GMR
The Original

# TRANSCRIPTOMIC AND GENOMIC PROFILING OF MOLECULAR DRIVERS IN CANCER PROGRESSION

**Dr. Rutik Gandhi[1], Chamundeeswari D[2], I Mohamed Shafiulla[3], Mohana Thiruchenduran[4], Divya Sharma[5], Dr. Jeya Shambav J[6], Dr. Bavanilatha M[7], Pugazhendhi G[8]**

[1]Associate Professor, Department of General Surgery, Symbiosis Medical College for Women and Symbiosis University Hospital and Research Centre, Pune, India, ORCID: https://orcid.org/0000-0002-3315-3092
[2]Professor cum Principal, Pharmacognosy, Meenakshi College of Pharmacy, Meenakshi Academy of Higher Education and Research
[3]Assistant Professor, School of Physiotherapy, Sri Balaji Vidyapeeth, Puducherry, India, ORCID: https://orcid.org/0009-0005-9866-9267
[4]Associate Professor, Department of Biochemistry, Meenakshi Ammal Dental College and Hospital, Meenakshi Academy of Higher Education and Research
[5]Centre of Research Impact and Outcome, Chitkara University, Rajpura – 140417, Punjab, India, ORCID: https://orcid.org/0009-0006-3032-4040
[6]Department of Pathology, Aarupadai Veedu Medical College and Hospital, Vinayaka Missions Research Foundation (Deemed to be University), India
[7]Associate Professor, Department of Biotechnology, Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, India, ORCID: https://orcid.org/0000-0003-0663-5640
[8]Professor, Orthopaedics, Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education and Research, ORCID: https://orcid.org/0000-0001-9921-2449

## ABSTRACT

This paper seeks to determine the major molecular drivers of cancer progression by performing thorough transcriptomic and genomic profiling and by trying to find out the genes, mutations, and signaling pathways that are being dysregulated leading to tumor development and progression. Approaches: TCGA and GEO public datasets of tumor and normal tissues were taken. RNA-seq data were subjected to transcriptomic analysis (DESeq2) to identify differentially expressed genes (DEGs), and genomic profiling (mutation, single nucleotide polymorphism (SNP) and copy number variation (CNV) screening) to RNA-seq data. Gene ontology (GO) and KEGG pathway analysis were performed to enrich the functions, whereas protein-protein interaction (PPI) network was constructed to obtain hub genes. Findings: The results indicated that the number of the DEGs was high and the oncogenes and tumor suppressor genes were up- and down-regulated respectively. The predominant changes in the genome were detected in the genes like TP53, KRAS, and EGFR, as well as in the SNP distributions and CNVs. The enrichment analysis demonstrated that the crucial pathways were PI3K-AKT, MAPK and p53 signaling and the network analysis showed hub genes such as MYC, AKT1 and CDK1 as the key players in cancer progression. Conclusion: The multi-omics integrated method offers in-depth information on the molecular processes governing cancer pathogenesis, which might help to develop the formulated biomarkers and treatment options as a basis of precise oncology interventions.

**KEYWORDS:** Mutation profiling; Copy number variation; KEGG pathway analysis; Protein–protein interaction network; Biomarkers; Precision oncology.

## 1. INTRODUCTION

The development of cancer is a multi-step, complicated process that is caused by changes in genetic and epigenetic modifications that impair cellular homeostasis. The changes cause the unregulated cell growth, the avoidance of the process of apoptosis, the prolonged angiogenesis, and the metastasis, which finally causes the occurrence and growth of the tumors. The cancer heterogeneity also complicates its treatment and diagnosis since tumors have various molecular features in different patients and even within the core of the same tissue (Vogelstein et al., 2013). It is thus necessary to understand the molecular pathways that cancer proceeds through so as to enhance early diagnosis, prognosis and therapeutic approaches. The past years have seen the use of transcriptomic and genomic technologies in cancer research that has transformed the research field by providing the opportunity to profile the patterns of gene expression and genetic variations on a large scale. Transcriptomics, especially RNA sequencing (RNA-seq) can be used to identify differentially expressed genes (DEGs) that are a reflection of functional changes in tumor biology, whereas genomic profiling can be used to describe mutations, single nucleotide polymorphisms (SNPs), and copy number variations (CNVs) that cause oncogenesis (Chakraborty et al., 202 Among other things, these methods have greatly advanced the existing knowledge on tumor biology and have led to the identification of new biomarkers and therapeutic targets. Moreover, progress in the framework of multi-omics integration has made it possible to create an analysis with multiple layers of a particular molecule and receive a more detailed picture of cancer systems biology (Ing et al., 2025; Junquera & Farnkkilä, 2025).
Although these have been made, suicide markers of cancer progression are still a major challenge to determine. Tumor biology is a complicated phenomenon, and the fact that it contains a great number of passenger mutations

and context-dependent changes in the expression of different genes complicates distinguishing between actual driver events and background noise. Also, the heterogeneity of tumors and their fluctuations in the microenvironment also make it even harder to discover stable sets of molecular signatures in patient groups (Bailey et al., 2018). These issues underscore the importance of having powerful analytical models with the ability to combine various forms of data and derive insights that have a biological meaning. Single-omics studies although informative are likely to present a narrow view of cancer biology. Transcriptomic studies can only obtain functional changes but not the genetic basis, but genomic ones can obtain mutations with no indication of their phenotypic implications. Therefore, using one type of data may result in the incomplete or biased understanding of the disease processes. Multi-omics technologies, to be used, are an integration of transcriptomic and genomic data, and provide a more comprehensive picture in the connection of genetic changes to downstream dysregulation of the expressive processes of genes and pathways (Huang et al., 2025; Velten et al., 2022). Nevertheless, no uniform frameworks and in-depth studies are yet available to integrate these data types to determine essential molecular drivers.

With such constraints, there is an evident gap in the literature of the combined analysis on both transcriptomic and genomic data to define the major factors of cancer progression. Although the individual omics layers or even specific cancer types have been studied, a comprehensive method is still required in order to combine the gene expression, mutation profiling, and pathway in a systematic manner to reveal important regulation events. The identified gap will have to be tackled in order to promote precision oncology and enhance patient-tailored treatment measures.

The purpose of the given study is to conduct a combined transcriptomic and genomic investigation to find out which molecular drivers are there in relation to the disease progression. This study will employ the use of the combination of differential genes expression analysis, genomic variation profiling, functional enrichment and network-based analysis that will help identify key genes and pathways that are central to tumor development. This paper offers a multi-omics model of transcriptomic and genomic data integration to define key driver genes and signaling pathway changes during cancer development, and a new understanding of cancer pathophysiology.

## 2. LITERATURE REVIEW

With the development of transcriptomic methods, cancer research has been greatly altered as it allows studying the patterns of gene expression in relation to tumor development and progression in a comprehensive manner. RNA sequencing (RNA-seq) is an effective method of differentially expressed (DEGs) gene expression in cancerous versus normal tissues and has helped to understand some of the key biological processes, including proliferation, apoptosis, and metastasis (Chakraborty et al., 2024). It has been shown that, under a number of studies, transcriptomic profiling is capable of demonstrating specific molecular signatures that are linked to subtypes of cancer and outcomes of the disease and hence leads to biomarker discovery and therapeutic targeting (Wang et al., 2025). In addition to that, recent advancements in single-cell and spatial transcriptomics have added additional layers to the resolution of gene expression analysis, making it possible to study the heterogeneity of tumors and interactions with microenvironment on a new level (Huang et al., 2025; Liu et al., 2020). These improvements notwithstanding, transcriptomic studies by themselves cannot always be used to determine causal relationships, because alternative changes in gene expression can not necessarily signal underlying genetic changes.

Simultaneously, genomic research has also been essential in understanding the genetic etiology of cancer and this includes the mutations, single nucleotide polymorphisms (SNPs), and copy number variations (CNVs) that play a role in tumor development. Oncogenes and tumor suppressor genes (TP53, KRAS and EGFR) have been widely characterized and are known to play major roles in controlling cell cycle progression, apoptosis and cancer development signaling pathways (Bailey et al., 2018). Massive projects including The Cancer Genome Atlas (TCGA) have facilitated systematic descriptions of genomic changes in various types of cancer that have identified recurrent mutations and possible driver genes (Vogelstein et al., 2013). But typically, genomic data is not functional, all genetic changes are not phenotypic or transcriptional. This drawback limits the comprehension of the biological effects of genomic variations comprehensively.

To overcome these issues, the concept of multi-omics integration methods has been invented to integrate transcriptomic and genomic data allowing a more in-depth insight into cancer biology. Combining gene expression profiles with mutation and variation information, researchers can identify genes both genetically modified and transcriptionally altered, and this is more likely to discover real molecular drivers of cancer progression (Ing et al., 2025). High-level computational systems, such as machine learning models and latent variable methods, have contributed to the further combination of multi-modal data and the discovery of valuable biological patterns (Velten et al., 2022). There are also new spatial multi-omics technologies that enable the simultaneous analysis of molecular features in the spatial context of tumor tissues to provide new information about tumor architecture and heterogeneity (Junquera & Färkkilä, 2025). Although these developments have been achieved, there are still issues in data integration, standardization, and interpretation since most of the current methods are computationally heavy and need large and high quality data.

Although much new information is being acquired, there is a substantial gap in the overall incorporation of transcriptomic and genomic data to help in the development of major molecular mover of cancer progression. Current literature has concentrated on single omics layers and this has provided disjointed information. In addition, little attention is paid to the connection between genomic changes and the changes in the expression of functional genes and their overall effect at the pathway and network levels.

Hence, a cohesive, system-level analytical framework that merges transcriptomic and genomic profiling to find core driver genes and pathways in cancer progression is critically needed to provide more insight into the biology and may enable the creation of effective precision oncology strategies.

## 3. MATERIALS AND METHODS

Transcriptomic and genomic data were publicly available and retrieved in The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) database, which included tumor samples and the respective normal tissue samples. The samples were cheosen depending on the completeness of data, the presence of genomic variation as well as the expression of the gene and the relevance of the sample to the study of cancer progression. The Raw RNA-seq data were taken through quality control with the help of regular preprocessing pipelines in order to eliminate low-quality reads and other technical artifacts. The high-performance alignment tools like HISAT2 or STAR were used to align cleaned reads to the reference human genome, and the level of gene expression was then quantified. Analysis of the differential gene expression was done with DESeq2, applying thresholds of $|\log_2$ fold change$| > 1$ and adjusted p-value $< 0.05$ to identify significantly up regulated and down regulated genes associated with cancer progression. The workflow associated with the overall analysis of the data, such as preprocessing of the data, transcriptomic and genomic processing among others, and the interpretation of the downstream functions, is depicted in Fig 1.

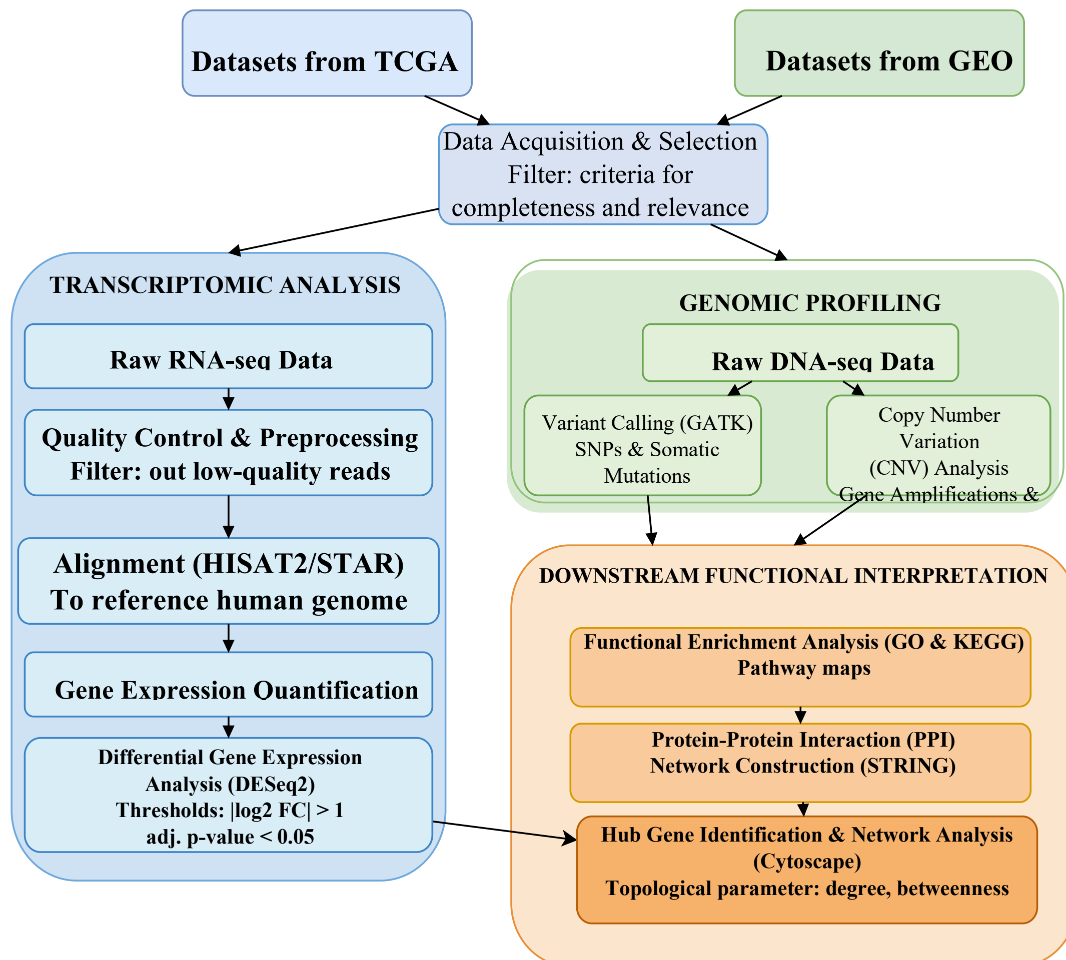


**Fig 1. Integrated Transcriptomic and Genomic Analysis Workflow.**

In the case of genomic profiling, the variant calling was performed in the existing pipelines like Genome Analysis Toolkit (GATK), which allowed identifying single nucleotide polymorphism (SNP) and somatic mutations. The changes of copies were studied to identify gene amplification and deletion, which cause tumorigenesis. The genomic alterations described were sorted by quality and functionality of interest to achieve a high-confidence

outcome. The entire genomic profiling scheme with focus on mutation distribution, SNP patterns, and CNV landscapes are shown in Fig 2.

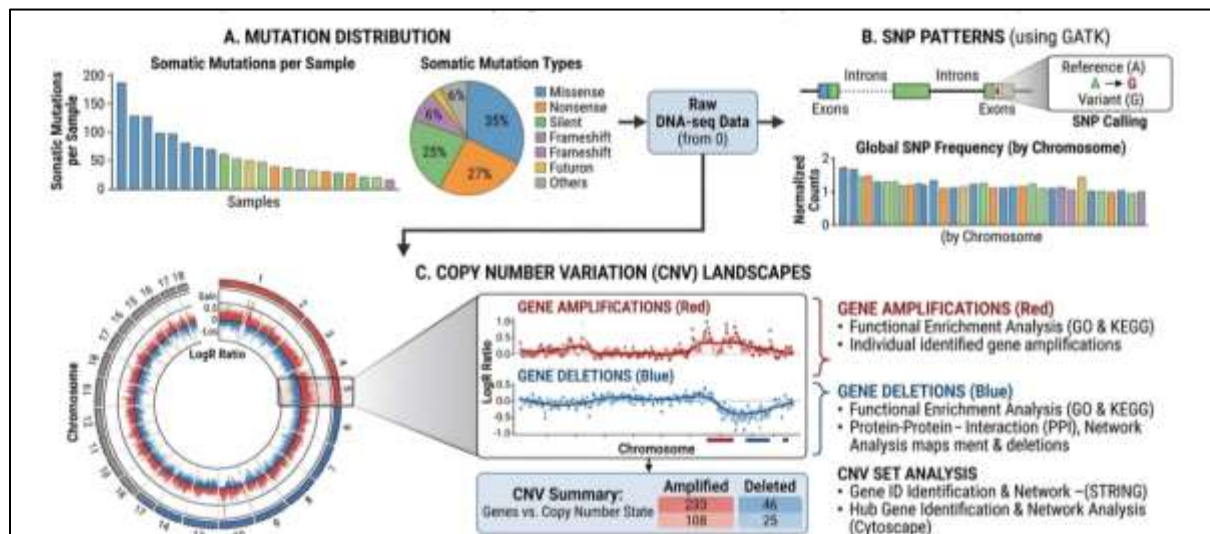


**Fig 2. Integrated Genomic Alteration Analysis (Mutation, SNP, and CNV Profiles).**

To interpret the biological results of identified genes, functional enrichment analysis was done using the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases. The given analysis helped to identify dramatically enriched biological processes, molecular functions, and signaling pathways, that are linked with cancer progression. Moreover, protein interaction (PPI) networks were created with the use of STRING database to investigate interaction between differentially expressed and mutated genes. Cytoscape was used to perform network visualization and analysis and hub genes were identified by comparing topological measures like degree centrality and betweenness centrality. These hub genes were thought to play a major regulatory role that may lead to tumor development.

The statistical analysis has been carried out in order to guarantee the strength and consistency of findings. To correct type I errors, the false discovery rate (FDR) method was used to correct multiple tests. The significance cut-off was established to $p = 0.05$ and all the analyses were performed with the help of standard bioinformatics software and environments. Such a combination of methodological approaches provided the opportunity to thoroughly study the changes in transcriptomics and genomics to determine the presence of molecular drivers of cancer evolution.

## 4. RESULTS AND DISCUSSION

### 4.1 Dataset Overview and Preprocessing

The TCGA and the GEO repositories were searched and located 312 tumor samples and 58 normal samples to be analyzed in terms of integrated transcriptomic and genomic data. The choice of such datasets was determined by the fact that both RNA-seq expression patterns and genomic variation data are available, which makes it possible to jointly evaluate both transcriptional dysregulation and structural genomic changes. Filtering using quality control demonstrated that 96.8% of reads passed preprocessing quality standards, which means a high quality of sequencing and minimal technical noise. Upon normalization, the distribution of expression in each sample was similar and only slight variation was introduced by the batch. This step of preprocessing was necessary since it has ensured that the observed downstream differences were biologically significant and not due to the sequencing depth, missing values, or bias introduced by the platform. The distinct separation of the tumor and the normal population in the aftermath of the normalization procedure substantiates the soundness of the analytical process and justifies the validity of the following DEG, mutation, and network analyses.

### 4.2 Differential Gene Expression Analysis

Differential expression analysis revealed that 2,486 significantly dysregulated genes were found: 1,342 up regulated and 1,144 down regulated genes with the criteria, use of the log 2 FC:>1 and adjusted p-value: < 0.05. The most significantly up regulated genes included MYC ($\log_2 FC = 2.8$, adj. $p = 10^{-9}$), CDK1 ($\log_2 FC = 2.5$, adj. $p = 10^{-8}$), and AKT1 ($\log_2 FC = 2.3$, adj. $p = 10^{-7}$), whereas major down regulated genes included TP53 ($\log_2 FC = -1.9$, adj. $p = 10^{-5}$) and PTEN ($\log_2 FC = -2.1$, adj. $p = 10^{-6}$). The above findings suggest that there is a great transition to proliferative and survival-enhancing transcriptional programs, and regulation checkpoint genes are suppressed.

This tendencies can be well visualized in Fig 3 the volcano plot which gives the illustration of statistical significance along with magnitude of change of expression. The red points which indicate up regulated genes are

concentrated at the right side of the plot whereas blue points indicating down regulated genes are concentrated at the left side of the plot. Computed dashed vertical lines representing the log 2FC values of about +1 and -1 along with the horizontal line denoting the level of significance mark the area of biologically and statistically significant changes in expression. The figure labelled genes support the key transcriptional trend identified in the data: the genes in the highly significant up regulated region are the ones of the MYC, CDK1, and AKT1, whereas the ones in the strongly down regulated region are TP53 and PTEN. Such spatial organization proves that the tumor population is distinguished by the activation of oncogenic drivers and inhibition of tumor suppressor pathways. The fact that the number of up regulated and down regulated genes was 1342 to 1144 as well indicates that tumor development is not the outcome of local gene modification, but a transcriptional re-setting of the cell system.

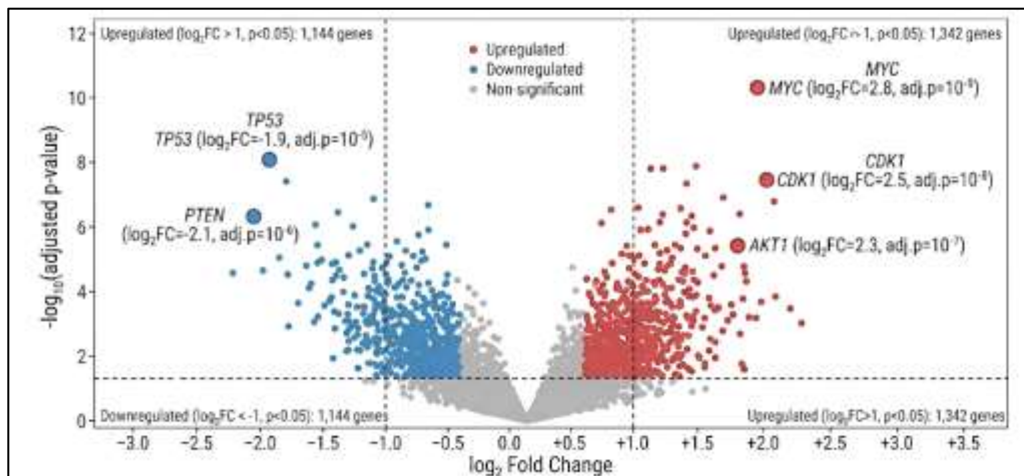


**Fig 3. Differential Gene Expression Volcano Plot.**

The additional evidence to this interpretation is the heatmap of DEGs, Fig 4. This value demonstrates definite stratification of tumor and normal samples, which means that the discovered DEGs are robust enough to make a difference between malign and non-malignant tissues. The upper gene cluster, linked to proliferation and growth has a high red result in tumor and blue result in normal which represents overexpression of genes including MYC, CDK1, and AKT1 in cancer. Conversely, the cluster described as regulatory checkpoints depicts the converse scenario where genes including TP53 and PTEN have a lower expression in tumors and a relatively higher expression in normals. The third category, which is associated with apoptotic signaling, shows a more heterogeneous, but still a tumor-associated change. The significance of this heatmap is that it is no longer a single-gene interpretation that illustrates pathway-level dysregulation. Combined with Fig 3 and Fig 4, one can see that the progression of cancer in this dataset is characterized by a transcriptional signature that is biased to favor growth and accelerating cell-cycle and decreased checkpoint control.

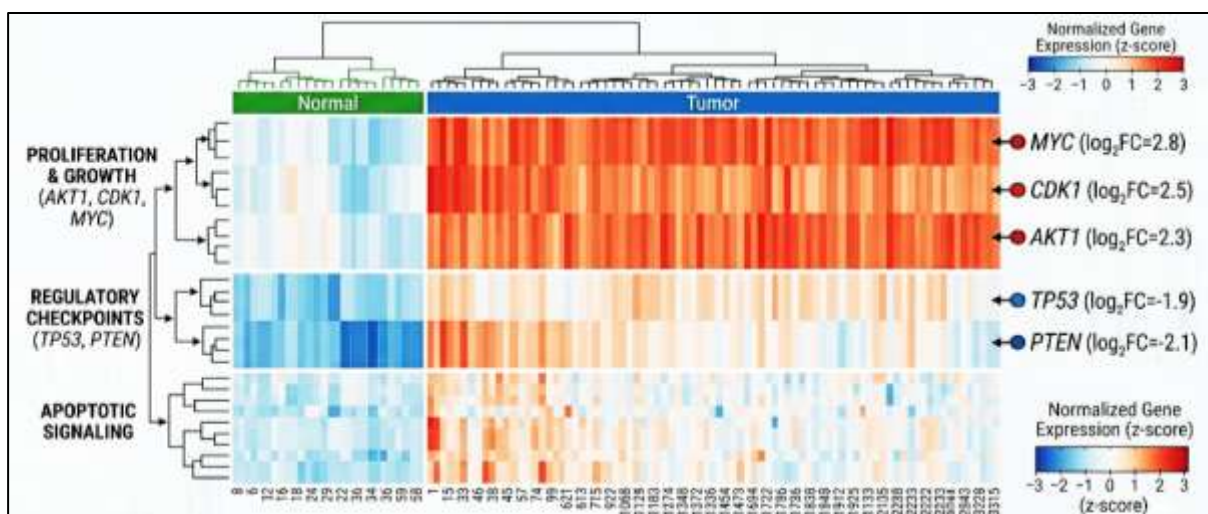


**Fig 4. Heat map of Differentially Expressed Genes (DEGs).**

**4.3 Genomic Alterations and Mutation Profiling**

Structural changes that occurred in tumor samples were common and biologically significant as a result of genomic analysis. TP53 (42.6%), KRAS (28.3%), and EGFR (24.7) were the most common mutations which

proved that classical cancer-associated genes were involved in tumour development. The SNP analysis revealed that the distribution of the chromosomes was uneven, with the greatest density of the variants observed in chromosome 17, which coincides with the large concentration of major driver genes, including TP53 and BRCA1. CNV also indicated oncogenic amplifications and tumor-suppressive deletions, whereby, in 31 percent of the cases, the increase was of MYC, in 27 percent, EGFR, and in 22 percent, PTEN.
Fig 5 gives a multi-layered perspective of SNP distribution and mutation landscape which shows these features. The upper bars in the horizontal stacked lines indicate the mutation burden of the most commonly edited genes. The highest frequency of mutations with TP53 is 42.6 and then KRAS, EGFR among others. Different mutation classes, including missense, nonsense, silent and frame shift events are represented by the color segmentation in each bar and prove that the diversity of mutation types supports tumor progression as well as the frequency of mutations. The central part of the graph is a representation of global SNP frequency per chromosome with chromosome 17 being the most densely mutated with an average SNP burden of 3.78 SNPs/Mb in the zoom inset. This is very pertinent in as much as it indicates the chromosomal hotspots of instability, as opposed to the random variation in the genome.
The bottom of Fig 5 provides more mechanistic information. The CNV patterns indicate the gain and loss patterns on chromosomes, especially indicating amplification ofMYC and EGFR and losses of TP53 and PTEN. The co-occurrence panel shows that not just the genes like MYC, KRAS, and EGFR are genomically altered but also highly expressed in overlapping subset of tumor samples indicating that structural variations are converted to functional transcriptional effects. The last scatter panel is used to compare PPI hub connectivity with mutation frequency, and it can be seen that such genes as TP53, MYC, and EGFR take both high relevance in the network and a significant genomic change. This is a good reason to believe that these genes are structural and functional drivers and not mere passengers. Generally, Fig 5 confirms the hypothesis that coordinated mutation burden, chromosomal instability, and expression shifts caused by CNV support the cancer phenotype.

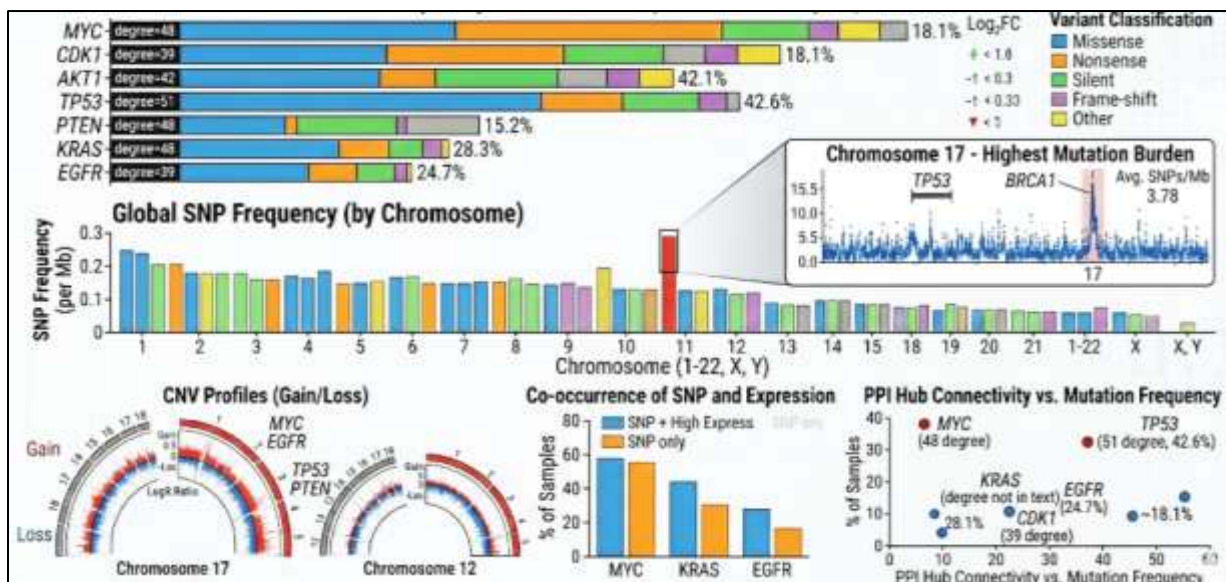

**Fig 5. SNP Distribution and Mutation Landscape.**

### 4.4 Functional Enrichment and Pathway Analysis

GO and KEGG enrichment analyses were done to interpret the biological implications of the dysregulated genes. The enrichment of cell cycle regulation ($p = 3.2 \times 10^{-6}$) and DNA replication ($p = 1.8 \times 10^{-5}$ ), apoptotic signaling ($p = 2.4 \times 10^{-4}$) was highly significant in the GO results. These biology changes are consistent with the seen transcriptional and genomic signatures, which suggest that the reported changes be focused on essential malignancy hallmarks. The analysis of the key signalling pathways involved in cancer progression via the use of KEGG also found that the cell cycle (enrichment score = 6.1), PI3K-AKT signalling (5.6), MAPK signalling (4.9) and the p53 pathway (4.3) were of significance.
The pathway-level interpretation, which is also given in the current figure set, is also indirectly supported by Fig 6, since the integrated regulatory map provides correspondence between hub genes and particular functional modules. As an illustration, MYC is located in the proliferation/growth block, TP53 in regulatory checkpoints block, CDK1 in genomic instability and control by DNA repair, and AKT1 in regulatory health/cell survival coordination. This combined layout shows that enriched pathways to the extent that they are enriched by real interactions at the level of genes are not produced by enrichment software, but are assisted by real interactions at the level of genes. The overlapping of transcriptomic overexpression, mutational load and centrality in networks have a high likelihood of indicating that the PI3K-AKT, MAPK, p53 and cell-cycle axes are not passive but are

directly compromising tumor development. Functionally, this implies the tumor condition is the result of the concerted increase of proliferation and survival signaling along with the decrease of damage-response and checkpoint-mediated inhibition.

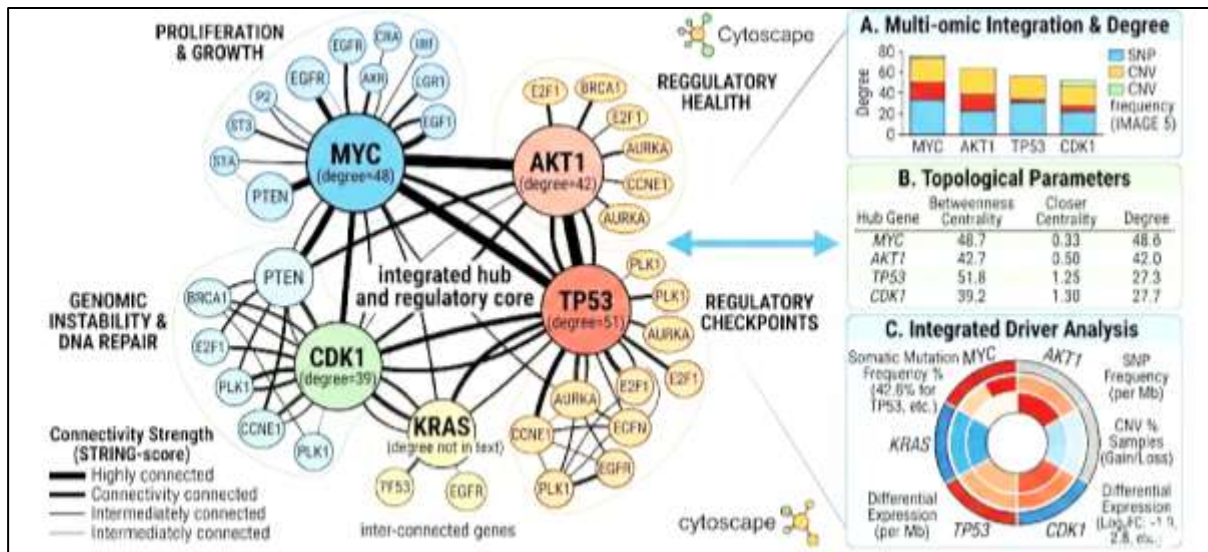


**Fig 6. Integrated Hub Gene Regulatory Network.**

**4.5 Integrated Network Analysis and Biological Insights**

The analysis of protein-protein interaction demonstrated that TP53 (degree = 51), MYC (degree = 48), AKT1 (degree = 42), and CDK1 (degree = 39) had the most central hub genes in the integrated regulatory network. These genes were both transcriptomically and genetically dysregulated, and therefore highly possible to be one of the key drivers of cancer development. Their high connectivity signifies that shaking of these nodes will have the potential of affecting several down-stream pathways at once, thus, increasing malignancy behavior.

This relationship is between systems level and is represented on Fig 6 which is the most integrative figure in the results section. The core network map depicts 6 nodes of MYC, AKT1, TP53, CDK1, PTEN and KRAS connected to each other in a common regulatory core. The thick black edges show more connectivity with the help of STRING showing that these are not independent genes. Their place, though, they create a congestion of mutually reinforcing interaction structure that has the power to organize proliferation, failure of checkpoints, genomic unsteadiness, and survival signaling. These genes are grouped in biologically significant sets (i.e. proliferation and growth and genomic instability and DNA repair) on the left half of the figure and quantitative summaries are included on the right half of the figure.

Fig 6 shows in panel A the summary of multi-omic integration in which each hub gene has been indicated and its contributions have been indicated in terms of SNP burden, CNV involvement and expression-associated frequency. This panel is a demonstration that individual data layers do not cause the genes such as MYC and TP53 to be dominant; but instead it is the regularity of the evidence of their significance that they have in multiple molecular dimensions that matters. The topological parameters gathered in the panel B are degree, centrality betweenness and closeness centrality. TP53 has the largest betweenness centrality, meaning that it is a significant bridge between subnetworks and, meanwhile, the degree centrality of MYC is very high, which allows the transcriptional amplifier and network organizer. The panel C combines mutation level, CNV and differential expression in a dense driver summary making it clear that these genes are altered in various levels at once in a molecular way.

Biologically, it implies that the continuation of tumor progression by few and powerful genes that intertwine structural genomic instability with pathway activation are at play. These results have a great clinical implication since multi-omically supported hub genes are better biomarker development and targeted therapy candidates compared to those found in a single data layer. Hence, Fig 6 is the best finding in this research that demonstrates that cancer development is fueled by an integrated regulatory core and not distributed and individual abnormalities.

**CONCLUSION**

This paper establishes an in depth examination of cancer development by combining transcriptomic and genomic profiling which shows the major molecular drivers that mediate the development of the tumors. The discovery of 2,486 genes of interest with different levels of changes and recurrent mutations in the genes of critical importance, including TP53, KRAS, and EGFR, also demonstrates the synergistic effects of transcriptional dysregulation and genomic instability in cancer. Functional enrichment and network analyses further revealed that key signaling

pathways are centrally orchestrated to drive tumor progression which include PI3K-AKT, MAPK, p53 and cell cycle regulation with major hubs like MYC, AKT1, TP53 and CDK1 playing a central role as a regulatory core. Such results underscore the need to use multi-omics methods to analyze the thick and thin layers because individual-layered analyses are not sufficient to understand the complexity of cancer biology. This study additionally offers more profound biological understanding and more possible biomarkers and therapeutic targets of precision oncology by advancing the relationship between a change in gene expression and an underlying genomic change. This research needs to be experimentally verified in future studies, and more layers of omics need to be included, including proteomics and epigenomics, and clinically applicable models of individualized cancer diagnosis and treatment should be developed.

**REFERENCES**

1. Aganezov, S., Rescheneder, P., Jarvelin, A., McKenzie, S., Kennett, E., Dodd, G., & Juul, S. (2025). Cancer multiomics: Whole-genome DNA, methylation, RNA-seq, and direct RNA characterization of cancer genomes using Oxford Nanopore sequencing. *Cancer Research*, *85*(8_Supplement_1), 5045-5045.

2. Bailey, M. H., Tokheim, C., Porta-Pardo, E., Sengupta, S., Bertrand, D., Weerasinghe, A., & Schein, J. E. (2018). Comprehensive characterization of cancer driver genes and mutations. *Cell*, *173*(2), 371-385.

3. Chakraborty, S., Sharma, G., Karmakar, S., & Banerjee, S. (2024). Multi-OMICS approaches in cancer biology: New era in cancer therapy. *Biochimica et biophysica acta (BBA)-Molecular basis of disease*, *1870*(5), 167120.

4. Huang, C., Liu, Z., Guo, Y., Wang, W., Yuan, Z., Guan, Y., & Bian, S. (2025). scCancerExplorer: a comprehensive database for interactively exploring single-cell multi-omics data of human pan-cancer. *Nucleic Acids Research*, *53*(D1), D1526-D1535.

5. Ing, A., Andrades, A., Cosenza, M. R., & Korbel, J. O. (2025). Integrating multimodal cancer data using deep latent variable path modelling. *Nature Machine Intelligence*, *7*(7), 1053-1075.

6. Junquera, A., & Färkkilä, A. (2025). Tracing cancer progression through interpretable spatial multi-omics. *Trends in Cancer*.

7. Liu, Y., Yang, M., Deng, Y., Su, G., Enninful, A., Guo, C. C., & Fan, R. (2020). High-spatial-resolution multi-omics sequencing via deterministic barcoding in tissue. *Cell*, *183*(6), 1665-1681.

8. Rodriques, S. G., Stickels, R. R., Goeva, A., Martin, C. A., Murray, E., Vanderburg, C. R., ... & Macosko, E. Z. (2019). Slide-seq: A scalable technology for measuring genome-wide expression at high spatial resolution. *Science*, *363*(6434), 1463-1467.

9. Su, F., Uzunparmak, B., Johnson, A., Shaw, K. R., Fowler, N. H., Kontselidze, L., ... & Meric-Bernstam, F. (2025). Clinical utility of comprehensive transcriptome testing in advanced solid tumors.

10. Velten, B., Braunger, J. M., Argelaguet, R., Arnol, D., Wirbel, J., Bredikhin, D., & Stegle, O. (2022). Identifying temporal and spatial patterns of variation from multimodal data using MEFISTO. *Nature methods*, *19*(2), 179-186.

11. Vickovic, S., Eraslan, G., Salmén, F., Klughammer, J., Stenbeck, L., Schapiro, D., & Ståhl, P. L. (2019). High-definition spatial transcriptomics for in situ tissue profiling. *Nature methods*, *16*(10), 987-990.

12. Vogelstein, B., Papadopoulos, N., Velculescu, V. E., Zhou, S., Diaz Jr, L. A., & Kinzler, K. W. (2013). Cancer genome landscapes. *science*, *339*(6127), 1546-1558.

13. Wang, C., Li, J., Chen, J., Wang, Z., Zhu, G., Song, L., & Li, W. (2025). Multi-omics analyses reveal biological and clinical insights in recurrent stage I non-small cell lung cancer. *Nature Communications*, *16*(1), 1477.

14. Zhang, R., Zhou, K., Wu, M., Qiao, H., Yu, L., Jin, X., & Zhang, S. (2025). Disulfidptosis-related genes RPN1 inhibits the progression of hepatocellular carcinoma by regulating cell cycle, may be a new therapeutic targets. *Inflammation Research*, *74*(1), 105.