

**Notification No:** 588/2025

**Notification Date:** 24.10.2025

**Date of Award:** 10.10.2025

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**Topic of Research:** Investigating the role of key prognostic genes in non-small cell lung cancer via network-based approach

### **Findings**

This Ph.D. thesis investigates the molecular heterogeneity of non-small cell lung cancer (NSCLC), including lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), using integrated bioinformatics and systems biology approaches. It has three core objectives. First, RNA-seq data from NSCLC cohorts are used to identify differentially expressed mitophagy-related genes and stage-specific metastatic genes linked to brain metastasis. Network, pathway and survival analyses highlight TDRKH as a novel diagnostic and prognostic biomarker in LUAD and construct the first bioinformatics-based gene–miRNA–TF network connecting advanced NSCLC to brain metastasis. Second, weighted gene co-expression network analysis of tumor-specific RNA-seq data delineates LUAD–LUSC molecular differences and reveals network-level prognostic hub genes. Ribosomal proteins, particularly RPS7, emerge as key LUSC determinants. A meta-analysis of GEO datasets comparing smokers and non-smokers identifies distinct immune, xenobiotic and repair pathways and prognostic genes, emphasizing smoking-status-specific biology. Third, mutation profiles from TCGA, processed by multiple standard callers, are interrogated to derive prognostic mutation signatures and mutational fingerprints for LUAD and LUSC using Cox models and enrichment analyses. Across objectives, findings are validated in multiple public platforms. The work proposes integrated expression–network–mutation biomarkers to refine risk stratification and support precision medicine in NSCLC. Limitations include dependence on public datasets and lack of experimental validation; future directions involve longitudinal, multi-omics, single-cell and machine-learning-based studies to translate these in-silico insights into clinically actionable tools.

**Keywords:** *NSCLC, Prognostic Biomarkers, WGCNA, Protein-Protein Interaction Network, Mutation Calling*