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COMPARATIVE PAN-CANCER ANALYSIS OF DRIVER GENE MUTATIONS, ALTERNATION PATTERNS AND ONCOGENIC PATHWAY ASSOCIATIONS ACROSS SIX TCGA TUMOR TYPES USING CBIOPORTAL

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ABSTRACT

Background: Cancer is a diverse set of diseases with the involvement of multiple genomic abnormalities that lead to the initiation and progression of cancer. Systematic assessment of mutations in driver genes and dysregulated signaling pathways is made feasible by public cancer genomics resources, such as The Cancer Genome Atlas (TCGA) and cBioPortal. In this study, a pan-cancer bioinformatics analysis was conducted to uncover recurrent genomic alterations and some important molecular pathways in selected TCGA cohorts. **Methods:** A retrospective cross-sectional bioinformatics study was conducted using TCGA datasets accessed through cBioPortal. Six cancer types were included: breast invasive carcinoma (BRCA), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), colon adenocarcinoma (COAD), prostate adenocarcinoma (PRAD) and skin cutaneous melanoma (SKCM). Driver gene alterations, mutation frequencies, genomic profiles and pathway involvement were evaluated. KEGG pathway enrichment analysis was performed to identify significantly enriched biological pathways. **Results:** TP53 showed the highest alteration frequency (36%), followed by KRAS (15%) and PIK3CA (13%). Recurrent alterations were also identified in KMT2C, BRAF, EGFR, PTEN, APC and NF1. Pathway analysis demonstrated prominent involvement of the RTK–RAS, PI3K–AKT–mTOR, TP53, WNT and cell cycle signaling pathways. KEGG enrichment analysis revealed significant enrichment of the MAPK (adjusted $p = 3.20 \times 10^{-6}$), PI3K–AKT (adjusted $p = 6.40 \times 10^{-6}$), FOXO, PD-L1/PD-1 checkpoint and apoptosis pathways. **Conclusion:** This study concluded that recurrent alterations in TP53, KRAS and PIK3CA, together with significant dysregulation of RTK–RAS, PI3K–AKT–mTOR, TP53, WNT and cell cycle pathways, represent key molecular features across multiple cancers.

KEYWORDS: Pan-cancer analysis, TCGA, cBioPortal, Driver gene mutations, TP53, KRAS, PIK3CA, Molecular pathways and Precision analysis.

INTRODUCTION

Cancer is a major global health problem and remains one of the leading causes of disease-related mortality worldwide, contributing to millions of newly diagnosed cases and deaths annually. According to reports published by the World Health Organization, the burden of cancer continues to rise because of population growth, increasing life expectancy, and exposure to environmental and lifestyle-associated risk factors.[1] While significant progress in cancer detection and therapeutic interventions has been made, cancer remains an incredibly complex disease that continues to present

challenges in effective disease management and the application of precision oncology approaches. The gradual accumulation of genetic changes, including mutations in driver genes that confer survival and growth advantages play a major role in cancer development. In contrast, passenger mutations usually have no major role in the behaviour of the tumour cells, while driver mutations play an active role in the process of carcinogenesis, by altering key processes such as cell proliferation, cell death, repair of DNA damage, and signal transduction pathways.[2]

The discovery of these key genes is essential for cancer biology understanding, uncovering new therapeutic targets, and better patient stratification for personalized treatment strategies. Next-generation sequencing (NGS) technologies and large-scale cancer genomics projects have greatly improved the ability to better characterize genomic alterations in diverse malignancies. The Cancer Genome Atlas (TCGA) has been a successful project that has created large multi-omics datasets from thousands of patient samples of various cancer types.[3] These resources, like cBioportal for Cancer Genomics, have made it possible to explore the mutation profile and molecular pathways and clinical outcomes of genetic alterations that underlie cancers in detail.[2] Pan-cancer analysis has proven to be a valuable method for uncovering common and cancer-specific molecular events in various types of cancer. By integrating genomic and clinical datasets from different cancer types, pan-cancer investigations provide valuable insights into recurrent driver mutations, pathway dysregulation and prognostic biomarkers that may remain undetected within individual tumor studies.[5]

Furthermore, age-associated differences in cancer genomics have attracted increasing research interest because aging is a well-established risk factor for cancer and may influence mutation burden, genomic instability, tumor progression and response to therapy.[6] Several major oncogenic signaling pathways, including PI3K–AKT, MAPK, p53, WNT and receptor tyrosine kinase signaling cascades, are frequently disrupted in human cancers and play essential roles in tumor initiation and progression.[7] Therefore, the present study was designed to perform a pan-cancer bioinformatics investigation of selected TCGA tumor cohorts to examine driver gene mutations and evaluate their associations with molecular pathways, age-related characteristics and survival outcomes using the cBioPortal platform.

OBJECTIVES

- To determine and compare the prevalence and distribution patterns of major driver gene mutations among breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, colon adenocarcinoma, prostate adenocarcinoma and skin cutaneous melanoma using data derived from TCGA.
- To examine the spectrum of genomic alterations, including missense variants, truncating mutations, gene amplifications and deletions, affecting selected driver genes across the included cancer cohorts.
- To investigate common and cancer-specific molecular pathways linked to recurrent driver gene alterations through the evaluation of established gene–pathway associations.

METHODOLOGY

Study Design

The present investigation was conducted as a cross-sectional pan-cancer bioinformatics analysis involving six major malignancies represented in The Cancer Genome Atlas (TCGA). The cancer cohorts included breast invasive carcinoma (BRCA), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), colon adenocarcinoma (COAD), prostate adenocarcinoma (PRAD) and skin cutaneous melanoma (SKCM). The goal was to analyze and profile, by using publicly available genomic data, the mutation landscape, pathway changes, demographic characteristics and clinical outcomes of these tumor groups.

Study Type and Duration

This study is a retrospective observational study using secondary genomic and clinical data. The activities to be undertaken are those concerned with retrieval, processing, analysis, interpretation, and manuscript preparation, which will be completed over six months.

Data Source

The cBioPortal for Cancer Genomics platform was used to obtain genomic and clinical data from TCGA. This resource contains detailed molecular and clinical data of numerous malignancies. Somatic mutation data were gathered for all six cancer cohorts, demographic data, and variables for survival were also collected. Recurrent driver gene alterations, pathway involvement, age-associated trends of mutations, and survival outcomes were selected as areas of focus. Candidates for driver genes were selected based on both their frequency of mutation and their consistent recurrence in every cohort of the TCGA. Information from curated TCGA datasets and previously reported pan-cancer investigations was utilized to support biological interpretation.

Study Population

Patients with histologically confirmed cancer included in TCGA were included in the study population. Only members of the six cancer cohorts selected and with both genomic and clinical data available were eligible for inclusion. The demographic variables studied were age at diagnosis, sex, cancer diagnosis, and related clinical information.

Study Criteria

Inclusion Criteria: Complete somatic mutation information, including single-nucleotide variants, insertions, or deletions, was available. Cases were also

asked to include key clinical information, including age at diagnosis and survival information. Only samples from the pre-defined cancer cohorts were included.

Exclusion Criteria: Cases were excluded if mutation data were not available or were incomplete. Samples that were missing critical clinical data, such as age, sex, or tumour classification, were excluded from the analysis. In addition, redundant entries and samples in other cancers were removed.

Data Collection Procedure

The clinical and genomic data were obtained from TCGA through the TCGA cBioPortal website in a retrospective manner. Available clinical data were abstracted, including patient-related factors such as age, sex, tumor type, disease stages, and the survival data. The mutation profiles were obtained for all samples to identify alteration frequencies and the mutation features. Clinical variables and the nature of the tumour were standardised before analysis. The data was explored, analysed, and visualised within the cBioPortal environment.

Analysis of Driver Gene Mutations

Analysis of recurrent driver mutations was performed in each cancer cohort separately. Comparative evaluations were conducted to look for similarities and differences between the distribution of mutations in the six malignancies. Alterations were categorized according to mutation type, including missense mutations, nonsense mutations, frameshift variants, gene amplifications, deletions and truncating alterations. Potential driver genes were identified as frequently altered ones and these were analysed for biological relevance.

Pathway Analysis

Established molecular pathways were used with known gene–pathway annotation resources to investigate the biological implications of the recurrent mutations identified, which were associated with these pathways. In this analysis, pathways were identified to be commonly affected in different types of cancer and pathways that were almost exclusively affected by specific tumour types. The findings offered insights into mechanisms leading to the initiation and progression of tumors.

Age-Based Mutation Analysis

Patients were classified into age groups (younger than 40, 40–60, and older than 60 years). The mutation frequencies and pathways involved were therefore compared across these age groups within each cancer cohort. This analysis aimed to detect age-related patterns in the genome and to see if certain mutations or pathways varied over age.

Survival Analysis

The clinical outcome data were incorporated with genomic data, which were used to assess the clinical significance of any identified driver gene changes. Patients with specific genomic changes were compared in terms of overall survival (OS) and disease-free survival (DFS). Survival probabilities were estimated with Kaplan–Meier survival curves and compared between groups using the log-rank test. Survival comparisons were made between selected cancer types for additional comparisons.

Statistical Analysis

Demographic characteristics (age and sex) were summarized using descriptive statistics, and together with the mutation frequency within and between the cancer cohorts. Differences in genomic alterations and pathway involvement were compared between tumour types. To investigate the effect of the demographic parameters on the mutations, age-stratified evaluations were carried out. The Kaplan–Meier method and log-rank tests were used for survival analyses. A p-value < 0.05 was considered statistically significant. Bioinformatics and statistical analysis via cBioPortal were used for all analyses.

Ethical Considerations

This study was based on only publicly available and anonymised datasets from well-known genomic repositories. During the investigation there was no direct involvement of human or animal subjects. No formal institutional ethical approval was necessary since all information was anonymized and came from secondary sources. All publications/presentations resulting from this research will contain appropriate mention of TCGA and cBioPortal resources.

Hypothesis

The following hypotheses were used to direct the investigation. The null hypothesis (H_0) was proposed that there is no difference in any of the driver gene mutations, pathway alterations, age-related mutation patterns, or in survival outcomes between the selected TCGA cancer cohorts and that any difference observed could be attributed to chance. The alternative hypothesis (H_1) was that there would be significant differences between the selected cancers in terms of genomic alterations, pathway dysregulation, age-related mutation trends, and prognosis/survival, and that these differences would be influenced by the age of the patient.

RESULTS

Overview of Selected TCGA Cohorts

A pan-cancer analysis was carried out in six TCGA tumor types: breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, colon adenocarcinoma, prostate adenocarcinoma and skin cutaneous melanoma. The focus of the investigation was to compare mutation profiles, biological pathways affected, age-associated demographic patterns and clinical outcome of these different cancer types.

Landscape of Driver Gene Mutations

The distribution of mutations of the selected driver genes is summarized in Table 1 and Figure 1. The most altered

gene (36%) was TP53, which has been found to be altered in many types of cancer. The next two were KRAS (15%) and PIK3CA (14%), both of which have already been known to drive the development of a range of cancers. Moderate alteration frequencies were identified for KMT2C (11%), BRAF (10%), EGFR (10%), APC (9%), NF1 (8%) and PTEN (8%), whereas GATA3 (6%), CDH1 (4%) and NRAS (3%) displayed relatively lower mutation rates. The most commonly observed genomic changes were: missense mutations, truncating mutations, gene amplifications and deep deletions.

Table 1: Frequency of genomic alterations in selected driver genes across TCGA pan-cancer cohorts obtained from cBioPortal analysis.

Gene	Number of Samples Altered	Percent Samples Altered
TP53	959	36%
KRAS	394	15%
PIK3CA	360	13%
KMT2C	274	10%
BRAF	259	10%
EGFR	255	10%
PTEN	222	8%
APC	219	8%
NF1	199	7%
GATA3	142	5%

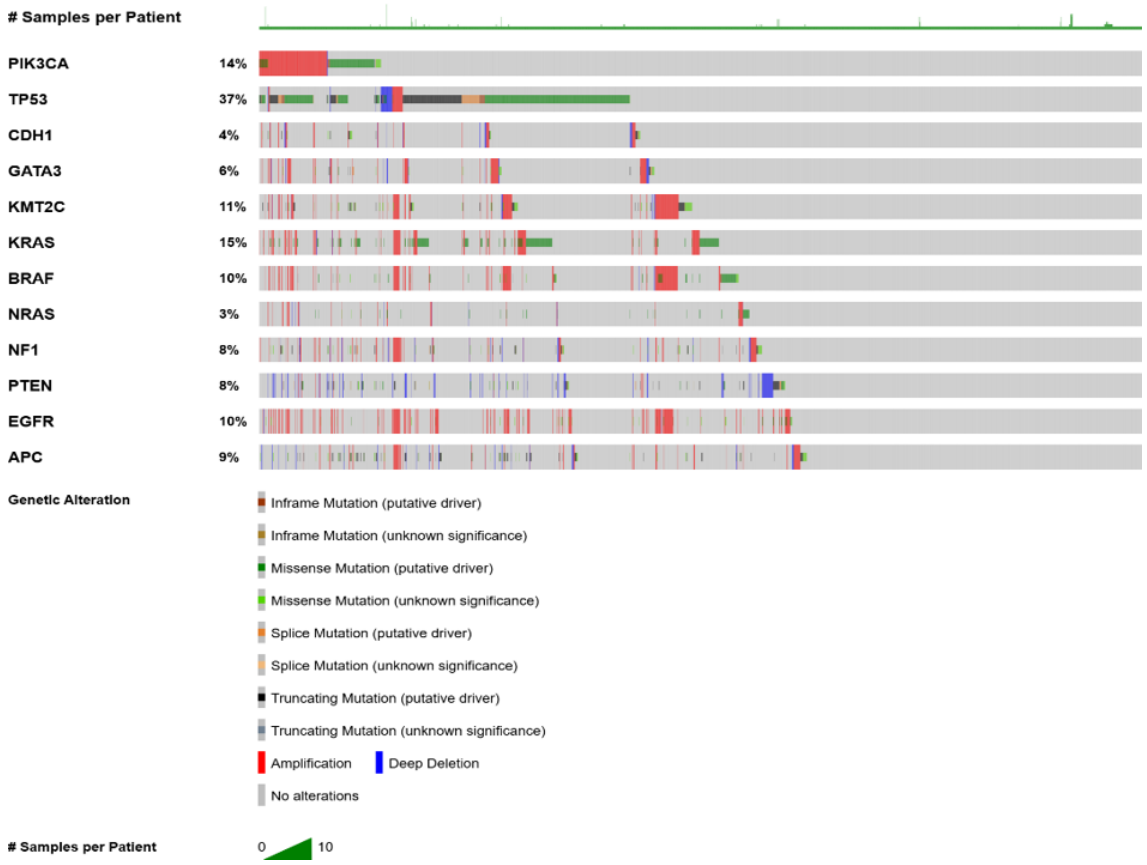

Figure 1: OncoPrint showing the mutation landscape of selected driver genes across TCGA cancer cohorts. Each column represents a patient sample and each row represents a gene. Different colors indicate types of genomic alterations.

There is significant intra- and inter-cohort variation in mutation patterns among the cancers presented in the OncoPrint shown in Figure 1. TP53 was found to be the most frequently mutated gene and highlights its importance as a tumor suppressor in many cancers. Changes in KRAS and PIK3CA were also common, but varied by tumor type. TP53 mutations were particularly prevalent in lung cancers and colorectal cancers with KRAS mutations being mainly found in colon adenocarcinoma and lung adenocarcinoma. In contrast, mutations of PIK3CA were more prevalent in breast invasive carcinoma, suggesting a cancer specific role in tumor initiation and progression.

Cancer Pathway Alterations

The module "Pathway enrichment analysis" was performed in cBioPortal of the selected driver genes, resulting in the involvement of several major oncogenic signaling pathways. Of these, the RTK–RAS signaling pathway was the most extensively involved in genetic changes, such as in the genes KRAS, BRAF, NRAS, NF1, and EGFR. Other pathways that were affected were the pathways involving PI3K (PIK3CA/PTE) the TP53 pathway (TP53 mutation) and the WNT signaling pathway (primarily APC alteration). The alteration rate for TP53 was found to be 36.6%, indicating its crucial importance in maintaining genomic stability and controlling the expression of tumour suppressor genes in various cancer types.

a) RTK–RAS Pathway

Of the pathways analyzed, the RTK–RAS pathway showed the largest degree of alterations (Figure 2). In this pathway, KRAS was the most commonly mutated gene (15.3%), with RIT1 (13.3%), BRAF (10.1%) and EGFR (9.9%) showing the next highest frequencies. Additional alterations were detected in ERBB2 (7.8%), NF1 (7.6%) and NRAS (3.3%). Mutations in these important signaling molecules are indicative of widespread abrogation of the RTK–RAS–RAF–MEK–MAPK pathway, which is a critical pathway responsible for cell proliferation, differentiation and survival. The findings of these changes in different kinds of cancer provide strong evidence for the role of this pathway in the development and progression of cancer and thus for its therapeutic potential in precision oncology.

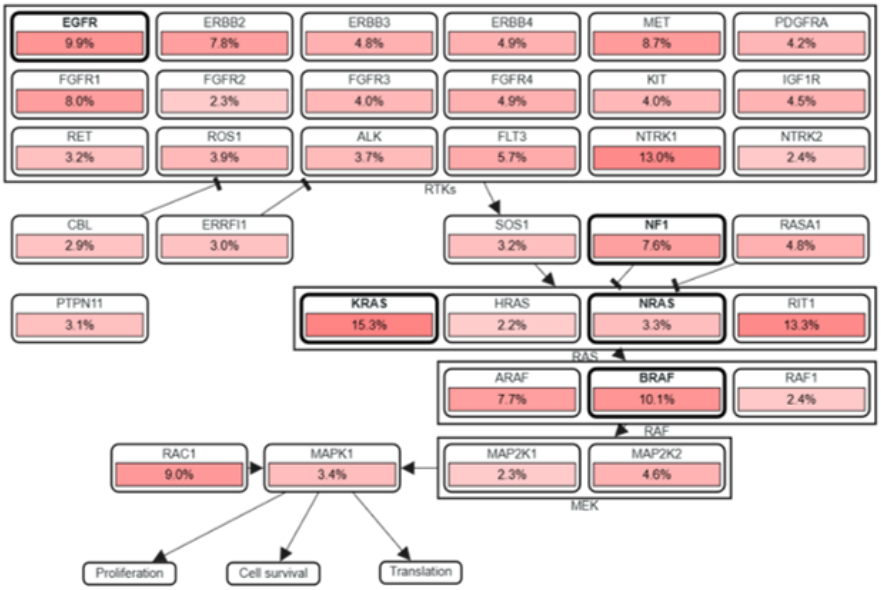

Figure 2: RTK–RAS signaling pathway alterations identified through the TCGA Pan Cancer Atlas pathway module in cBioPortal. Mutation frequencies of major pathway genes are represented within each node, illustrating prominent alterations in KRAS, BRAF, NF1, EGFR and related signaling components.

b) PI3K Pathway Alterations

The PI3K signaling pathway was also found to be altered in the genome, indicating its important role in the development of cancer (Figure 3). Of the genes examined, PIK3CA was the most commonly altered, with 13.8% alterations, followed by PTEN, a powerful negative regulator of PI3K signaling, with 8.2% alterations. Downstream pathway effectors, such as AKT3 (11.7%), AKT2 (6.5%), and AKT1 (4.2%) were also seen to have genomic changes. The alterations of members of the mTOR signaling complex were also remarkable: 9.0% for RICTOR, 6.9% for RPTOR, and 3.6% for MTOR. The results show that there is widespread dysregulation in the PI3K–AKT–mTOR pathway that regulates the growth, metabolic rate, proliferation, and survival of cells. These continuous changes observed in a variety of cancer types highlight the importance of this pathway in the progression of cancer and its therapeutic potential.

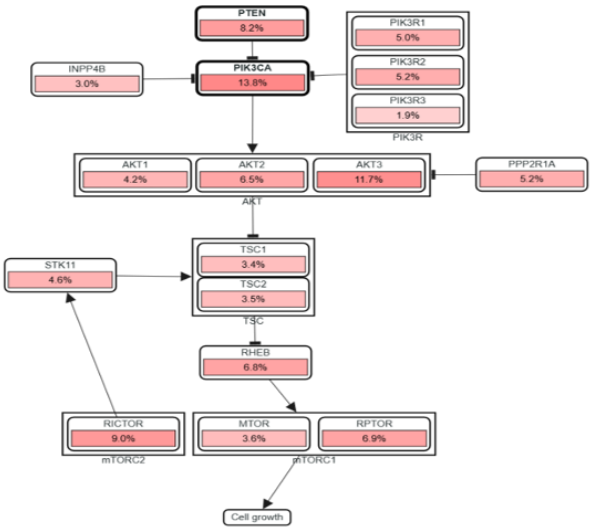

Figure 3: PI3K–AKT–mTOR signaling pathway alterations identified using the TCGA Pan Cancer Atlas pathway module in cBioPortal. Mutation frequencies are shown within each pathway component, highlighting significant alterations in PIK3CA and PTEN.

c) TP53 Tumor Suppressor Pathway

TP53 tumor suppressor pathway (also called DNA damage response pathway) had a widespread disruption of the genome in the cancer cohorts examined (Figure 4). The most commonly mutated gene was TP53, found in 36.6% of the mutations, indicating its importance in maintaining genomic stability and preventing malignant transformation. Notable alterations in several upstream regulators of TP53 were also observed. CDKN2A was found to be altered in 19.5% of cases, MDM4 in 11.2% of cases and MDM2 in 5.3% of cases. Other genes involved in DNA damage detection and repair were also impacted, such as ATM (6.3%) which is needed for the activation of TP53 in response to cell stress, and CHEK2 (3.3%) which functions to regulate the activity of ATM. Further evidence of disruption of stress-response signaling pathways comes from alterations in RPS6KA3 (8.8%). Together, these data demonstrate a significant dysfunction of TP53 pathway that could lead to unchecked cell growth, genomic instability, and cancer progression.

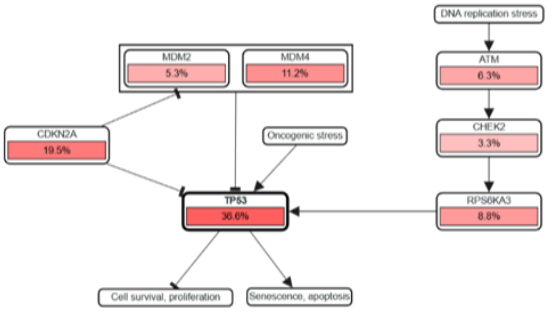

Figure 4: Genomic alterations in the TP53 tumor suppressor signaling pathway identified using the TCGA PanCancer Atlas module in cBioPortal. Percentages indicate alteration frequencies of key pathway components.

d) WNT Signaling Pathway Alterations

Changes in the WNT pathway were also identified, but at lower rates compared to the changes seen in the pathway activated by the RTK–RAS, PI3K and TP53 pathways (Figure 5). Alteration frequency was highest for the pathway genes, with APC having a 8.5% alteration frequency, the disruption of the β-catenin destruction complex. APC is an important negative regulator of WNT signaling through its ability to form a multiprotein complex with AXIN, GSK3B and other proteins to facilitate degradation of β-catenin. Mutations in APC disrupt this regulation, causing the constant accumulation and stabilization of the protein β-catenin inside the cell. The stabilized β-catenin then moves into the nucleus where it interacts with TCF/LEF transcription factors and turns on genes that control cell growth and survival. Mutations of other parts of the WNT pathway were found with relatively low frequencies, but APC mutations are often enough to induce abnormal WNT signaling, especially in colorectal tumorigenesis.

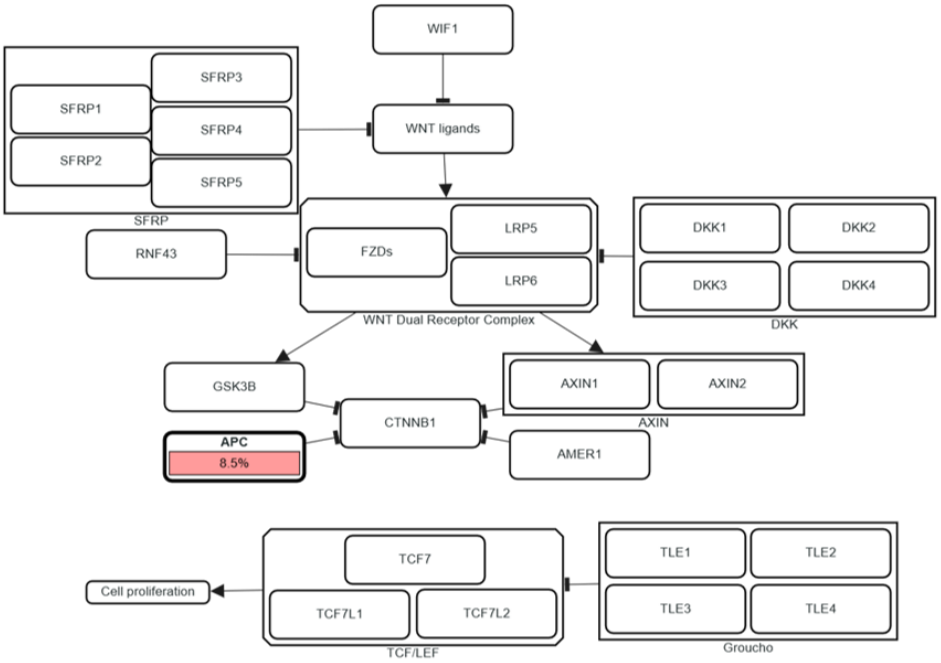

Figure 5: Genomic alterations in the WNT/β-catenin signaling pathway identified using cBioPortal. Percentages indicate alteration frequencies of key pathway components, with APC showing the highest alteration frequency.

e) Cell Cycle Pathway Alterations

Genomic changes in the cell cycle regulatory pathway were noted in the analysis, reflecting a high level of disturbance of the control of cell proliferation (Figure 6). The pathway-associated genes with the highest frequency of alterations were TP53 (36.6%), which is important in the regulation of cell cycle checkpoints, DNA repair and apoptosis. Many changes were observed in CDKN2A (19.5%), indicative of abnormalities in the G1/S checkpoint mechanism and cell cycle control.

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Additional genomic changes were observed in key cyclin-related genes, including CCNE1 (8.5%) and CCND1 (7.0%), both of which facilitate cell cycle progression. Alterations in ATM (6.3%), a major regulator of the DNA damage response, may weaken checkpoint activation and limit TP53-dependent growth arrest following genomic damage. Furthermore, genomic changes in E2F3 (6.3%) and FBXW7 (4.3%) indicate further disruption of pathways involved in cell cycle progression and protein degradation.

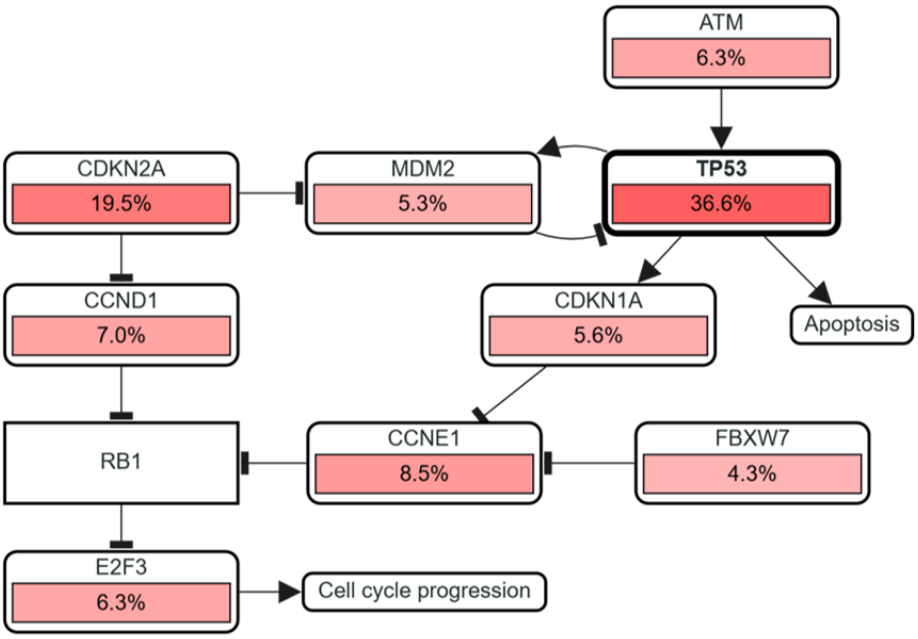

Figure 6: Genomic alterations in the cell cycle regulatory pathway identified using cBioPortal. Percentages indicate alteration frequencies of key genes involved in cell cycle progression and checkpoint regulation.

KEGG Pathway Enrichment Analysis

KEGG pathway enrichment analysis identified several significantly enriched cancer-associated signaling pathways linked to the selected driver genes (Figure 7 & Table 2). Among these, the MAPK signaling pathway showed the strongest enrichment ($p = 4.993 \times 10^{-7}$; adjusted $p = 3.200 \times 10^{-6}$; OR = 48.35), emphasizing its key role in controlling cellular proliferation, differentiation and survival. The PI3K–AKT signaling pathway also showed significant enrichment (adjusted $p = 6.395 \times 10^{-6}$; OR = 40.08), which is known to play a broad role in the metabolic control and growth of tumors.

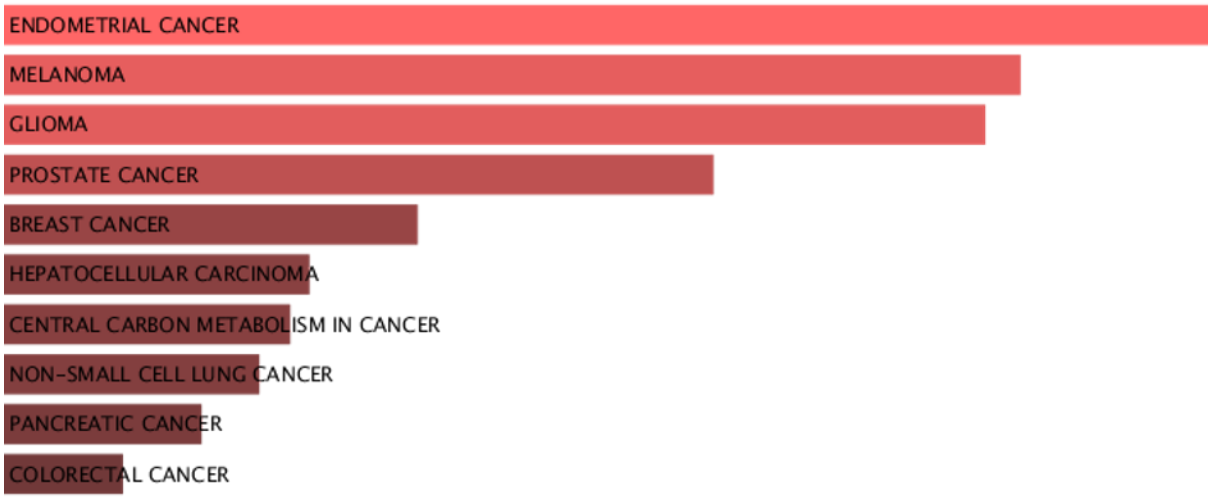

Figure 7: KEGG pathway enrichment analysis of selected driver genes showing significantly enriched cancer-related pathways ranked by p-value. Bar length corresponds to enrichment significance.

Table 2: KEGG pathway enrichment analysis of selected driver genes showing significantly enriched cancer-related signaling pathways based on p-value, adjusted p-value, odds ratio and combined score.

Name	P-value	Adjusted P-value	Odds Ratio	Combined Score
MAPK Signaling Pathway	4.993×10^{-7}	3.200×10^{-6}	48.35	701.53
PI3K-AKT SIGNALING PATHWAY	0.000001225	0.000006395	40.08	545.57
FOXO SIGNALING PATHWAY	8.199e-9	9.634e-8	113.50	2113.34
PD-L1 EXPRESSION AND PD-1 CHECKPOINT PATHWAY IN CANCER	1.686e-7	0.000001188	118.48	1847.74
APOPTOSIS	0.00006469	0.0001900	49.76	480.00

One of the most highly enriched pathways, with a very high OR and p value ($p = 8.199 \times 10^{-9}$; OR = 113.50), was the FOXO signaling pathway, which reflects strong over-representation of genes that regulate cellular stress responses, apoptosis and cell cycle regulation. Immune-associated pathways were also significantly enriched, including the PD-L1 expression pathway and PD-1 checkpoint pathway in cancer ($p = 1.686 \times 10^{-7}$; OR = 118.48), which indicates an important role for immune escape mechanisms in tumor progression. Furthermore, the apoptosis pathway was highly enriched (adjusted $p = 1.900 \times 10^{-4}$; OR = 49.76), suggesting that the impairment of programmed cell death is a contributing factor in the development of cancer. Altogether, most of the enrichment patterns were associated with recurrent alterations of major oncogenes (BRAF, EGFR, NRAS, PIK3CA) and tumour suppressor genes (PTEN, TP53). These results collectively highlight the relationship between different signaling networks and their roles in modulating tumor initiation, progression, immune regulation, and the immune response to therapy in the cancer types examined.

DISCUSSION

In the present pan-cancer study, we analyzed six cohorts from the TCGA, including breast invasive carcinoma (BRCA), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), colon adenocarcinoma (COAD), prostate adenocarcinoma (PRAD) and skin cutaneous melanoma (SKCM). A combination of integrated mutation profiling and pathway analysis identified both shared and tumor-specific genomic changes to gain insight into the key driver genes and molecular pathways in cancer initiation and progression in these malignancies. Out of all the genes analysed, the TP53 gene showed the greatest alteration frequency (36%), thus confirming its critical role as a key tumor suppressor gene in human tumors. TP53 is a key player in maintaining the integrity of the genome, and is responsible for coordinating DNA repair, cell cycle arrest and apoptosis. The frequent change in these protective mechanisms in the cohorts selected suggests that disruption of them is a common event in the process of tumorigenesis.

As previously reported, TP53 mutations were particularly common in lung and colorectal cancers, suggesting that these mutations are linked to genomic instability and the aggressiveness of the disease. Along with TP53, oncogenic drivers KRAS and PIK3CA were found to be recurrently altered. Adenocarcinoma of the colon and lung were the most common sites in which a KRAS mutation was found, as is consistent with its known ability to activate downstream proliferative signaling pathways. Similarly, breast cancer had a higher proportion of PIK3CA alterations, highlighting its involvement in tumor growth and therapeutic resistance. From these observations, it is clear that while there are a number of driver genes that are shared across various types of cancer, the frequency of mutations in these genes varies and the biological effect of the mutations differs with tumour type. Amongst the most heavily altered signaling pathways identified was the RTK–RAS signaling pathway by pathway analysis. The recurrent genomic changes that involve genes such as KRAS, BRAF, EGFR, NF1 and NRAS indicate the widespread disruption of the RTK–RAS–RAF–MEK–MAPK signaling cascade. This pathway is important for the control of cell proliferation, differentiation and survival and continuous activation can lead to uncontrolled tumour growth.

The results confirm the clinical relevance of targeting components of the RTK–RAS pathway in precision oncology. The PI3K–AKT–mTOR pathway was also heavily altered, with many genomic changes that involved PIK3CA, PTEN, AKT family genes and genes associated with mTOR. The dysregulated signaling cascade will increase cell survival, metabolic adaptation and resistance to apoptosis. Cooperation between multiple oncogenic signaling pathways is suggested by that both RTK–RAS and PI3K pathway alterations are present in the same cells, and may account, in part, for the resistance to single agent treatment and explain the rationale for combination therapy.

There were also marked changes noted in the TP53 tumor suppressor pathway and the cell cycle regulatory pathway. Impaired checkpoint control and defective DNA damage response mechanisms are suggested by genomic changes to CDKN2A, ATM, CCND1, CCNE1 and E2F3 and FBXW7. These abnormalities allow for out-of-control proliferation and the gradual build-up of genetic mutations that facilitate the growth and internal diversity of tumors. While the WNT signaling pathway had relatively few genomic changes, mutations to the APC gene were often detected, and might contribute to the disruption of normal β-catenin signaling on their own.

This is especially important in colorectal cancer, where APC mutation and inactivation are known to be early and important steps in the process of carcinogenesis. KEGG pathway enrichment analysis was used to further verify the biological relevance of the driver genes identified. MAPK, PI3K–AKT, FOXO, apoptosis and PD-L1/PD-1 pathway enrichment are also substantial, suggesting that mechanisms beyond uncontrolled proliferation also play a role in the progression of cancer.Important enrichment of the MAPK, PI3K–AKT, FOXO, apoptosis and PD-L1/PD-1 checkpoint pathways also suggests mechanisms beyond dysregulated proliferation are involved in cancer progression. The enrichment of immune checkpoint pathways is especially relevant as the use of immunotherapy is growing in contemporary cancer treatment.

CONCLUSION

This study finds that pan-cancer analysis of six TCGA cancer cohorts reveals recurrent alterations in key genes driving cancer initiation, progression, and major dysregulated signaling pathways. The genes that were most commonly altered were TP53, KRAS, and PIK3CA, while the pathways involved in the RTK–RAS, PI3K–AKT–mTOR, TP53, WNT, and cell cycle pathways showed extensive involvement in multiple cancer types. The importance of pathways related to MAPK, FOXO, apoptosis, and immune checkpoint was also highlighted via KEGG enrichment analysis. Overall, these studies shed new light on shared and tumour-specific molecular mechanisms and highlight possible biomarkers and therapeutic targets that could contribute to precision oncology and future cancer translational research.

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CONFLICT OF INTEREST: Nil.

REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2024; 74(3): 229–263.
2. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. Science, 2013; 339(6127): 1546–1558.
3. Tomczak K, Czerwińska P, Wiznerowicz M. The Cancer Genome Atlas (TCGA): an immeasurable source of knowledge. Contemp Oncol (Pozn), 2015; 19(1A): A68–A77.
4. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio Cancer Genomics Portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov, 2012; 2(5): 401–404.
5. Hoadley KA, Yau C, Hinoue T, Wolf DM, Lazar AJ, Drill E, et al. Cell-of-origin patterns dominate the molecular classification of 10,000 tumors from 33 types of cancer. Cell, 2018; 173(2): 291–304.
6. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell, 2013; 153(6): 1194–1217.

7. Sanchez-Vega F, Mina M, Armenia J, Chatila WK, Luna A, La KC, et al. Oncogenic signaling pathways in The Cancer Genome Atlas. Cell, 2018; 173(2): 321–337.