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# Identification of Lung Cancer Metabolomics Profile and Molecular Interactions Using Bioinformatic Methods

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ABSTRACT

Lung cancer remains a major public health concern and a leading cause of cancer-related deaths worldwide. Despite its prevalence, existing diagnostic approaches for early detection face significant challenges, including limited clinical resources and insufficient screening techniques. As a result, many cases are diagnosed at advanced stages, delaying critical treatment. Advances in omics technologies—such as metabolomics, proteomics, and genomics—have shown promise in improving early lung cancer detection. Metabolomics, in particular, provides a detailed analysis of cellular and tissue metabolism, offering valuable insights into disease mechanisms. By examining endogenous metabolites in biological systems, metabolomics has demonstrated strong potential for early cancer detection and personalized therapy. In this study, we conducted an extensive review of online metabolomic databases, including the Metabolomics Workbench, to identify critical metabolites associated with various forms of lung cancer. Additionally, using network analysis tools like Metagenes, we established links between metabolomic genes and 43 genes involved in lung cancer progression. Our integrated analysis reveals a comprehensive metabolic and molecular profile of lung cancer, highlighting 10 key metabolic pathways—particularly amino acid metabolism—that play a role in disease development. These findings contribute to a deeper understanding of lung cancer biology and may guide future research and clinical strategies for improved diagnosis and treatment.

**Keywords: Bioinformatics; Lung Cancer; Metabolomics; Molecular Interaction**

## INTRODUCTION:

Lung cancer is a significant global health concern, with approximately 2.3 million new cases and 1.7 million deaths reported in 2020 [1]. The delayed diagnosis of lung cancer has been identified as a major contributor to the high mortality rate, emphasizing the critical need for techniques that enable early detection [2]. Metabolomic profiling, which explores the molecular invasion at various levels such as the transcriptome, proteome, metabolome, genome, and epigenome, has emerged as a promising approach to understanding the pathogenesis of diseases, including lung cancer [3]. Metabolites have been recognized to play a substantial role in the development of cancer. Variations in metabolite concentrations in body fluids have shown potential as biomarkers for various diseases, including lung cancer [4]. The existing literature highlights the growing interest in the use of metabolomics for studying lung cancer and the identification of potential biomarkers and related pathways [5, 6]. However, further research and validation are necessary to establish the utility of metabolomic profiling in the diagnosis of lung cancer. Recent studies have identified specific metabolites such as palmitic acid, heptadecanoic acid, 4-oxoproline, tridecanoic acid, and ornithine that are considered promising biomarkers for the diagnosis and prognosis of lung cancer [7]. These findings underscore the potential of metabolomic profiling as a tool for improving the diagnosis of lung cancer. In addition, targeted metabolomic profiling of plasma samples from individuals with non-small cell lung cancer (NSCLC) has been conducted to identify specific biomarkers [8]. Bioinformatics approaches are required to manage, integrate, and analyze large-scale data and generate network information from various omics platforms [9] to achieve precision oncology. The use of bioinformatics in lung cancer research offers several benefits, including the development of new treatment and diagnostic methods, individualized treatment improvements, and the identification of potential biomarkers. The objective of this study is to present a metabolomic profile for lung cancer diagnosis through the integration of data from multiple databases and identifying related metabolite genes that play a significant role in pathway analysis and genomics.

## Methods:

### 1. Metabolomics

Metabolomics datasets search. To identify appropriate metabolomics profiles within Mass Spectrometry (MS) datasets, a search was performed in the Metabolomics Workbench database (https://www.metabolomicsworkbench.org).

Differential metabolite analyses (DMA). The differential metabolite analyses (DMAs) were performed utilizing the web-based tools, Volcano plot and Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA), available in the Metabolomics Workbench database to compare two sample selected groups. A cutoff threshold of p value > 0.2 was applied to identify metabolites that exhibited significant differences.

#### Overlapped DMA identification.

A Venn diagram creator tool provided by the Bioinformatics & Evolutionary Genomics source was utilized (http://bioinformatics.psb.ugent.be/webtools/Venn/) to identify the overlapping metabolomes across multiple datasets. Metabolomes that are present in at least five datasets selected for further analysis to ensure comprehensive coverage of metabolomes and avoid overlooking critical metabolomes that might not exhibit differences in individual studies for various reasons. This approach aimed to capture a broader spectrum of metabolomic information and minimize the possibility of excluding important metabolites.

Metabolome-Gene analysis. MetaBridge database [10] was employed to ascertain the genes linked to the identified metabolites. MetaBridge utilizes Kyoto Encyclopedia of Genes and Genomes (KEGG) [11] and MetaCyc [12] to identify the pertinent genes and pathways associated with the metabolites. Obtained results of KEGG and MetaCyc databases integrated with the OPLS-DA analysis using a Venn diagram.

### 2. Genomics

#### Microarray dataset search.

Appropriate gene expression profiles within microarray datasets were identified using an extensive literature search with keywords such as “Computational Biology,” “Gene Expression Profiling,” and “Lung Neoplasms”. To ensure data integrity and avoid duplication, redundant datasets were subsequently removed, resulting in a refined collection of datasets for further analysis.

Differentially expressed genes (DEGs) detection. The

differentially expressed genes (DEGs) were determined using the online tool GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r) available in the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo). This tool utilizes the GEO query and Limma R packages from the Bioconductor project to compare two sample groups within a GEO dataset. Prior to analysis, the gene expression data underwent normalization using the RMA algorithm. To mitigate false-positive and false-negative results, as well as account for variations across microarray platforms, the gene expression profiles of the lung cancer groups were individually compared to the normal groups or normal adjacent tissue groups within each dataset. A log2FC (RMA signal intensity) of ≥0 or ≤0 and an adjusted p-value > 0.05 (Benjamini & Hochberg correction) were set as thresholds to identify statistically significant DEGs.

3. Integrated transcriptomics

Overlapped Gene identification. Overlapped genes derived from metabolomics analysis (Metabolomics Workbench datasets) and genomic analysis (GEO datasets) were discovered utilizing the Venny diagram. Gene Ontology (GO) and Pathway Enrichment Analysis. The EnrichR platform (https://maayanlab.cloud/Enrichr), which is used for analysis, utilizes the KEGG databases (https://www.genome.jp/kegg), which contain genomic information and biological pathways, for analysis. EnrichR offers multiple tools to investigate diverse gene functions. A significance threshold of P-value < 0.05 was applied for statistical analysis. Uniform Manifold Approximation and Projection (UMAP) analysis was performed to cluster the more similar gene sets closer. GO is employed to identify and characterize genes and proteins, enabling the exploration of the underlying biological properties within the chip database.

Protein-Protein Interaction (PPI) Networks Functional Enrichment Analysis. To construct the protein-protein interaction (PPI) network for the dysregulated genes shared among the datasets, the STRING database (https://string-db.org/) was utilized with default parameters. The generated network was subsequently visualized using Cytoscape software. Within the PPI network, the degree of a node denoted the number of interactions it had with other nodes. Co-expression scores based on RNA expression patterns were provided using ProteomeHD [13].

## Results:

### Study Workflow and Dataset Selection

The study workflow is illustrated in Figure 1. Out of 20 initially considered datasets, 8 met the inclusion criteria, which required MS-based metabolomic profiling of pathologically confirmed lung cancer subtypes in human subjects. Studies using cell lines or animal models were excluded (Supplementary Table S1).

### Identification of Significantly Altered Metabolites

Differential metabolomics analysis (DMA) revealed 251 metabolites with significant changes between tumor and non-tumor samples via OPLS-DA (Supplementary Table S2) and 225 metabolites via Volcano analysis (Supplementary Table S3). Integration across datasets identified 6 overlapping metabolites from OPLS-DA and 13 from Volcano plots consistently altered in ≥5 studies (Supplementary Table S4).

### Gene-Metabolite Integration Analysis Using MetaBridge and Venny

MetaBridge database analysis mapped metabolites from OPLS-DA and Volcano analyses to their corresponding genes (Supplementary Tables S5 and S6). Venny analysis identified 35 overlapping genes shared between the KEGG and MetaCyc databases (Figure 2; Supplementary Table S7).

### Identification of Differentially Expressed Genes (DEGs) via GEO Database Screening

Analysis of 20 GEO datasets (Supplementary Table S8) using GEO2R (adjusted P < 0.05, |log2FC| > 0) identified 30 DEGs in lung cancer vs. normal groups (Supplementary Tables S9–S10) and 40 DEGs in tumor vs. adjacent normal tissue (Supplementary Tables S11–S12).

### Potential biomarker analysis

We identified 43 overlapping genes between metabolite-related genes and DEGs obtained from the GEO database (Supplementary 1, Table S4). EnrichR analysis revealed enrichment of 35 pathways (P value < 0.05) associated with the interaction networks of the overlapping genes (Supplementary 1 Table S5), suggesting that amino acid metabolism plays a critical role in lung cancer pathophysiology. (Figure 3-B) Among these pathways, alanine, aspartate, and glutamate metabolism pathways showed the highest

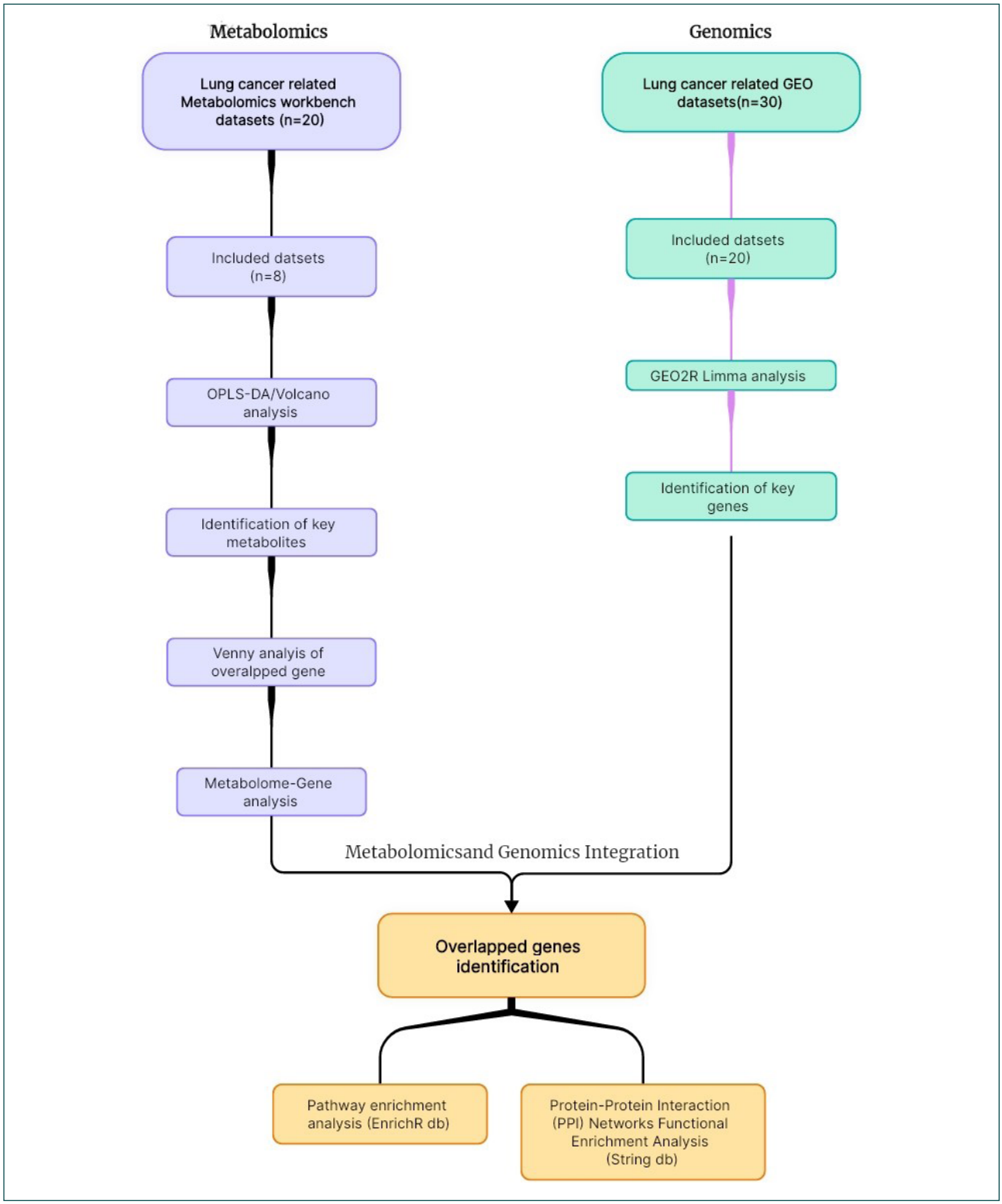


**Figure 1:** An overview of study workflow for identifying

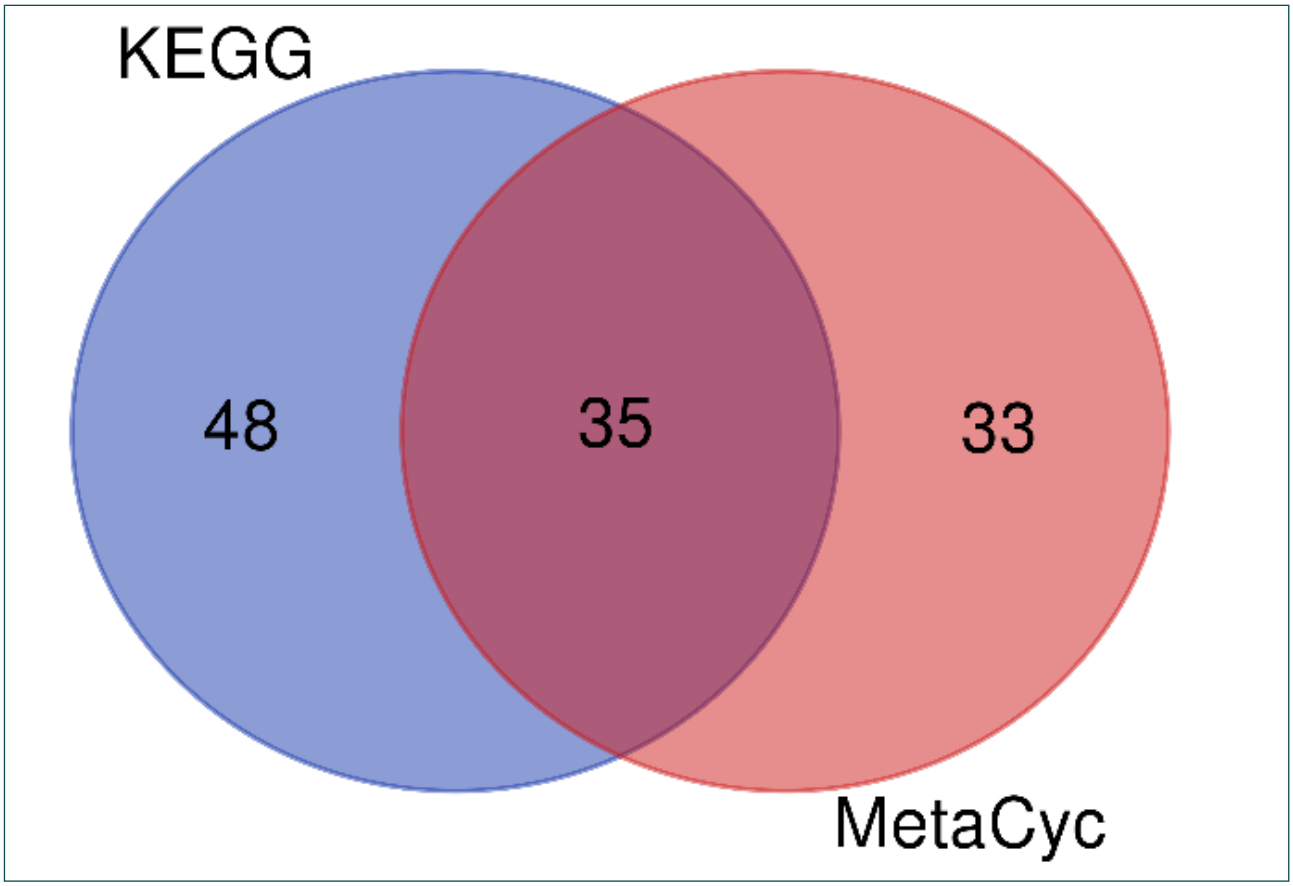


**Figure 2:** Venny diagram for OPLS-DA extracted metabolomic genes

significance in the volcano plot with an odds ratio (OR) of 362.82, followed by Cysteine and methionine metabolism with an OR of 111.17. (Figure 4-B) The Manhattan plot also confirmed these findings. (Figure 3-A) Additionally, the UMAP plot revealed 11 clusters of related gene pathways. (Figure 4-A) GO term analysis categorized the DEGs into biological process (BP), cellular component (CC), and molecular function (MF). The CC of DEGs was predominantly enriched in the Mitochondrial matrix, Cytoplasm, Extracellular exosome, Cytoophidium, Cytosol, and mitochondria. The MF of the DEGs was mainly enriched in catalytic activity, ligase activity, and small molecule binding. The BP of the DEGs showed enrichment in processes such as cellular amino acid metabolic process, carboxylic acid metabolic process, and glutamine family amino acid metabolic process.

## PPI and Modular Analysis

STRING PPI network analysis presented the core candidate and vital gene modules in Lung cancer, involving 43 nodes and 272 edges. (Supplementary 2) GLUD1 with node degree equal to 28 and ALDH18A1, ASNS, GLUD2 with 25 regarded as the most important core of this network. (Figure 5) The co-expression of 43 genes presented in Figure 6 reveals the strong relationship between PAICS with PPAT, GART, and GMPS.

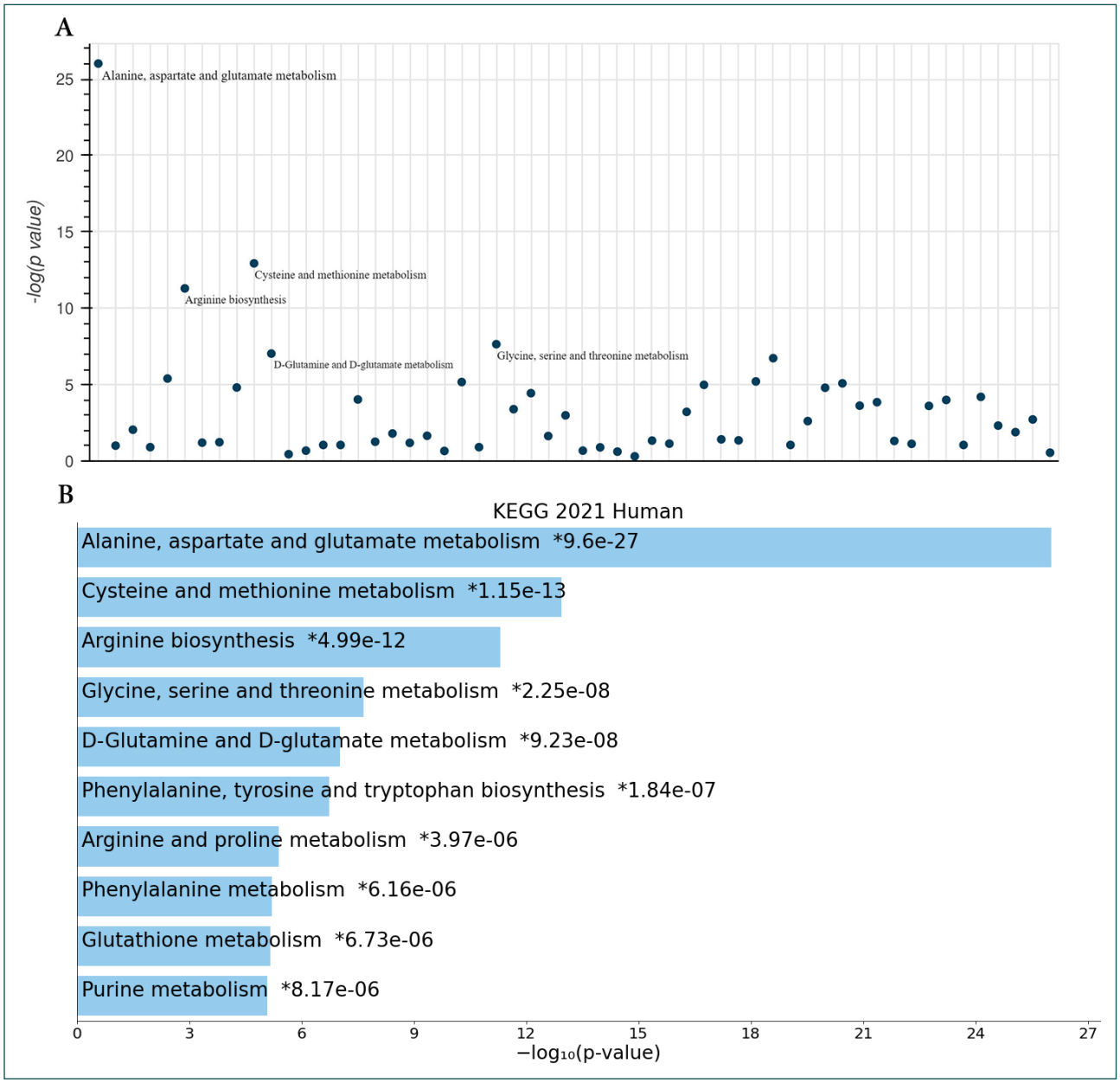


**Figure 3:** Manhattan plot of terms from the KEGG 2021 Human gene set. Each point represents a single term along the x-axis. The y-values represent the -log10(p-value) corresponding to the enrichment of the input gene set for the term gene set. Hovering over the point will display the gene set term and the enrichment analysis p-value. B) Bar chart of top enriched terms from the KEGG 2021 Human gene set library. The top 10 enriched terms for the input gene set are displayed based on the -log10(p-value), with the actual p-value shown next to each term. The term at the top has the most significant overlap with the input query gene set.

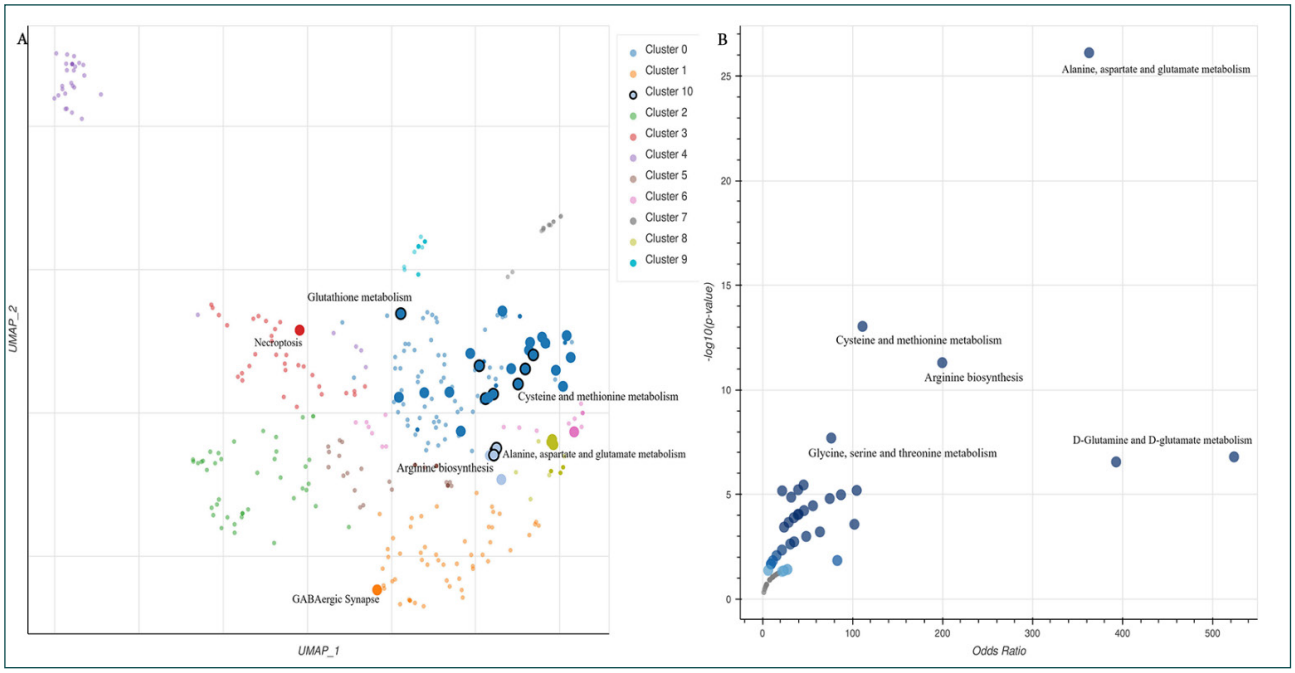


**Figure 4:** Scatterplot of all terms in the KEGG 2021 Human gene set library. Each point represents a term in the library. Term frequency-inverse document frequency (TF-IDF) values were computed for the gene set corresponding to each term, and UMAP was applied to the resulting values. The terms are plotted based on the first two UMAP dimensions. Generally, terms with more similar gene sets are positioned closer together. Terms are colored by automatically identified clusters computed with the Leiden algorithm applied to the TF-IDF values. The darker and larger the point, the more significantly enriched the term. Hovering over points will display the term, the p-value from the enrichment calculation, and the automatically assigned cluster. B) Volcano plot of terms from the KEGG 2021 Human gene set. Each point represents a single term, plotted by the corresponding odds ratio (x-position) and -log10(p-value) (y-position) from the enrichment results of the input query gene set. The larger and darker-colored the point, the more significantly enriched the input gene set is for the term. Hovering over the point will display the gene set term, the odds ratio, and the enrichment analysis p-value.

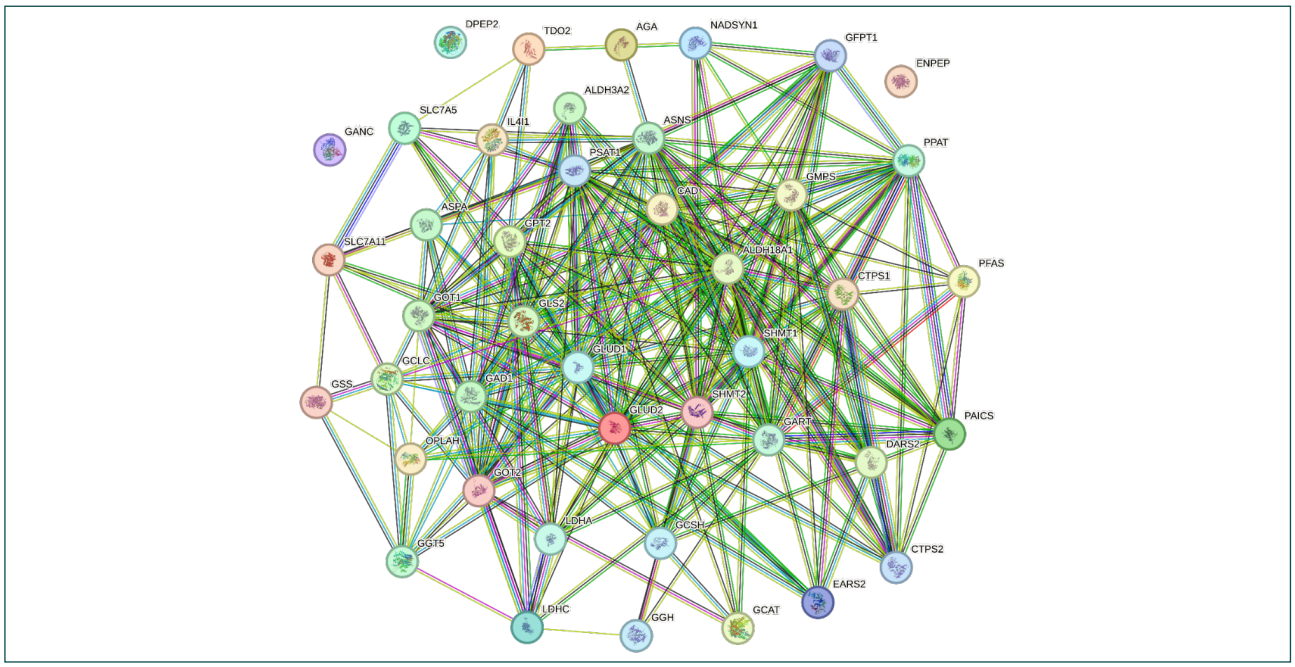


**Figure 5:** PPI analysis using STRING: number of nodes:43, number of edges:272, average node degree:12.7, avg. local clustering coefficient: 0.617, expected number of edges:16, PPI enrichment p-value: < 1.0e-16.

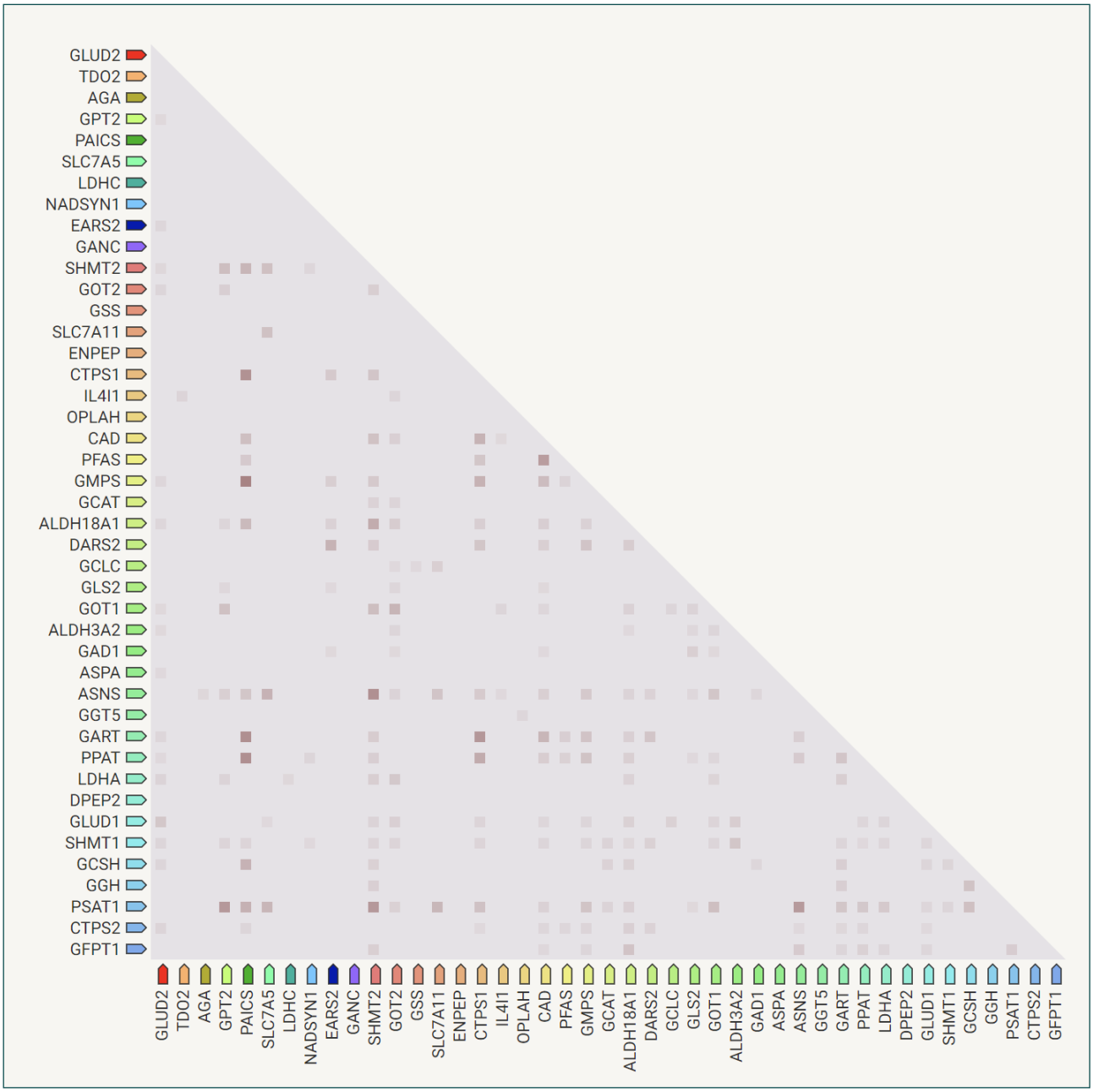


**Figure 6:** Co-expression scores based on RNA expression patterns, and on protein co-regulation provided by ProteomeHD

## Discussion:

The findings highlighted the involvement of significant metabolites such as Lactic acid, Glutamic acid, Maltose, Aspartic acid, Tryptophan, Glycine, Glutamine, Citrulline, Linoleic acid, Oleic acid, Maltotriose, Isothreonic acid, 5-hydroxynorvaline, Linolenic acid, and Taurine in lung cancer. Some of these metabolites had been previously identified in metabolomics studies [5, 15]. The identification of metabolite-related genes with the use of MetaBridge and differentially expressed genes (DEGs) came from 20 relevant GEO datasets with the use of Limma analysis, further elucidating the molecular mechanisms underlying lung cancer. The integration of metabolomics data with gene expression data led to the identification of 43 metabolic genes, including LDHA, LDHC, GSS, GCLC, PSAT1, GCSH, SHMT1, SHMT2, GLS2, GLUD1, GLUD2, GPT2, GFPT1, PPAT, GOT1, GOT2, IL4I1, GGT5, GAD1. The pathway analysis revealed enrichment of key pathways associated with amino acid metabolism, Alanine, aspartate, and glutamate metabolism, Cysteine and methionine metabolism, Arginine biosynthesis, Glycine, serine, and threonine metabolism, and D-Glutamine and D-glutamate metabolism are the top 5 pathways showing association with lung cancer progression. The GO term analysis further categorized the DEGs based on biological processes, cellular components, and molecular functions, providing a comprehensive understanding of the functional roles of these genes in lung cancer. Using enrichment analysis, we found that these common dysregulated genes were significantly enriched in 6 cellular components, 104 biological processes, and 38 molecular functions. Through the construction of the PPI network, several hub genes associated with lung cancer were discerned, and modular analysis provided a comprehensive perspective on the interplay among various proteins implicated in the pathophysiology of lung cancer. Notably, GLUD1, GLUD2, GOT1, GOT2, IL4I1, and GLS2 exhibited the highest node degrees in the network analysis.

GOT1 and GOT2 are the cytoplasmic and mitochondrial forms of glutamic-oxaloacetic transaminase, which is a pyridoxal phosphate-dependent enzyme. GOT plays a role in amino acid metabolism and the urea and tricarboxylic acid cycles. [16-18] Based on the KEGG analysis, these two genes are implicated in various metabolic pathways, including alanine, aspartate, glutamate, cysteine, methionine, arginine, phenylalanine, tyrosine, proline, and tryptophan metabolism. [18] Furthermore, GOT1 and GOT2 exhibit co-expression with each other and with PSAT1 and GLUD1, respectively. (Figure 6) These enzymes are homodimeric in structure and display significant sequence similarity [19]. IL4I1 encodes a secreted L-amino acid oxidase protein which primarily catabolizes L-phenylalanine and, to a lesser extent, L-arginine. This protein may play a role in immune system escape, as it is expressed in tumor-associated macrophages and suppresses T-cell responses [20-22]. This protein also contains domains thought to be involved in the binding of flavin adenine dinucleotide (FAD) cofactor [23]. Multiple transcript variants encoding distinct isoforms have been identified for IL4I1. Certain transcripts of this gene exhibit a shared promoter and exons within the 5' untranslated region (5' UTR) with the overlapping NUP62 gene [24]. The primary functions of this gene are predominantly associated with the metabolic pathways of tyrosine, phenylalanine, and tryptophan [25]. Furthermore, the current investigation has demonstrated the participation of this gene in the metabolic pathways related to alanine, aspartate, glutamate, and cysteine metabolism. The GLS2 gene encodes the mitochondrial phosphate-activated glutaminase that catalyzes the hydrolysis of glutamine to stoichiometric amounts of glutamate and ammonia. Alternative splicing results in multiple transcript variants that encode different isoforms [26]. GLS2 primarily functions in pyrimidine metabolism, while also contributing to arginine biosynthesis and the metabolic pathways involving alanine, aspartate, and glutamate [27, 28]. Co-expression of this gene with GAD1 has been observed. GLUD encodes glutamate dehydrogenase, which is a mitochondrial matrix enzyme that catalyzes the oxidative deamination of glutamate to alpha-ketoglutarate and ammonia [29, 30]. This enzyme has an important role in regulating amino acid-induced insulin secretion [31]. It is allosterically activated by ADP and inhibited by GTP and ATP [32]. Activating mutations in this gene are a common cause of congenital hyperinsulinism [33]. Alternative splicing of this gene results in multiple transcript variants. The related glutamate dehydrogenase 2 gene on the human X-chromosome originated from this gene via retro-transposition and encodes a soluble form of glutamate dehydrogenase. Related pseudogenes have been identified on chromosomes 10, 18, and X [18]. Both GLUD1 and GLUD2 are involved in arginine biosynthesis and the metabolic pathways of alanine, aspartate, and glutamate [34].

Currently, a multitude of studies have been carried out in the field of bioinformatics, with a significant focus on genomics research utilizing datasets such as The Cancer Genome Atlas Program (TCGA) and GEO. These investigations have aimed to identify biomarkers for cancer diagnosis and prognosis through the integration and re-analysis of genomic datasets [35-39]. However, research in the field of metabolomics, specifically pertaining to the integration of metabolomics data, remains limited. Some metabolomics studies have employed integrative approaches to examine the impact of metabolites on the genome or proteome [35, 40-42]. Wang et al. [42] conducted a study investigating the tissue-based metabolomics profile of gastric cancer using LC-MS/MS analysis, which led to the identification of several different metabolites. With the help of TCGA transcriptomics data, they discovered an association between Glycerophospholipid (GPL) metabolism and gastric cancer progression. Similarly, Fang et al. [40] utilized a machine learning (ML) approach that incorporates various omics features to enhance the accuracy of predicting metastatic prostate cancer prognosis. In contrast to earlier studies that relied on limited sample sets of genomic profiles, our research systematically searched GEO datasets and selected 20 datasets to identify optimal genomic markers. Furthermore, for metabolome identification, multiple metabolomics datasets were incorporated to enhance the robustness and credibility of this project.

However, some limitations hinder the comprehensive analysis of genomic and metabolomic data. The presence of missing values in genomics and metabolomics datasets posed challenges in drawing the accuracy of the analysis. Secondly, the scarcity of metabolomics datasets compared to genomics databases limited the comprehensive exploration of metabolic pathways and interactions, hindering a thorough understanding of metabolic signatures. Additionally, incomplete staging information for lung cancer in some datasets complicates the differentiation between early and advanced stages, impeding the exploration of stage-specific metabolic and genomic profiles crucial for personalized treatment strategies. Overcoming these limitations requires a concerted effort to address data completeness issues, expand metabolomics databases, and integrate multi-omics approaches to enhance the characterization of biological mechanisms in the context of lung cancer progression.

In conclusion, this study presents a comprehensive bioinformatic integration of genomic and metabolomic datasets, employing specialized computational tools. Our analysis reveals that the identified genomic alterations and metabolomic pathways offer dual clinical value: they serve as potential targets for personalized therapeutic interventions while simultaneously functioning as biomarkers and early diagnostic indicators.

The investigation focuses on two fundamental omics layers in lung cancer pathogenesis. While genomic alterations exhibit long-term effects, we demonstrate that somatic mutations alone are insufficient for oncogenesis, requiring complementary dysregulation to drive the development of distinct lung cancer subtypes. Importantly, our findings establish that persistent genetic instability must induce subsequent metabolomic perturbations to facilitate malignant progression. This hierarchical relationship explains why metabolomic imbalances show a stronger temporal association with cancer incidence and more acute effects compared to genomic aberrations.

These results have significant implications for research prioritization. Longitudinal studies of lung cancer predisposition should emphasize hereditary genetic factors and their cumulative impacts, whereas investigations targeting individualized medicine may benefit from focusing on dynamic metabolomic profiles. Notably, the differential kinetics between these omics layers is striking: genomic changes occur infrequently and manifest gradually, while metabolomic perturbations respond rapidly to environmental influences and demonstrate more immediate correlation with tumor initiation.

**Declarations:**

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Not applicable

**Conflict of Interest**

The authors declare no competing interests.

**Ethics Approval**

Not applicable

**Consent to participate**

Consented

**Conset to publication**

Consented

**Availability of data and materials**

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**Contributions of individuals**

Haniyeh Rafiepoor: Co-author, data analysis (co-authors contributed the same)
Saman Asadi: Co-author (co-authors contributed the same)
Alireza Ghorbankhanloo: Data analysis
Maryam Edalatifard: Scientific supervision, conceptual guidance
Seyyed Hamidreza Abtahi: Methodology development, critical review
Saeid Amanpour: Corresponding author

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