s performance and compatibility to balance the representation of the biological signals.

Multiple models trained using the latent dimensions, including 5, 10, 25, 50, 75, and 100, and evaluated their ability to reconstruct the same sample using the parameters based on reconstruction error in both training and validation sets **(Figure 3.2A)**. As the number of latent nodes increases, the reconstruction errors reduce as per the change, representing higher capacity of reconstruction. However, the improvement stops after 50 dimensions, which implies that higher nodes can increase the risk of overfitting the data as well as the complexity of the process.

Therefore, we selected 50 nodes of latent to finalize the PEM models and got multiple folds of latent from all the models in each fold. This hyperparameter tuning helped us to reach the most

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**Figure 3.1. Preprocessing and PCA of gene expression data. (A)** Boxplot of standardized expression values for 11,020 genes across 643 finalized samples. Each box represents one sample, where dots represent outliers. **(B)** PCA scatterplot, containing the first two principal components for all samples; X axis containing PC1 and Y axis containing PC2 **(C)** Scree plot showing the proportion of variance explained by the first 50 principal components. The variance contribution is uniformly low, supporting their use in downstream neural network training.

relevant latent spaces, understand the core biology of OC from the complex environment of the data. To extract the biological meaning of every latent, an integrated model was implemented to the trained PEM model. This attribution method quantified the contribution of each 500PCs (input features) to each latent variable. These attributions were traced back to the original gene space using PCA loadings, resulting in gene-level attributions scores for each latent dimension.

**Figure 3.2B**, a sample representation of the top 10 genes in the first latent dimension, showing the strong connection with the latent node 0, ranked by their importance score. These genes, including MSRB1 (0.00416), TTI2 (0.00389), MPP5 (0.00358), ATF3 (0.00354), PYHIN1 (0.00349), HPCAL1 (0.00349), PICALM (0.00342), COMMD8 (0.0033), SFT2D2 (0.00325),



**Figure 3.2. Model Performance and Gene Attribution. (A)** Barplot showing reconstruction error for both training and validation sets across different latent dimensions. X axis represents the latent nodes selected for model training and Y axis showing the reconstruction error values. **(B)** Barplot showing the top 10 genes contributed to Latent Node 0, based on absolute Integrated Gradients (IG) scores from the ensemble attribution matrix. These top 10 genes are the strongest contributors to the biological signal captured by latent space 0.

RNF130 (0.00320), are the primary drivers of the representation/signal captured by this latent space. Top 10 drivers of the representation from all 50 lanterns mentioned in **Appendix I**.

## **3.3 Latent Variables Capture Distinct Gene Programs and Biological Pathways**

To characterize the biological meaning of the latent space learned by the PEM model, we analyzed gene-level attributions using Integrated Gradients. We computed mean attribution scores for each gene across all 50 latent variables (latent nodes) and selected the top 20 genes with the highest overall contributions **(Figure 3.3A)**. These included genes such as DDX43, FABP4, RAP1GAP2, KCNK5, XIST, ZNF839, CTH, ERC2, and PDK3, among others. Mean attribution scores across latents ranged from 0.0035 to 0.0055, with FABP4 and CTH contributing strongly to Latent 24 and 25, and ERC2 and ZNF839 dominating Latent 28, indicating distinct gene modules regulating each latent.

Hierarchical clustering of latent variables based on gene attribution profiles revealed modular structures, where sets of genes co-regulated subsets of latent nodes. For instance, Latents 24, 25, and 28 clustered closely and shared top-contributing genes involved in lipid metabolism and oxidative stress response, such as FABP4, CTH, and SAA2-SAA4.

**Figure 3.3B** illustrates the g: Profiler enrichment analysis of top-ranking genes from individual latent variables. Each dot represents a significantly enriched biological process, mapped to its corresponding latent node. Several latent variables were linked to distinct and functionally relevant pathways. For example, Latent 9 showed strong enrichment for DNA integration, suggesting potential involvement in genomic stability or viral interaction processes. Latent 20 was enriched for Golgi lumen acidification and Golgi-associated signaling, indicating a role in intracellular trafficking and post-translational modification. Latent 5 was associated with regulation of nervous system development, while Latent 33 was enriched for ECM-receptor interaction, pointing toward microenvironmental and adhesion-related mechanisms. Pathways related to RNA degradation (Latent 39), base excision repair (Latent 34), and neuromuscular junction development (Latent 45) were also identified, reflecting the biological diversity embedded within the latent dimensions.

The distribution of these enriched processes across latent nodes highlights the ability of the PEM model to capture biologically meaningful and distinct regulatory programs. A complete table of enriched pathways, including adjusted p-values, enrichment scores, and associated gene sets for all 50 latent, is provided in **Appendix II**.

These findings demonstrate that PEM’s latent variables are not only mathematically structured

**A close-up of a chart

AI-generated content may be incorrect.Figure 3.3. Interpretation of PEM latent variables through gene attribution and pathway enrichment. (A)** Heatmap showing the mean Integrated Gradients attribution scores of the top 20 genes across all 50 latent variables. Both rows (genes) and columns (latents) were hierarchically clustered, revealing modular structures among gene-latent relationships. **(B)** Dot plot summarizing the most significantly enriched biological pathways for selected latent variables. Each dot represents a latent-pathway pair, with dot size and color corresponding to the enrichment significance (−log₁₀ adjusted p-value).

but also biologically meaningful, capturing diverse processes such as development, signaling, immune response, metabolism, and DNA repair. This confirms the interpretability and relevance of the latent representations in modeling the underlying biology of OC.

## **3.4 Functional Characterization of Latent Variables via GSEA**

To further evaluate the functional relevance of the latent space, we performed Gene Set Enrichment Analysis (GSEA) using the ranked gene attributions for each of the 50 latent variables and visualized the results in a pathway–latent heatmap **(Figure 3.4A)**. The heatmap displays the Normalized Enrichment Scores (NES) across a curated panel of KEGG pathways, capturing the direction and magnitude of enrichment. Red tones indicate positive enrichment (NES > 0), whereas blue tones indicate negative enrichment (NES < 0).

Several latent variables were significantly enriched for known cancer-related and immune-related pathways. Latent 6 and Latent 21 were positively enriched for *Ribosome* and *Oxidative Phosphorylation*, processes often upregulated in proliferative tumor cells. Latent 15 and Latent 24 showed strong positive enrichment in immune pathways such as *JAK-STAT signaling*, *Cytokine–cytokine receptor interaction*, and *Antigen processing and presentation*. Latent 36 and Latent 48 were associated with *Mismatch repair*, *Fanconi anemia*, and *Cell cycle*, indicating potential links to genomic instability. Negative enrichment was observed for several inflammation-related pathways (e.g., *Inflammatory bowel disease*, *Primary immunodeficiency*, *NF-kappa B signaling*), particularly in Latents 3, 9, and 18. Other Results of GSEA mentioned in **Appendix III.**

The diversity of enriched processes across the latent variables suggests that PEM captures a broad spectrum of biologically meaningful signatures, ranging from metabolic and proliferative programs to immune modulation and DNA repair pathways.

## **3.5 Deep Learning-Based Classification of Candidate Driver Genes in Oropharyngeal Carcinoma**

To visualize the expression profiles of the 20 candidate driver genes across control and OC samples, we generated violin plots **(Figure 3.5A)** and boxplots in **Appendix IV**. Several genes exhibited substantial differential expressions between the two groups. Notably, RAP1GAP2, CTH, and FABP4 were

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**Figure 3.4.** **Pathway enrichment heatmap of PEM latent variables using GSEA.**  
Heatmap shows Normalized Enrichment Scores (NES) for pathways enriched across 50 latent variables. Each row represents a pathway and each column a latent node. Red shades indicate positive enrichment (NES > 0) and blue shades indicate negative enrichment (NES < 0).

highly expressed in OC samples compared to controls, suggesting their potential role as diagnostic or functional markers. Conversely, genes like XIST and ERC2 displayed more variable patterns, hinting at subtype-specific or microenvironmental influences.

We then assessed the ability of the 20-gene panel to classify OC using supervised deep learning models. As shown in the performance plots **(Figure 3.5B & C)**, the MLP model consistently outperformed CNN and LSTM across all evaluation folds. The MLP achieved a mean AUPRC of 0.86 and mean AUROC of 0.80, followed by the CNN with an AUPRC of 0.81 and AUROC of 0.79, and the LSTM with an AUPRC of 0.78 and AUROC of 0.70. Precision–recall curves showed a steeper and more stable shape for the MLP, indicating its superior ability to maintain high precision at varying recall thresholds. Similarly, the MLP's ROC curve demonstrated a better trade-off between sensitivity and specificity compared to the other models.

These results indicate that the MLP model is best suited for classifying OC based on the selected latent-informed gene set. The consistently high AUPRC and AUROC suggest that the PEM-derived genes, particularly RAP1GAP2, PDK3, and FABP4, may serve as effective driver markers or classifiers for oropharyngeal carcinoma in high-throughput transcriptomic data **(Table 3.1), (Appendix V)**. This model framework provides a biologically informed, interpretable route to gene-based diagnosis or biomarker discovery, bridging unsupervised latent feature learning with supervised validation on independent clinical cohorts.

## **3.6 RAP1GAP2 Emerges as the Most Predictive Gene in Single-Feature Classification Models**

To identify the most predictive gene within the consensus panel, we trained single-feature models for each of the 20 genes and computed their individual feature importances using the supervised MLP model described previously. The resulting importance scores are visualized in **Figure 3.6A**, where RAP1GAP2 ranked as the most informative gene, followed closely by XIST, SLC9A7, and FABP4. This suggests that RAP1GAP2 holds strong discriminative power for separating oropharyngeal carcinoma from control samples, reinforcing its prominence in both latent attribution analysis and expression profiling.

To validate its predictive strength, we constructed a single-gene MLP classifier using only the expression values of RAP1GAP2. The resulting Precision–Recall curve, shown in **Figure 3.6B**, achieved a mean AUPRC of 0.769, indicating robust classification performance using this gene alone. This further supports the hypothesis that RAP1GAP2 may serve as a potent driver or biomarker of oropharyngeal carcinoma and warrants further experimental validation.

**Table 3.1 Performance metrics for single-gene classification models**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Gene | AUROC | AUPRC | Accuracy | F1 | Precision | Recall |
| **WDR41** | 0.640 | 0.650 | 0.556 | 0.711 | 0.560 | 0.971 |
| **KCNK5** | 0.540 | 0.560 | 0.524 | 0.686 | 0.545 | 0.924 |
| **GATA3** | 0.590 | 0.580 | 0.620 | 0.667 | 0.657 | 0.676 |
| **DDX43** | 0.550 | 0.570 | 0.513 | 0.629 | 0.550 | 0.733 |
| **DTWD1** | 0.650 | 0.640 | 0.535 | 0.679 | 0.554 | 0.876 |
| **XIST** | 0.594 | 0.708 | 0.540 | 0.688 | 0.556 | 0.905 |
| **SAA2-SAA4** | 0.557 | 0.621 | 0.556 | 0.709 | 0.561 | 0.962 |
| **ERC2** | 0.550 | 0.560 | 0.610 | 0.709 | 0.610 | 0.848 |
| **ENO3** | 0.610 | 0.590 | 0.567 | 0.722 | 0.565 | 1.000 |
| **SLC9A7** | 0.710 | 0.710 | 0.594 | 0.689 | 0.604 | 0.800 |
| **CTH** | 0.590 | 0.590 | 0.604 | 0.711 | 0.603 | 0.867 |
| **PDK3** | 0.570 | 0.600 | 0.567 | 0.675 | 0.583 | 0.800 |
| **GSTT2** | 0.643 | 0.664 | 0.642 | 0.735 | 0.628 | 0.886 |
| **RPARP-AS1** | 0.528 | 0.619 | 0.540 | 0.699 | 0.552 | 0.952 |
| **ZNF839** | 0.550 | 0.590 | 0.556 | 0.711 | 0.560 | 0.971 |
| **FABP4** | 0.520 | 0.530 | 0.535 | 0.695 | 0.550 | 0.943 |
| **RAP1GAP2** | 0.710 | 0.769 | 0.730 | 0.760 | 0.700 | 0.940 |
| **HAPLN1** | 0.606 | 0.676 | 0.615 | 0.692 | 0.628 | 0.771 |

**A diagram of a gene

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**Figure 3.5. Identification of key driver genes and classification performance in oropharyngeal carcinoma. (A)** Violin plots showing the expression distributions of 20 consensus genes, derived from PEM latent space attribution scores, across control and oropharyngeal OC samples in an external high-throughput RNA-seq dataset. **(B)** Precision–Recall (PR) curves comparing three supervised deep learning models trained on the expression profiles of the 20 genes. **(C)** Receiver operating characteristic (ROC) curves for the same models.

## **3.7 RAP1GAP2 Emerges as a Key Latent Driver Despite Non-Significance in Differential Expression Analysis**

**Figure 3.7A & B** show the gene expression distributions of the RNA-seq datasets before and after normalization, respectively. **Figure 3.7A** illustrates the raw, unnormalized transcript counts, highlighting variability across samples. In contrast, **Figure 3.7B** demonstrates the effect of DEseq2 normalization, resulting in more comparable and standardized expression profiles across all samples, ensuring the reliability of downstream analyses.

To explore hidden regulatory signals not captured by traditional methods, we applied a deep learning framework trained on latent representations derived from transcriptomic data. Among the most notable findings was the gene RAP1GAP2, which consistently ranked as a top contributor across all 50 latent variables. Moreover, when used in supervised classification tasks, RAP1GAP2 exhibited the highest predictive performance among the 20 common genes shared across latent dimensions.

However, differential gene expression (DGE) analysis failed to identify RAP1GAP2 as statistically significant. As shown in **Figure 3.7C**, RAP1GAP2 resides within the "not significant" region of the volcano plot, indicating that it was not differentially expressed based on standard thresholds (log2 fold change and FDR-adjusted p-value). This contrast between latent-space importance and conventional differential expression underscores a critical disconnect between statistical significance and functional relevance.



**Figure 3.6. RAP1GAP2 identified as the top predictive gene for oropharyngeal carcinoma classification. (A)** Feature importance scores for each of the 20 genes in the supervised MLP model. RAP1GAP2 ranked highest, suggesting its dominant role in classification. **(B)** Precision–Recall curve for the single-gene classifier trained exclusively on RAP1GAP2 expression. The model achieved a mean area under the precision–recall curve (AUPRC) of 0.769, indicating strong predictive capacity from this gene alone.



**Figure 3.7. Identification of RAP1GAP2 as a latent driver despite non-significance in differential expression analysis. (A)** Raw gene expression across samples before normalization. **(B**) Normalized expression profiles of all samples. **(C)** Volcano plot of differential gene expression analysis: upregulated, downregulated, and non-significant genes are shown. RAP1GAP2, highlighted in red, was not significantly differentially expressed but was identified as a top contributor across all latent variables and showed the highest classification ability in the deep learning model, supporting its role as a hidden driver in oropharyngeal carcinoma.

**Chapter Four**

# **Discussion**

## **4.1 Summary of Key Results and Methodological Insight**

We used a deep learning-based framework in this study to figure out the hidden biological signals in transcriptomic data from oropharyngeal carcinoma (OC). We used a variational autoencoder (PEM) and then integrated gradients to find 50 interpretable latent dimensions, each linked to a different gene program and biological pathway **(Figure 3.3, 3.4)**. We wanted to go beyond standard differential expression analysis and find nonlinear, hidden factors that drive cancer biology that might not be found otherwise. Using this method, we found a group of high-impact genes that affect many latent variables. RAP1GAP2 stood out as the most consistent and predictive gene **(Figure 3.6)**. It's surprising that RAP1GAP2 wasn't found to be significantly differentially expressed **(Figure 3.7C)**, even though it was a top contributor in the latent space and did well in a single-gene model. This difference between statistical insignificance and biological relevance shows the main point of our study: deep models can find molecular drivers that linear transcriptomic tools can't. Our results not only show that PEM-derived features can be understood in a biological way, but they also show how deep representation learning can add to and improve traditional genomic analyses.

## **4.2 Significance of Identified Latent Drivers**

Our integrative deep learning method found a group of latent driver genes that shed light on previously unknown aspects of oropharyngeal carcinoma biology. The most important discovery is that RAP1GAP2 is a key molecular driver of tumor invasion, even though traditional differential expression analysis didn't show it. This highlights an important point: important regulatory genes can avoid being found by standard statistical methods but still have a big impact on how cancer grows. Using Probabilistic Embedding Models and attribution techniques, we found that RAP1GAP2 was always one of the top contributors to latent features linked to the tumor phenotype. In real life, RAP1GAP2 alone was very good at telling tumor samples apart from normal samples (single-gene classifier AUPRC ≈ 0.77), which shows that it could be a latent oncogenic driver in oropharyngeal carcinoma. This discovery gives us a new way to think about our research question. It shows that there is a layer of latent genomic regulation "beyond differential expression" where genes like RAP1GAP2 can control cancerous behavior without making big changes in how they are expressed.

It's important to note that our results are in line with and add to what is already known in the field. Researchers have known for a long time that the Ras-related GTPase Rap1 and its regulators play a role in how cancer cells stick to each other and move around (Zhang et al. 2017). Active Rap1 signaling has been shown to make head and neck cancers more invasive (for example, by causing β-catenin and MMP7 to be produced) (Zhang et al. 2017). On the other hand, the well-known Rap1 inactivator Rap1GAP (a paralog of RAP1GAP2) is known to stop Rap1–ERK signaling and tumor growth (Zhang et al. 2006). So, our discovery of RAP1GAP2 builds on this model but also adds a new twist. RAP1GAP2 is a pro-invasion factor here, while Rap1GAP stops HNSCC progression in a broad way (Zhang et al. 2006). When you look at the whole picture, this seeming contradiction makes sense: Rap1 regulators often have different effects on different types of cells (Zhang et al. 2017). In fact, research shows that Rap1GAP usually stops invasion in many cancers, but in some cases, higher levels of Rap1GAP can actually make cells more invasive (Zhang et al. 2017). Our findings suggest that oropharyngeal carcinoma is one of those situations where RAP1GAP2, working in a certain part of the cell, causes cancer to grow. This is a new discovery because RAP1GAP2 has never been studied in oropharyngeal cancer before; it was basically a "hidden" driver that our latent-space profiling was able to find. We found other latent drivers besides RAP1GAP2, such as PDK3 and FABP4, which support the biological validity of our method. PDK3 (pyruvate dehydrogenase kinase 3) is a known mediator of the Warburg effect and is upregulated in hypoxic tumors, which leads to metabolic reprogramming and aggressive behavior (Lu et al. 2011). Also, FABP4 (fatty acid–binding protein 4) has been shown to help tumors spread and resist treatment by speeding up lipid transport and signaling in cancer cells (Sun and Zhao 2022). Our model seems to have captured important features of cancer, like metabolic plasticity and microenvironmental adaptation, in addition to the Rap1 signaling axis. This is shown by the presence of PDK3 and FABP4 among our top latent genes. In conclusion, the fact that our data-driven findings match up with known cancer pathways supports the results of this study. We have not only found a new driver (RAP1GAP2) and supporting cast of genes for oropharyngeal carcinoma invasion, but we have also shown how deep neural profiling can find biologically important targets that standard analyses would miss.

## **4.3 Proposed Mechanism of RAP1GAP2 in Oropharyngeal Carcinoma Invasion and Metastasis**

RAP1GAP2 is a GTPase-activating protein (GAP) for Rap1 (Johansen et al. 2023). It changes active GTP-bound Rap1 into an inactive GDP-bound state, which changes how cells stick together and send signals. Active Rap1 stabilizes integrins and E-cadherins, which helps cells stick together and keeps epithelial cells looking like epithelial cells (Price et al. 2004). RAP1GAP2 stops Rap1 from working, which breaks up these stable interactions and makes A diagram of a cell line

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**Figure 4.1. Schematic model illustrates the proposed role of RAP1GAP2 in promoting invasion and metastasis in oropharyngeal carcinoma through Rap1 inactivation, MAPK signaling, and Golgi-mediated secretion.**

cells lose their ability to stick together. This is necessary for tumor cells to start moving and invading.

RAP1GAP2 inactivates Rap1, which not only stops adhesion but also stops Rap1 from stopping Ras–MAPK/ERK signaling. This makes the ERK pathway more active (Zhang et al. 2017). ERK signaling helps cells grow, move, and turn on invasive genes, such as matrix metalloproteinases (MMPs). This makes tumors even more aggressive (Mitra et al. 2008).

RAP1GAP2 also affects how tumors invade by changing how vesicles move around. It works with the synaptotagmin-like protein 1 (Slp1) and Rab27 complex to control secretory vesicles that come from the Golgi apparatus (Neumüller et al. 2009; Li et al. 2018). This interaction leads to the release of enzymes that break down the matrix, like MMP-2 and MMP-9, into the extracellular space. This makes it easier for tissues to break down and makes them more invasive (Mitra et al. 2008; Beroun et al. 2019).

So, RAP1GAP2 controls a coordinated, multi-dimensional invasion strategy: it weakens cellular adhesion, turns on pro-invasive ERK/MAPK signaling, and boosts the Golgi's ability to secrete proteases (Guo et al. 2020). This integrated mechanism shows how RAP1GAP2 can help metastasis even though it acts as a Rap1 inhibitor. Future experiments can test whether changing the expression of RAP1GAP2 affects the strength of cell adhesion, the levels of ERK activation, and the release of invasive factors. This would confirm its many roles in the progression of oropharyngeal carcinoma.

## **4.4 Limitations of the Study**

Based on integrative analyses of transcriptomic data, our study identifies RAP1GAP2 as a promising computationally predicted driver gene in oropharyngeal carcinoma (OC). To preserve a fair interpretation, a few restrictions must be noted.

First off, we didn't carry out functional tests to confirm RAP1GAP2's involvement in cellular functions like invasion and metastasis. Therefore, our results are still correlative, and there is no proof that RAP1GAP2 causes tumor behavior. Second, even with batch effect correction and gene harmonization, heterogeneity is introduced because we used retrospective integration of several public datasets from various platforms and clinical subgroups. Variations in tumor subsite, treatment history, and HPV status could affect the latent features that are extracted. Third, some candidate genes (such as RAP1GAP2) showed only slight expression changes and might contribute to false positives because our machine learning pipeline gave predictive power precedence over statistical significance. Although this risk was reduced by cross-validation, biological significance still needs to be ascertained through experimentation. Furthermore, we were unable to assess the prognostic significance of the identified drivers due to the restricted availability of comprehensive clinical endpoints, such as survival and metastasis data. Lastly, we only looked at the mRNA level, leaving out other regulatory mechanisms that could have a significant impact on RAP1GAP2's function, like mutations, epigenetic changes, and post-translational events. All of these drawbacks highlight the necessity of additional research that includes multi-omic integration and experimental validation in order to completely clarify the biological and therapeutic significance of our findings.

## **4.5 Future Directions**

Our results provide several avenues for additional research to confirm and broaden the biological significance of RAP1GAP2 in oropharyngeal carcinoma (OC). First and foremost, functional validation is essential. RAP1GAP2's function would be directly tested by knocking down or overexpressing it in OC cell lines and evaluating cell invasion, Rap1-GTP activity, and downstream signaling (such as ERK/MAPK and MMP secretion). Its pro-metastatic role may be further supported by in vivo models. RAP1GAP2's value as a biomarker may be defined clinically by assessing its expression in larger patient cohorts or tissue arrays, which may show associations with tumor stage, metastasis, HPV status, or prognosis.

From a therapeutic standpoint, RAP1GAP2's downstream pathways, like MAPK signaling or Rab27-mediated secretion, provide actionable targets, even though directly targeting it may be challenging. Inhibitors of these effectors in RAP1GAP2-high models may be investigated in future research. To find cross-layer or context-specific drivers, our deep profiling framework can be methodologically extended to other cancers or combined with proteomic and epigenetic data. New patterns may be found by applying the pipeline to datasets related to head and neck cancer that are HPV-stratified.

Lastly, more research is necessary to fully understand the network of interactions between latent drivers such as RAP1GAP2, PDK3, and FABP4. Studies on gene perturbation and systems biology may shed light on whether these genes are linked by common regulators (like hypoxia) and provide combinatorial intervention points. Collectively, these avenues will enhance our comprehension of the function of RAP1GAP2 and facilitate the realization of our computational approach's translational potential.

**Chapter Five**

# **Conclusion**

In summary, this study demonstrates that new cancer-causing factors can be identified by combining deep learning with high-dimensional transcriptome data. We discovered that RAP1GAP2, a gene that is rarely observed to exhibit differential expression, might play a secret role in regulating the invasion of other tissues by oropharyngeal cancer. This new knowledge links biological mechanisms to data-driven modeling. It implies that these cancers become more aggressive due to dysregulation of Rap1 signaling (via RAP1GAP2), as well as modifications in metabolism and secretion. Our discussion demonstrates how this finding aligns with our current understanding of cancer pathways and provides a fresh perspective on and method for testing metastasis. We are one step closer to improved prognostic tools and customized treatments for oral cancers now that RAP1GAP2 is recognized as a molecular driver (Zhang et al. 2006). Ultimately, the study's methodology and findings highlight the significance of looking beyond conventional research to comprehend the intricate genetic elements influencing cancer behavior. This makes it possible to conduct cancer genomics research using more comprehensive and innovative methods.

**Chapter Six**

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**Chapter Seven**

# **Appendices**

**Appendix I**

A chart of bar code

AI-generated content may be incorrect.

**Appendix II**

**Selected Latent Variable-Enriched Pathways**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Pathway Name | P-value | Term Size | Query Size | Intersection Size | Precision | Recall | Latent Node |
| regulation of nervous system development | 0.0236186136151001 | 457 | 16 | 5 | 0.3125 | 0.0109409190371991 | 7 |
| DNA integration | 0.0287922088818914 | 10 | 15 | 2 | 0.1333333333333333 | 0.2 | 9 |
| Glucagon signaling pathway | 0.0134641808035551 | 107 | 10 | 3 | 0.3 | 0.02803738317757 | 18 |
| Cushing syndrome | 0.0499569897009377 | 153 | 11 | 3 | 0.2727272727272727 | 0.0196078431372549 | 19 |
| Vibrio cholerae infection | 0.0246555455325596 | 50 | 6 | 2 | 0.3333333333333333 | 0.04 | 20 |
| Golgi lumen acidification | 0.0370534161963728 | 13 | 13 | 2 | 0.1538461538461538 | 0.1538461538461538 | 20 |
| Cushing syndrome | 0.0499569897009377 | 153 | 11 | 3 | 0.2727272727272727 | 0.0196078431372549 | 23 |
| tRNA metabolic process | 0.0414263692639973 | 210 | 18 | 4 | 0.2222222222222222 | 0.019047619047619 | 25 |
| ECM-receptor interaction | 0.010145054293642 | 89 | 11 | 3 | 0.2727272727272727 | 0.0337078651685393 | 31 |
| Glyoxylate and dicarboxylate metabolism | 0.012188180777088 | 30 | 7 | 2 | 0.2857142857142857 | 0.0666666666666666 | 34 |
| cellular response to 2,3,7,8-tetrachlorodibenzodioxine | 0.0038484693649248 | 4 | 15 | 2 | 0.1333333333333333 | 0.5 | 41 |
| response to 2,3,7,8-tetrachlorodibenzodioxine | 0.0179299300313183 | 8 | 15 | 2 | 0.1333333333333333 | 0.25 | 41 |
| Base excision repair | 0.0263601360727707 | 44 | 7 | 2 | 0.2857142857142857 | 0.0454545454545454 | 42 |
| RNA degradation | 0.0412133286559642 | 79 | 5 | 2 | 0.4 | 0.0253164556962025 | 43 |
| neuromuscular junction development | 0.0215300187657582 | 54 | 19 | 3 | 0.1578947368421052 | 0.0555555555555555 | 47 |
| regulation of response to external stimulus | 0.0390732084249658 | 1082 | 19 | 7 | 0.3684210526315789 | 0.0064695009242144 | 47 |

**Appendix III**

**GSEA Info for Top 50 Pathways**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Name | Term | ES | NES | NOM p-val | FDR q-val | FWER p-val | Tag % | Gene % | latent |
| prerank | Ribosome | -0.2538932143878554 | -3.142324180841197 | 0.0 | 0.0 | 0.0 | 64/112 | 30.62% | 0 |
| prerank | Oxidative phosphorylation | -0.2407197097865659 | -2.611673921650873 | 0.0 | 0.0 | 0.0 | 70/86 | 56.60% | 0 |
| prerank | Thermogenesis | -0.158950904011502 | -2.405693731233716 | 0.0 | 0.0 | 0.0 | 87/159 | 37.50% | 0 |
| prerank | Taste transduction | -0.3048429308211678 | -2.350171914030135 | 0.0 | 0.0 | 0.0 | 26/32 | 50.10% | 0 |
| prerank | Epstein-Barr virus infection | 0.0556416038563949 | 0.8350148290636356 | 0.603448275862069 | 1.0 | 1.0 | 115/179 | 59.99% | 0 |
| prerank | Oxidative phosphorylation | 0.1142496981063722 | 1.2249093076286393 | 0.1525423728813559 | 0.7361948188317199 | 1.0 | 52/86 | 50.47% | 1 |
| prerank | Epstein-Barr virus infection | -0.0756836049783082 | -1.1357622653143702 | 0.3448275862068966 | 0.6369253352905851 | 1.0 | 62/179 | 25.54% | 1 |
| prerank | Thermogenesis | 0.0748845499516672 | 1.0927577331087608 | 0.2948717948717949 | 0.8631416491166021 | 1.0 | 134/159 | 77.74% | 1 |
| prerank | Ribosome | 0.0936709992384217 | 1.062166029297325 | 0.3787878787878788 | 0.8778851648488162 | 1.0 | 24/112 | 13.53% | 1 |
| prerank | Taste transduction | -0.1334816003429303 | -0.9706323778105916 | 0.4444444444444444 | 0.7495123224441576 | 1.0 | 23/32 | 57.23% | 1 |
| prerank | Ribosome | -0.3256476601525599 | -4.022551650465103 | 0.0 | 0.0 | 0.0 | 82/112 | 40.25% | 2 |
| prerank | Oxidative phosphorylation | -0.2609235596349908 | -2.837492429056554 | 0.0 | 0.0 | 0.0 | 53/86 | 34.95% | 2 |
| prerank | Epstein-Barr virus infection | -0.1484226108201942 | -2.3752365815471905 | 0.0 | 0.0057049714751426 | 0.06 | 88/179 | 33.48% | 2 |
| prerank | Thermogenesis | -0.0882268099454029 | -1.3402073272558992 | 0.0975609756097561 | 0.2926098272734442 | 1.0 | 113/159 | 61.71% | 2 |
| prerank | Taste transduction | -0.133293065125292 | -0.9230062434315842 | 0.4888888888888889 | 0.6908604815084033 | 1.0 | 13/32 | 26.30% | 2 |
| prerank | Oxidative phosphorylation | -0.3275733015959381 | -3.400119111390953 | 0.0 | 0.0 | 0.0 | 67/86 | 44.66% | 3 |
| prerank | Ribosome | -0.2617170297897189 | -3.2861659380353325 | 0.0 | 0.0 | 0.0 | 87/112 | 51.10% | 3 |
| prerank | Epstein-Barr virus infection | -0.1059999709738502 | -1.86209483044086 | 0.0 | 0.0579973024510487 | 0.56 | 88/179 | 37.69% | 3 |
| prerank | Thermogenesis | -0.1212049069795281 | -1.8205604074176376 | 0.0 | 0.0682293846797823 | 0.64 | 72/159 | 32.36% | 3 |
| prerank | Taste transduction | -0.2244361798488704 | -1.5172067052040372 | 0.0256410256410256 | 0.1659770744115658 | 1.0 | 14/32 | 19.96% | 3 |
| prerank | Ribosome | -0.2232951808963537 | -2.8364443956286745 | 0.0 | 0.0 | 0.0 | 79/112 | 47.23% | 4 |
| prerank | Oxidative phosphorylation | -0.1384100937509499 | -1.484898203180035 | 0.025 | 0.3228428314904074 | 0.99 | 72/86 | 69.16% | 4 |
| prerank | Taste transduction | -0.1599142914597349 | -1.1002297033883486 | 0.4193548387096774 | 0.6523335661482501 | 1.0 | 27/32 | 67.63% | 4 |
| prerank | Thermogenesis | 0.0627232772891256 | 0.8261903765388551 | 0.717948717948718 | 0.8583973003841902 | 1.0 | 139/159 | 82.01% | 4 |
| prerank | Epstein-Barr virus infection | 0.0475756092253786 | 0.6652826145585135 | 0.8552631578947368 | 0.951003837479759 | 1.0 | 101/179 | 53.24% | 4 |
| prerank | Epstein-Barr virus infection | -0.2321369172794 | -3.8752412064043895 | 0.0 | 0.0 | 0.0 | 76/179 | 18.53% | 5 |
| prerank | Ribosome | -0.2331264509898629 | -3.037331039310221 | 0.0 | 0.0 | 0.0 | 87/112 | 53.96% | 5 |
| prerank | Oxidative phosphorylation | -0.2113046485189271 | -2.5688251815532457 | 0.0 | 0.0008765821089591 | 0.01 | 68/86 | 57.49% | 5 |
| prerank | Thermogenesis | 0.0767866793683777 | 1.1101762451219783 | 0.3225806451612903 | 1.0 | 1.0 | 136/159 | 78.48% | 5 |
| prerank | Taste transduction | -0.1278100605290263 | -0.8108845295541842 | 0.6666666666666666 | 0.8161653728339712 | 1.0 | 21/32 | 51.73% | 5 |
| prerank | Ribosome | -0.3293229152882386 | -4.450933710867719 | 0.0 | 0.0 | 0.0 | 68/112 | 27.16% | 6 |
| prerank | Oxidative phosphorylation | -0.2803922514121083 | -2.9523157014033363 | 0.0 | 0.0 | 0.0 | 70/86 | 52.93% | 6 |
| prerank | Epstein-Barr virus infection | -0.1612168197723371 | -2.83990224960349 | 0.0 | 0.0 | 0.0 | 80/179 | 27.60% | 6 |
| prerank | Thermogenesis | -0.1045309528713468 | -1.6119871628753508 | 0.0526315789473684 | 0.1086496401862565 | 0.98 | 102/159 | 52.93% | 6 |
| prerank | Taste transduction | -0.0803663969469782 | -0.5944365699407909 | 0.9473684210526316 | 0.950402144772118 | 1.0 | 22/32 | 59.83% | 6 |
| prerank | Epstein-Barr virus infection | -0.1065109835343221 | -1.744106362733484 | 0.0 | 0.1176882575158902 | 0.78 | 49/179 | 15.52% | 7 |
| prerank | Ribosome | 0.1120774229219907 | 1.279890247034121 | 0.1076923076923077 | 0.7245521177194651 | 1.0 | 58/112 | 42.30% | 7 |
| prerank | Oxidative phosphorylation | 0.108161573283124 | 1.119584501050699 | 0.3442622950819672 | 0.9349297823532704 | 1.0 | 75/86 | 77.11% | 7 |
| prerank | Thermogenesis | 0.0715029801756083 | 1.0268194922167353 | 0.463768115942029 | 0.9815923459967548 | 1.0 | 129/159 | 75.05% | 7 |
| prerank | Taste transduction | 0.1249958881658193 | 0.8067070959874992 | 0.6229508196721312 | 1.0 | 1.0 | 23/32 | 61.00% | 7 |
| prerank | Thermogenesis | 0.1367508982822331 | 1.9891285890048445 | 0.0 | 0.1958251871161404 | 0.47 | 88/159 | 42.83% | 8 |
| prerank | Ribosome | 0.1454806205398361 | 1.7462592473255552 | 0.0408163265306122 | 0.3844675970986771 | 0.87 | 84/112 | 61.29% | 8 |
| prerank | Oxidative phosphorylation | 0.1309589399054042 | 1.3715003663606282 | 0.0666666666666666 | 0.7863250756787104 | 1.0 | 31/86 | 24.00% | 8 |
| prerank | Epstein-Barr virus infection | -0.0775275389761539 | -1.2408344861416116 | 0.1379310344827586 | 0.4750103126804719 | 1.0 | 105/179 | 50.05% | 8 |
| prerank | Taste transduction | -0.1302957666471551 | -0.876358542353001 | 0.5769230769230769 | 0.8278352697259158 | 1.0 | 12/32 | 23.35% | 8 |
| prerank | Thermogenesis | -0.1337794037804547 | -2.100302981011935 | 0.0 | 0.0240763092961898 | 0.22 | 50/159 | 16.67% | 9 |
| prerank | Oxidative phosphorylation | -0.1564861632838065 | -1.6899188229068458 | 0.0 | 0.1199516123863745 | 0.88 | 29/86 | 16.56% | 9 |
| prerank | Epstein-Barr virus infection | -0.0805443311691613 | -1.3345202650671202 | 0.125 | 0.3780101242756428 | 1.0 | 74/179 | 31.81% | 9 |
| prerank | Ribosome | -0.0944119478879425 | -1.2113882241551532 | 0.2222222222222222 | 0.5218758215459836 | 1.0 | 24/112 | 10.81% | 9 |
| prerank | Taste transduction | 0.142512319190756 | 0.8988740228825484 | 0.5555555555555556 | 1.0 | 1.0 | 8/32 | 12.37% | 9 |
| prerank | Ribosome | -0.1971230410161868 | -2.6788469240337296 | 0.0 | 0.0025584472871636 | 0.01 | 72/112 | 43.60% | 10 |
| prerank | Epstein-Barr virus infection | -0.1636372192150541 | -2.540005734409352 | 0.0 | 0.0031980591089545 | 0.02 | 85/179 | 29.82% | 10 |
| prerank | Oxidative phosphorylation | 0.1500924419982399 | 1.5510957038556674 | 0.0307692307692307 | 0.3611661477497877 | 0.99 | 52/86 | 46.85% | 10 |
| prerank | Thermogenesis | 0.1123031774550938 | 1.5077141535503211 | 0.088235294117647 | 0.4161262137117119 | 0.99 | 90/159 | 46.85% | 10 |
| prerank | Taste transduction | 0.1335782743774241 | 0.8638481365202263 | 0.65625 | 0.9752898173595196 | 1.0 | 21/32 | 53.91% | 10 |
| prerank | Epstein-Barr virus infection | -0.1548800515752707 | -2.431047289293832 | 0.0 | 0.0014575470250698 | 0.01 | 82/179 | 28.95% | 11 |
| prerank | Oxidative phosphorylation | 0.1182173254761076 | 1.1944193154577427 | 0.2622950819672131 | 0.6175221922037823 | 1.0 | 66/86 | 65.98% | 11 |
| prerank | Thermogenesis | 0.0840036749263786 | 1.118619955095944 | 0.28125 | 0.6860132448708288 | 1.0 | 95/159 | 52.77% | 11 |
| prerank | Ribosome | -0.0782791132880562 | -1.0479330673375782 | 0.3823529411764705 | 0.5760692258123907 | 1.0 | 71/112 | 54.18% | 11 |
| prerank | Taste transduction | -0.142353790073346 | -0.9466568114068772 | 0.4883720930232558 | 0.7009968306571455 | 1.0 | 12/32 | 21.73% | 11 |
| prerank | Ribosome | -0.1590080895545469 | -2.112035134935741 | 0.0 | 0.0280182897168985 | 0.25 | 82/112 | 56.27% | 12 |
| prerank | Oxidative phosphorylation | -0.1324742005360538 | -1.4618884159029404 | 0.081081081081081 | 0.2967726739750436 | 1.0 | 61/86 | 56.39% | 12 |
| prerank | Epstein-Barr virus infection | -0.0828798991794913 | -1.3064769028044512 | 0.1304347826086956 | 0.3912372091377831 | 1.0 | 61/179 | 24.35% | 12 |
| prerank | Taste transduction | -0.1640753539772809 | -1.2020766986467593 | 0.2285714285714285 | 0.4926908484063849 | 1.0 | 9/32 | 10.31% | 12 |
| prerank | Thermogenesis | 0.0430498109286673 | 0.6098984184263628 | 0.935064935064935 | 1.0 | 1.0 | 138/159 | 83.46% | 12 |
| prerank | Thermogenesis | 0.1106799758428105 | 1.552844450861132 | 0.1212121212121212 | 0.501035356316775 | 1.0 | 84/159 | 43.54% | 13 |
| prerank | Taste transduction | 0.1898271430862881 | 1.238439155252835 | 0.2 | 0.8120975144105445 | 1.0 | 8/32 | 7.70% | 13 |
| prerank | Ribosome | 0.101008067665986 | 1.158800145280816 | 0.2816901408450704 | 0.7224988615683561 | 1.0 | 57/112 | 42.36% | 13 |
| prerank | Oxidative phosphorylation | 0.0893802743756362 | 0.9178164713944112 | 0.5151515151515151 | 0.7740193224552736 | 1.0 | 75/86 | 79.11% | 13 |
| prerank | Epstein-Barr virus infection | -0.0369440849574122 | -0.5773223972275305 | 1.0 | 0.9895624758934112 | 1.0 | 162/179 | 86.23% | 13 |
| prerank | Ribosome | -0.2499602236106113 | -3.402811022966832 | 0.0 | 0.0 | 0.0 | 70/112 | 36.31% | 14 |
| prerank | Oxidative phosphorylation | -0.2533110757351272 | -2.8823733635911024 | 0.0 | 0.0 | 0.0 | 58/86 | 40.98% | 14 |
| prerank | Epstein-Barr virus infection | -0.1403322253608299 | -2.563615113060528 | 0.0 | 0.0026311111111111 | 0.01 | 89/179 | 34.09% | 14 |
| prerank | Thermogenesis | -0.0782485007267294 | -1.1257550331930222 | 0.2941176470588235 | 0.5246178861788618 | 1.0 | 110/159 | 60.17% | 14 |
| prerank | Taste transduction | 0.1120801633981848 | 0.7121301279549598 | 0.8653846153846154 | 1.0 | 1.0 | 29/32 | 79.91% | 14 |
| prerank | Epstein-Barr virus infection | -0.1564731165548349 | -2.6231667792912323 | 0.0 | 0.0 | 0.0 | 58/179 | 15.80% | 15 |
| prerank | Oxidative phosphorylation | -0.1427779365221995 | -1.5459902681911917 | 0.0714285714285714 | 0.1606630509590157 | 1.0 | 45/86 | 37.13% | 15 |
| prerank | Ribosome | -0.0835052583452637 | -1.0457258246958143 | 0.4473684210526316 | 0.6350407605087761 | 1.0 | 64/112 | 47.89% | 15 |
| prerank | Thermogenesis | 0.0685810193717143 | 0.9241792850269684 | 0.609375 | 0.9146829405107706 | 1.0 | 86/159 | 48.40% | 15 |
| prerank | Taste transduction | -0.1089751365711126 | -0.8046743421424567 | 0.7021276595744681 | 0.85876914142102 | 1.0 | 22/32 | 56.79% | 15 |
| prerank | Oxidative phosphorylation | -0.1934690155536926 | -2.25791714368282 | 0.0 | 0.013528491052921 | 0.1 | 70/86 | 61.20% | 16 |
| prerank | Thermogenesis | -0.119985713017665 | -2.059011466760391 | 0.0 | 0.0243252675663099 | 0.25 | 118/159 | 61.23% | 16 |
| prerank | Ribosome | -0.0986916187640376 | -1.2343055799625748 | 0.2413793103448276 | 0.5549282964592411 | 1.0 | 93/112 | 72.43% | 16 |
| prerank | Epstein-Barr virus infection | -0.0735439406826843 | -1.2010141513757822 | 0.25 | 0.5515253606328525 | 1.0 | 121/179 | 59.04% | 16 |
| prerank | Taste transduction | -0.1417973572809813 | -0.9239386376720244 | 0.6538461538461539 | 0.8495865697820095 | 1.0 | 15/32 | 31.04% | 16 |
| prerank | Ribosome | -0.1429843414461468 | -1.935132220388343 | 0.0 | 0.0402945619335347 | 0.44 | 86/112 | 61.80% | 17 |
| prerank | Epstein-Barr virus infection | -0.0989803694223771 | -1.6377537736470795 | 0.0 | 0.1405948784347576 | 0.95 | 86/179 | 37.03% | 17 |
| prerank | Oxidative phosphorylation | -0.1321516800386444 | -1.5503137660883377 | 0.0294117647058823 | 0.1873047842836362 | 0.98 | 47/86 | 40.21% | 17 |
| prerank | Thermogenesis | -0.0495010447489337 | -0.753272068712083 | 0.8709677419354839 | 0.9325568175837132 | 1.0 | 80/159 | 44.25% | 17 |
| prerank | Taste transduction | 0.0837504809450444 | 0.5391166734889357 | 1.0 | 0.986275292019886 | 1.0 | 18/32 | 49.33% | 17 |
| prerank | Ribosome | -0.2300643695538789 | -3.032637747261451 | 0.0 | 0.0 | 0.0 | 67/112 | 36.08% | 18 |
| prerank | Oxidative phosphorylation | -0.2258420027873637 | -2.426969664198208 | 0.0 | 0.0030002293168904 | 0.03 | 61/86 | 47.80% | 18 |
| prerank | Epstein-Barr virus infection | -0.163436713082365 | -2.312736020117996 | 0.0 | 0.0060671303963784 | 0.07 | 66/179 | 19.74% | 18 |
| prerank | Thermogenesis | -0.0540860555409017 | -0.8808549381934389 | 0.6428571428571429 | 0.7158308325876414 | 1.0 | 137/159 | 80.28% | 18 |
| prerank | Taste transduction | 0.0903422763299656 | 0.5715602775591783 | 0.9423076923076924 | 0.9854396948327132 | 1.0 | 12/32 | 29.38% | 18 |
| prerank | Ribosome | -0.2865315189205287 | -3.5741418374315392 | 0.0 | 0.0 | 0.0 | 80/112 | 41.74% | 19 |
| prerank | Oxidative phosphorylation | -0.228410490583011 | -2.4631593708013453 | 0.0 | 0.0 | 0.0 | 40/86 | 22.24% | 19 |
| prerank | Epstein-Barr virus infection | -0.1084580718550667 | -1.9171496093342697 | 0.0 | 0.0473985890652557 | 0.4 | 77/179 | 30.61% | 19 |
| prerank | Thermogenesis | -0.0895152851569006 | -1.32764710460203 | 0.1363636363636363 | 0.420344560588463 | 1.0 | 132/159 | 73.22% | 19 |
| prerank | Taste transduction | 0.1926586094746618 | 1.1079070707887402 | 0.3859649122807017 | 0.806349607678106 | 1.0 | 30/32 | 74.82% | 19 |
| prerank | Epstein-Barr virus infection | -0.0853369011310599 | -1.5479124740309584 | 0.0303030303030303 | 0.2999792957090357 | 0.97 | 46/179 | 15.94% | 20 |
| prerank | Ribosome | -0.1077871147797501 | -1.3732178053318371 | 0.0666666666666666 | 0.3707169657065273 | 1.0 | 59/112 | 40.58% | 20 |
| prerank | Taste transduction | -0.147339358915744 | -1.0153596695405562 | 0.4722222222222222 | 0.697960819046414 | 1.0 | 12/32 | 21.09% | 20 |
| prerank | Thermogenesis | 0.0542222308163235 | 0.7571389446423754 | 0.7866666666666666 | 0.9763971347870776 | 1.0 | 150/159 | 89.39% | 20 |
| prerank | Oxidative phosphorylation | 0.0704483502934994 | 0.7206262365493948 | 0.8235294117647058 | 0.9541908068839632 | 1.0 | 84/86 | 90.89% | 20 |
| prerank | Ribosome | 0.227543804362252 | 2.561665516577705 | 0.0 | 0.0061374558508482 | 0.01 | 72/112 | 42.71% | 21 |
| prerank | Epstein-Barr virus infection | -0.1441302848400509 | -2.324946604635544 | 0.0 | 0.0037351456909816 | 0.05 | 112/179 | 47.05% | 21 |
| prerank | Taste transduction | 0.2050893693918116 | 1.3499798123440814 | 0.1639344262295081 | 1.0 | 1.0 | 31/32 | 76.55% | 21 |
| prerank | Oxidative phosphorylation | -0.11407752268435 | -1.2261204071398637 | 0.2258064516129032 | 0.3921902975530735 | 1.0 | 28/86 | 20.10% | 21 |
| prerank | Thermogenesis | -0.0423312481418022 | -0.7048522598483786 | 0.935483870967742 | 0.919570897674442 | 1.0 | 152/159 | 91.18% | 21 |
| prerank | Epstein-Barr virus infection | -0.104099107261312 | -1.5395196576693624 | 0.08 | 0.137222527976518 | 0.99 | 38/179 | 9.71% | 22 |
| prerank | Ribosome | -0.1188469970281153 | -1.5179883663741862 | 0.0666666666666666 | 0.1478504771584324 | 0.99 | 32/112 | 15.52% | 22 |
| prerank | Oxidative phosphorylation | -0.1063207806531286 | -1.2234510409142016 | 0.1666666666666666 | 0.3499987708812442 | 1.0 | 64/86 | 62.78% | 22 |
| prerank | Taste transduction | -0.1162346220625998 | -0.8115098576982108 | 0.6571428571428571 | 0.7833040746558256 | 1.0 | 17/32 | 39.94% | 22 |
| prerank | Thermogenesis | 0.0308342620424767 | 0.4293938133054199 | 1.0 | 0.9970842273202398 | 1.0 | 29/159 | 16.15% | 22 |
| prerank | Epstein-Barr virus infection | -0.1490222125794351 | -2.4517198895361614 | 0.0 | 0.0081440791451449 | 0.04 | 94/179 | 36.77% | 23 |
| prerank | Oxidative phosphorylation | -0.1900501123715608 | -1.909310181176379 | 0.0 | 0.0470320570632122 | 0.42 | 71/86 | 63.12% | 23 |
| prerank | Taste transduction | -0.1815968266524949 | -1.3009534103446785 | 0.1428571428571428 | 0.3487975389103511 | 1.0 | 10/32 | 12.03% | 23 |
| prerank | Thermogenesis | -0.0755688546724218 | -1.0832749743737218 | 0.303030303030303 | 0.5208393115793502 | 1.0 | 61/159 | 29.92% | 23 |
| prerank | Ribosome | 0.0520079995085884 | 0.64139179465484 | 0.8679245283018868 | 0.955425070683007 | 1.0 | 53/112 | 43.18% | 23 |
| prerank | Oxidative phosphorylation | -0.2140088342006968 | -2.5581159053371945 | 0.0 | 0.0010142228443316 | 0.01 | 46/86 | 31.19% | 24 |
| prerank | Epstein-Barr virus infection | -0.1580411043735501 | -2.550278082209685 | 0.0 | 0.0009466079880428 | 0.01 | 60/179 | 16.72% | 24 |
| prerank | Taste transduction | -0.1907365919825491 | -1.293927415862764 | 0.2156862745098039 | 0.3142951241198439 | 1.0 | 17/32 | 32.98% | 24 |
| prerank | Ribosome | -0.0860341248910368 | -1.1004974235817673 | 0.3103448275862069 | 0.4815245370754795 | 1.0 | 106/112 | 85.90% | 24 |
| prerank | Thermogenesis | -0.0711413956891996 | -1.0751266704488225 | 0.3333333333333333 | 0.5077702335860602 | 1.0 | 117/159 | 65.75% | 24 |
| prerank | Thermogenesis | 0.1659622741611206 | 2.2467535634369544 | 0.0 | 0.041135225375626 | 0.17 | 116/159 | 57.68% | 25 |
| prerank | Oxidative phosphorylation | 0.188872351022407 | 2.166578649559165 | 0.0 | 0.0467445742904841 | 0.25 | 40/86 | 29.28% | 25 |
| prerank | Ribosome | -0.1565338198474687 | -1.860725280286564 | 0.0285714285714285 | 0.1290420066485343 | 0.64 | 69/112 | 44.77% | 25 |
| prerank | Taste transduction | -0.166541500257256 | -1.2417514094893585 | 0.1489361702127659 | 0.5870489573889394 | 1.0 | 11/32 | 16.31% | 25 |
| prerank | Epstein-Barr virus infection | -0.0471492858169478 | -0.753211572826966 | 0.8888888888888888 | 0.9572471118372036 | 1.0 | 148/179 | 77.11% | 25 |
| prerank | Epstein-Barr virus infection | -0.1120298340814006 | -2.0146072424615937 | 0.0 | 0.0252861368312757 | 0.23 | 103/179 | 44.77% | 26 |
| prerank | Oxidative phosphorylation | -0.1609719325626107 | -1.7046833340244654 | 0.03125 | 0.1078765707671957 | 0.75 | 44/86 | 33.41% | 26 |
| prerank | Ribosome | -0.1061645417419538 | -1.3642996693988605 | 0.15 | 0.3313058609825103 | 1.0 | 73/112 | 53.04% | 26 |
| prerank | Taste transduction | 0.1592193386692686 | 1.0458250483076112 | 0.3461538461538461 | 0.9616015093405912 | 1.0 | 10/32 | 17.21% | 26 |
| prerank | Thermogenesis | 0.0563497911713277 | 0.7360008639741472 | 0.8260869565217391 | 0.9576472894762056 | 1.0 | 90/159 | 52.59% | 26 |
| prerank | Ribosome | -0.1964814337453577 | -2.496369619941877 | 0.0 | 0.0 | 0.0 | 89/112 | 58.81% | 27 |
| prerank | Epstein-Barr virus infection | -0.1227396672517917 | -2.377325966460432 | 0.0 | 0.0035433331129767 | 0.02 | 102/179 | 42.99% | 27 |
| prerank | Taste transduction | -0.116205108934208 | -0.8434816132145562 | 0.6415094339622641 | 0.767727265474158 | 1.0 | 11/32 | 21.36% | 27 |
| prerank | Thermogenesis | 0.0549077516421173 | 0.7168894036733295 | 0.8412698412698413 | 0.9068752813784474 | 1.0 | 62/159 | 35.14% | 27 |
| prerank | Oxidative phosphorylation | -0.0615741373995872 | -0.6477804376991224 | 0.9117647058823528 | 0.9522364394893263 | 1.0 | 33/86 | 30.82% | 27 |
| prerank | Epstein-Barr virus infection | -0.1655189474382541 | -2.870958226917452 | 0.0 | 0.0 | 0.0 | 77/179 | 25.63% | 28 |
| prerank | Ribosome | -0.2069016676747544 | -2.800232676708195 | 0.0 | 0.0 | 0.0 | 80/112 | 50.28% | 28 |
| prerank | Thermogenesis | 0.1313157689829146 | 1.88494187185635 | 0.0 | 0.4625279304305816 | 0.67 | 110/159 | 56.99% | 28 |
| prerank | Taste transduction | -0.1471600495573211 | -0.9981835364480396 | 0.391304347826087 | 0.6522519625967902 | 1.0 | 30/32 | 78.87% | 28 |
| prerank | Oxidative phosphorylation | -0.0719395400172545 | -0.7948374235753343 | 0.7 | 0.858257819010995 | 1.0 | 85/86 | 91.65% | 28 |
| prerank | Ribosome | -0.3640114664957908 | -4.447733367143593 | 0.0 | 0.0 | 0.0 | 77/112 | 31.66% | 29 |
| prerank | Oxidative phosphorylation | -0.2743933145830459 | -3.267497189735176 | 0.0 | 0.0 | 0.0 | 57/86 | 37.99% | 29 |
| prerank | Thermogenesis | -0.1322448508758917 | -2.085066924759269 | 0.0227272727272727 | 0.0196933560477001 | 0.24 | 96/159 | 46.08% | 29 |
| prerank | Epstein-Barr virus infection | 0.0919162478505591 | 1.2637288151803443 | 0.1571428571428571 | 0.5393307349274904 | 1.0 | 58/179 | 24.48% | 29 |
| prerank | Taste transduction | -0.1409379951415683 | -0.9495072224306784 | 0.6 | 0.9666477380276356 | 1.0 | 15/32 | 31.53% | 29 |
| prerank | Oxidative phosphorylation | -0.2601385384155186 | -3.008403321908917 | 0.0 | 0.0 | 0.0 | 69/86 | 53.33% | 30 |
| prerank | Ribosome | -0.2225102822614033 | -2.9368797355344225 | 0.0 | 0.0 | 0.0 | 73/112 | 41.60% | 30 |
| prerank | Thermogenesis | -0.1091719810812835 | -1.7218181735948006 | 0.0 | 0.0964372318597276 | 0.76 | 114/159 | 59.59% | 30 |
| prerank | Taste transduction | -0.1681589880592587 | -1.1892261384806169 | 0.2325581395348837 | 0.4385299727053663 | 1.0 | 26/32 | 63.47% | 30 |
| prerank | Epstein-Barr virus infection | 0.0557083601545044 | 0.8433363336922206 | 0.625 | 0.7871948695747323 | 1.0 | 25/179 | 9.59% | 30 |
| prerank | Ribosome | -0.3088603817864165 | -4.5095090913599805 | 0.0 | 0.0 | 0.0 | 67/112 | 27.76% | 31 |
| prerank | Oxidative phosphorylation | -0.2280577290437473 | -2.633010961111174 | 0.0 | 0.0067149673087117 | 0.03 | 46/86 | 29.19% | 31 |
| prerank | Thermogenesis | -0.1089243720432984 | -1.6118959971372937 | 0.0357142857142857 | 0.1765077121147098 | 0.94 | 58/159 | 24.24% | 31 |
| prerank | Taste transduction | 0.1692150451803977 | 1.1212167825319377 | 0.2666666666666666 | 1.0 | 1.0 | 8/32 | 9.57% | 31 |
| prerank | Epstein-Barr virus infection | -0.0540938598818739 | -0.8876800724429279 | 0.5625 | 0.8275281530626998 | 1.0 | 108/179 | 53.43% | 31 |
| prerank | Ribosome | -0.2578530355840409 | -3.32931674505725 | 0.0 | 0.0 | 0.0 | 51/112 | 18.35% | 32 |
| prerank | Oxidative phosphorylation | -0.3010482068914579 | -3.251304941949133 | 0.0 | 0.0 | 0.0 | 55/86 | 32.65% | 32 |
| prerank | Thermogenesis | -0.195088115043457 | -3.1460939081379293 | 0.0 | 0.0 | 0.0 | 84/159 | 31.91% | 32 |
| prerank | Taste transduction | -0.1598448791793256 | -1.1499614807625744 | 0.2391304347826087 | 0.5808088388094853 | 1.0 | 9/32 | 10.34% | 32 |
| prerank | Epstein-Barr virus infection | 0.0430492200213103 | 0.6365137133053301 | 0.8985507246376812 | 0.9827247306416328 | 1.0 | 116/179 | 61.99% | 32 |
| prerank | Ribosome | -0.3630708010063278 | -4.739782665252094 | 0.0 | 0.0 | 0.0 | 85/112 | 39.11% | 33 |
| prerank | Oxidative phosphorylation | -0.3017187042155527 | -3.166046240333104 | 0.0 | 0.0 | 0.0 | 70/86 | 50.74% | 33 |
| prerank | Thermogenesis | -0.1383763649312712 | -2.030776858527007 | 0.0 | 0.0216223562388516 | 0.33 | 107/159 | 52.73% | 33 |
| prerank | Epstein-Barr virus infection | -0.1147388570848083 | -1.731023342971171 | 0.0344827586206896 | 0.0902363833497384 | 0.8 | 68/179 | 25.48% | 33 |
| prerank | Taste transduction | -0.2120107719433776 | -1.489015373061367 | 0.0980392156862745 | 0.2118406523401002 | 0.99 | 14/32 | 21.31% | 33 |
| prerank | Oxidative phosphorylation | -0.2545196538658869 | -2.853425457553988 | 0.0 | 0.0 | 0.0 | 59/86 | 41.96% | 34 |
| prerank | Epstein-Barr virus infection | -0.1406276819473865 | -2.199380839754852 | 0.0 | 0.0069618490671122 | 0.08 | 101/179 | 40.64% | 34 |
| prerank | Ribosome | -0.1404734864995973 | -1.6958172669378744 | 0.0 | 0.0890740364424574 | 0.86 | 55/112 | 33.62% | 34 |
| prerank | Taste transduction | -0.1327015686283943 | -0.9523420525198376 | 0.4772727272727273 | 0.6694432158828444 | 1.0 | 8/32 | 10.41% | 34 |
| prerank | Thermogenesis | -0.0642275325875987 | -0.9438060795186816 | 0.5121951219512195 | 0.6694621168305378 | 1.0 | 46/159 | 21.19% | 34 |
| prerank | Epstein-Barr virus infection | -0.1337794321853186 | -2.1911135547340184 | 0.0 | 0.0103028113374597 | 0.14 | 66/179 | 22.07% | 35 |
| prerank | Thermogenesis | 0.1169191327605175 | 1.5391984192601724 | 0.0422535211267605 | 0.8218183832899328 | 1.0 | 88/159 | 45.25% | 35 |
| prerank | Oxidative phosphorylation | 0.0975026009723607 | 1.0324645616114798 | 0.4 | 0.9667967358698148 | 1.0 | 53/86 | 53.19% | 35 |
| prerank | Taste transduction | -0.1216536857868528 | -0.8727845560307057 | 0.5957446808510638 | 0.7538368738593555 | 1.0 | 19/32 | 45.99% | 35 |
| prerank | Ribosome | -0.0485747667164141 | -0.5931017707095675 | 0.9393939393939394 | 0.9753651291582288 | 1.0 | 84/112 | 69.03% | 35 |
| prerank | Oxidative phosphorylation | -0.2263274299523434 | -2.737231883792341 | 0.0 | 0.0 | 0.0 | 64/86 | 50.58% | 36 |
| prerank | Thermogenesis | -0.1201911536898513 | -1.9299521792350136 | 0.0 | 0.0538910872432636 | 0.44 | 93/159 | 44.78% | 36 |
| prerank | Taste transduction | 0.211778769747215 | 1.3365944361544937 | 0.173076923076923 | 0.5778762826788498 | 1.0 | 24/32 | 55.02% | 36 |
| prerank | Ribosome | -0.1034471847868074 | -1.2945477592320158 | 0.125 | 0.3413102192073362 | 1.0 | 49/112 | 31.63% | 36 |
| prerank | Epstein-Barr virus infection | -0.0576208425867244 | -0.9646737080773496 | 0.5 | 0.700175868349978 | 1.0 | 43/179 | 16.70% | 36 |
| prerank | Ribosome | -0.2780402190998905 | -3.7626702164566943 | 0.0 | 0.0 | 0.0 | 80/112 | 42.60% | 37 |
| prerank | Oxidative phosphorylation | -0.1833048188200864 | -2.050333616747916 | 0.0 | 0.0303655660377358 | 0.28 | 76/86 | 69.50% | 37 |
| prerank | Epstein-Barr virus infection | -0.0958088948657161 | -1.629439063271938 | 0.0 | 0.1462421909509686 | 0.86 | 102/179 | 46.10% | 37 |
| prerank | Thermogenesis | -0.0836067027722523 | -1.3190298606653903 | 0.1666666666666666 | 0.3955309627479438 | 1.0 | 152/159 | 87.09% | 37 |
| prerank | Taste transduction | 0.1273989683571168 | 0.8722501590968771 | 0.576271186440678 | 0.7863051117965717 | 1.0 | 6/32 | 7.30% | 37 |
| prerank | Thermogenesis | 0.1543315294185555 | 2.100021315152871 | 0.0149253731343283 | 0.2416159380188157 | 0.42 | 97/159 | 47.08% | 38 |
| prerank | Ribosome | -0.1395500689620349 | -2.0428100405841603 | 0.0 | 0.0313967673071058 | 0.19 | 88/112 | 63.77% | 38 |
| prerank | Epstein-Barr virus infection | -0.0968682231117353 | -1.5861196199728786 | 0.0 | 0.163543404553038 | 0.91 | 48/179 | 15.98% | 38 |
| prerank | Oxidative phosphorylation | 0.1404503366589868 | 1.4065092972713316 | 0.1166666666666666 | 0.7813613724405091 | 1.0 | 51/86 | 46.79% | 38 |
| prerank | Taste transduction | -0.1333043674603921 | -0.933825652743302 | 0.5853658536585366 | 0.7637583520474647 | 1.0 | 23/32 | 57.40% | 38 |
| prerank | Epstein-Barr virus infection | -0.1208544640341385 | -1.8792193758859483 | 0.0 | 0.0779192913084126 | 0.6 | 71/179 | 26.75% | 39 |
| prerank | Ribosome | -0.1214087761786404 | -1.6738897666231272 | 0.0277777777777777 | 0.1330911766058209 | 0.86 | 64/112 | 44.26% | 39 |
| prerank | Oxidative phosphorylation | -0.1337418025070802 | -1.4844452740123826 | 0.0909090909090909 | 0.2296105568072095 | 0.98 | 66/86 | 62.70% | 39 |
| prerank | Taste transduction | -0.1912523199587957 | -1.3816456726391608 | 0.1333333333333333 | 0.3064158024799114 | 1.0 | 13/32 | 20.46% | 39 |
| prerank | Thermogenesis | 0.0383834139505656 | 0.5746257618987081 | 0.9696969696969696 | 1.0 | 1.0 | 140/159 | 84.73% | 39 |
| prerank | Ribosome | -0.1330614426196696 | -1.6552021458471902 | 0.0476190476190476 | 0.1990882759126407 | 0.9 | 96/112 | 71.95% | 40 |
| prerank | Taste transduction | -0.1995615584775341 | -1.532337126571576 | 0.0465116279069767 | 0.2384375715795661 | 1.0 | 9/32 | 6.79% | 40 |
| prerank | Oxidative phosphorylation | -0.1128483370623297 | -1.2799354987414728 | 0.1707317073170731 | 0.3859904273473485 | 1.0 | 50/86 | 45.85% | 40 |
| prerank | Thermogenesis | -0.069802249076307 | -0.9963950374822887 | 0.4615384615384615 | 0.6727154407149333 | 1.0 | 47/159 | 21.68% | 40 |
| prerank | Epstein-Barr virus infection | -0.0423759172324384 | -0.6557109849000161 | 0.9333333333333332 | 0.9560671357686714 | 1.0 | 36/179 | 15.15% | 40 |
| prerank | Oxidative phosphorylation | -0.3178452567996256 | -3.2308443138546794 | 0.0 | 0.0 | 0.0 | 60/86 | 36.90% | 41 |
| prerank | Ribosome | -0.2398031423342298 | -3.2183620427351154 | 0.0 | 0.0 | 0.0 | 62/112 | 29.85% | 41 |
| prerank | Epstein-Barr virus infection | -0.0925176446724106 | -1.5139748150739774 | 0.0714285714285714 | 0.1867903688977247 | 1.0 | 94/179 | 41.80% | 41 |
| prerank | Thermogenesis | -0.0858185058777302 | -1.2891483325508557 | 0.1388888888888889 | 0.362055310413939 | 1.0 | 73/159 | 35.91% | 41 |
| prerank | Taste transduction | 0.1355329698643851 | 0.9167825200406078 | 0.6101694915254238 | 0.8683607535453032 | 1.0 | 11/32 | 22.45% | 41 |
| prerank | Ribosome | -0.1640123151182866 | -2.203301450185885 | 0.0 | 0.0058554195650259 | 0.03 | 47/112 | 24.40% | 42 |
| prerank | Epstein-Barr virus infection | -0.1240266084660245 | -2.058553522884664 | 0.0 | 0.0156144521734026 | 0.12 | 58/179 | 18.85% | 42 |
| prerank | Oxidative phosphorylation | -0.1371541527892488 | -1.525522447158714 | 0.0789473684210526 | 0.164211988690284 | 0.99 | 31/86 | 21.18% | 42 |
| prerank | Thermogenesis | 0.0720718234332094 | 1.0664691857698492 | 0.4 | 0.6857369966176559 | 1.0 | 76/159 | 41.91% | 42 |
| prerank | Taste transduction | 0.1515671345565241 | 1.030931393872168 | 0.4230769230769231 | 0.7313310413885615 | 1.0 | 18/32 | 42.56% | 42 |
| prerank | Oxidative phosphorylation | -0.2727001833743558 | -3.240032787152209 | 0.0 | 0.0 | 0.0 | 61/86 | 42.59% | 43 |
| prerank | Ribosome | -0.2035206597539268 | -2.6583790691907123 | 0.0 | 0.0 | 0.0 | 54/112 | 26.37% | 43 |
| prerank | Epstein-Barr virus infection | -0.1166104695400355 | -1.923537561138284 | 0.0 | 0.0455769077000986 | 0.48 | 63/179 | 22.09% | 43 |
| prerank | Thermogenesis | -0.1254676352054362 | -1.845754742062561 | 0.0 | 0.0558676937018577 | 0.64 | 118/159 | 60.51% | 43 |
| prerank | Taste transduction | -0.0841319508329352 | -0.5943039962466512 | 0.9310344827586208 | 0.9839238785681922 | 1.0 | 5/32 | 6.19% | 43 |
| prerank | Oxidative phosphorylation | -0.2321417570446411 | -2.608379742905366 | 0.0 | 0.0050045703839122 | 0.03 | 45/86 | 27.77% | 44 |
| prerank | Thermogenesis | -0.1553811792791847 | -2.413857190150817 | 0.0 | 0.0033363802559414 | 0.03 | 73/159 | 29.10% | 44 |
| prerank | Epstein-Barr virus infection | -0.0995353249186391 | -1.777463698855575 | 0.0 | 0.0973110907982937 | 0.78 | 65/179 | 24.97% | 44 |
| prerank | Ribosome | -0.082706191996807 | -1.1703424936817148 | 0.1891891891891892 | 0.5609355503322596 | 1.0 | 94/112 | 74.95% | 44 |
| prerank | Taste transduction | -0.115225257303539 | -0.7379242450079108 | 0.8333333333333334 | 0.9559267559120128 | 1.0 | 18/32 | 43.30% | 44 |
| prerank | Epstein-Barr virus infection | -0.1483740711922618 | -2.5401627938768514 | 0.0 | 0.0028021015761821 | 0.01 | 94/179 | 36.32% | 45 |
| prerank | Ribosome | -0.1752683634281028 | -2.1107840486152813 | 0.0 | 0.0196147110332749 | 0.12 | 104/112 | 75.04% | 45 |
| prerank | Thermogenesis | -0.0971470308528347 | -1.6584616343711849 | 0.0344827586206896 | 0.1473697865992086 | 0.9 | 91/159 | 46.24% | 45 |
| prerank | Oxidative phosphorylation | -0.109608407267224 | -1.2988032557097435 | 0.1481481481481481 | 0.4687428614939465 | 1.0 | 33/86 | 26.02% | 45 |
| prerank | Taste transduction | -0.1551495073391745 | -1.0785825390232742 | 0.3076923076923077 | 0.6719363847209733 | 1.0 | 20/32 | 45.38% | 45 |
| prerank | Ribosome | -0.1431119957761128 | -1.872286502984436 | 0.0 | 0.0499218630888855 | 0.55 | 73/112 | 49.78% | 46 |
| prerank | Epstein-Barr virus infection | -0.0793189315278572 | -1.3118898412789644 | 0.1481481481481481 | 0.2911412835816963 | 1.0 | 123/179 | 59.66% | 46 |
| prerank | Thermogenesis | 0.0936037460391565 | 1.2548579471203485 | 0.1969696969696969 | 1.0 | 1.0 | 111/159 | 61.67% | 46 |
| prerank | Oxidative phosphorylation | 0.0813586157156401 | 0.8352347040497169 | 0.6470588235294118 | 0.9734071341051324 | 1.0 | 59/86 | 61.67% | 46 |
| prerank | Taste transduction | -0.0950583728437162 | -0.6570628315004804 | 0.8235294117647058 | 0.918104559291236 | 1.0 | 26/32 | 70.77% | 46 |
| prerank | Epstein-Barr virus infection | -0.1052548510684108 | -1.6942473121961907 | 0.0 | 0.1527238882643749 | 0.83 | 70/179 | 27.11% | 47 |
| prerank | Taste transduction | -0.1665622841165926 | -1.1589575677115576 | 0.1578947368421052 | 0.5307371527555014 | 1.0 | 27/32 | 66.92% | 47 |
| prerank | Ribosome | 0.0928670008454053 | 1.0481938467277976 | 0.3174603174603174 | 0.9726296283829868 | 1.0 | 60/112 | 46.00% | 47 |
| prerank | Oxidative phosphorylation | 0.0764689987773298 | 0.8349208881250927 | 0.6190476190476191 | 0.9295712285133726 | 1.0 | 27/86 | 25.32% | 47 |
| prerank | Thermogenesis | 0.0516962539223096 | 0.6632178111894441 | 0.8947368421052632 | 0.9660380807615692 | 1.0 | 77/159 | 44.90% | 47 |
| prerank | Ribosome | -0.2086899163590077 | -2.8344373214639305 | 0.0 | 0.0 | 0.0 | 92/112 | 60.70% | 48 |
| prerank | Oxidative phosphorylation | -0.1847751109308437 | -2.06696296442626 | 0.0 | 0.0289672920968369 | 0.27 | 57/86 | 46.54% | 48 |
| prerank | Taste transduction | -0.2350461769872571 | -1.5705780859429173 | 0.0344827586206896 | 0.229022653140617 | 0.97 | 17/32 | 27.56% | 48 |
| prerank | Epstein-Barr virus infection | -0.087385234757465 | -1.4178785746948572 | 0.0625 | 0.3207701610135031 | 1.0 | 53/179 | 19.58% | 48 |
| prerank | Thermogenesis | 0.0805316014676845 | 1.1124624427720406 | 0.2876712328767123 | 0.7825594377496813 | 1.0 | 56/159 | 28.71% | 48 |
| prerank | Oxidative phosphorylation | -0.2510168501713146 | -2.7585729333414672 | 0.0 | 0.0094270547318323 | 0.01 | 61/86 | 44.79% | 49 |
| prerank | Thermogenesis | -0.0826014889987527 | -1.424594202281424 | 0.0 | 0.3296102350879946 | 1.0 | 85/159 | 43.73% | 49 |
| prerank | Epstein-Barr virus infection | 0.1011614267036261 | 1.4215808102880614 | 0.1111111111111111 | 0.4581956717621208 | 1.0 | 46/179 | 17.31% | 49 |
| prerank | Taste transduction | -0.1487174195437644 | -1.1160397511139348 | 0.35 | 0.6191689547867472 | 1.0 | 20/32 | 46.14% | 49 |
| prerank | Ribosome | -0.0626830455571333 | -0.8321608130739544 | 0.6756756756756757 | 0.9056015526361488 | 1.0 | 109/112 | 90.87% | 49 |

**Appendix IV**

**A graph showing a line graph

AI-generated content may be incorrect.**

**Appendix V**

**A diagram of a gene expression

AI-generated content may be incorrect.**