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Research Article

Co-Mutation Landscape of PIK3CA Across Multiple Adenocarcinomas: Insights from TCGA Data

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Abstract

Objective: PIK3CA is one of the most frequently mutated oncogenes across multiple cancer types, playing a crucial role in tumorigenesis via the PI3K/AKT/mTOR signaling pathway. Understanding its genuine co-mutation landscape is essential for identifying oncogenic interactions and refining targeted therapeutic strategies. In this study, we analyzed the true functional co-mutation patterns of PIK3CA in colorectal adenocarcinoma (COAD), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), stomach adenocarcinoma (STAD), and lung adenocarcinoma (LUAD).

Method: Somatic mutation data were obtained from The Cancer Genome Atlas (TCGA). Co-mutation and mutual exclusivity analyses were performed using R (maftools). To rigorously distinguish genuine biological cooperativity from confounding background mutation rates, multivariate logistic regression models were implemented, incorporating tumor mutational burden (TMB) as a continuous covariate.

Results: TMB-adjusted analyses revealed distinct, robust co-occurrence and mutual exclusivity relationships across cancer types, filtering out passenger mutations. In COAD, PIK3CA mutations significantly co-occur with KRAS, suggesting a cooperative role in tumorigenesis, while maintaining strict mutual exclusivity with TP53. In STAD, PIK3CA exhibits a strong, true functional co-occurrence with the chromatin remodeling gene ARID1A, while maintaining mutual exclusivity with TP53 and CSMD3. Interestingly, in both LUAD and CESC, PIK3CA demonstrates a highly significant mutual exclusivity with the mucin gene MUC17, pointing to context-specific evolutionary trajectories.

Conclusion: These findings highlight the complex, TMB-independent molecular landscape of PIK3CA-driven tumors, emphasizing the necessity of cancer-type-specific therapeutic approaches. By utilizing robust TMB-adjusted models, this study successfully isolates true genetic interactions, providing valuable insights into potential drug resistance mechanisms and novel combination therapy strategies for PIK3CA-mutant cancers.

Keywords: PIK3CA, Co-Mutation Analysis, TCGA, Cancer Genomics, Precision Onv vcology

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INTRODUCTION

Cancer is a multifactorial disease triggered by genetic and epigenetic alterations, which disrupt fundamental cellular pathways. PIK3CA is one of the most frequently mutated genes across multiple cancer types(1). This gene encodes the catalytic subunit of the enzyme phosphatidylinositol 3-kinase (PI3K). PI3K is a crucial component of the PI3K/AKT/mTOR signaling pathway, which regulates critical processes such as cellular proliferation, survival, and metabolism(2). Alterations in this pathway lead to an uncontrolled increase in cellular growth and the development of resistance to apoptosis, thereby causing tumor development(3). Therefore, PIK3CA mutations are of great importance in cancer research and have yielded significant implications for personalized cancer therapy.

PIK3CA mutations have been detected in various human cancers, such as colorectal adenocarcinoma (COAD), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), stomach adenocarcinoma (STAD), and lung adenocarcinoma (LUAD)(3). These mutations typically occur in hotspot regions such as E542K, E545K, and H1047R, leading to the constitutive activation of the PI3K pathway(4). Although PIK3CA alterations are sometimes sufficient on their own to trigger oncogenesis, their effects are generally modulated by concurrent mutations in other oncogenes and tumor suppressor genes(5). Despite an increasing understanding of PIK3CA-driven oncogenesis, challenges remain in effectively targeting this pathway, such as complex regulatory mechanisms that limit the efficacy of single-agent therapies. Furthermore, concurrent mutations in genes such as TP53, PTEN, and KRAS affect tumor behavior and treatment responses, emphasizing the importance of comprehensive molecular profiling in the field of individualized therapy(6). Therefore, understanding the co-mutation relationships of PIK3CA is crucial for elucidating its role in different cancer types and identifying potential treatment strategies.

Co-mutation analysis is a powerful approach to uncover functional interactions among oncogenic factors. The presence of concurrent mutations indicates cooperative oncogenic mechanisms, whereas mutually exclusive mutations may point to alternative tumorigenic pathways. For instance, PIK3CA mutations frequently co-occur with KRAS in colorectal cancer, suggesting a potential crosstalk between the PI3K and MAPK signaling pathways(7). In some cancers, however, the mutual exclusivity between PIK3CA and TP53 mutations may indicate that tumors rely on distinct oncogenesis mechanisms(8,9). Such information is critical in the development of targeted therapies, as it enables the prediction of drug sensitivity or resistance based on mutational profiles.

Large-scale cancer genome studies, and particularly initiatives like The Cancer Genome Atlas (TCGA), have provided unique opportunities to systematically investigate co-mutation patterns. By utilizing TCGA data, researchers can identify statistically significant concurrent and mutually exclusive mutations across various cancer types. These analyses can help define molecular subtypes of cancer, improve patient stratification for targeted therapies, and uncover therapeutic vulnerabilities.

Given the clinical significance of PIK3CA mutations and their potential interactions with other oncogenic alterations, this study aims to comprehensively investigate the co-mutation interactions of PIK3CA across four different

cancer types. Using TCGA data, we aim to identify significant concurrent and mutually exclusive mutations, evaluate their potential functional impacts, and elucidate their relationship with current treatment strategies. Understanding these co-mutation patterns will contribute to refining precision medicine approaches, guiding the development of combination therapies, and ultimately improving clinical outcomes for patients harboring PIK3CA mutations.

METHOD

To analyze the co-mutations of PIK3CA across four different cancer types (COAD, CESC, STAD, and LUAD), we utilized the TCGA database. Mutation data were retrieved from TCGA and processed using R (v4.4.3) to obtain accurate and reproducible results.

Data Collection and Preprocessing

Mutation data (Simple Nucleotide Variation, Masked Somatic Mutation) for the selected cancer types were obtained from TCGA using the TCGAbiolinks R package(10). Specifically, the "Aliquot Ensemble Somatic Variant Merging and Masking" workflow was utilized to download the data (accessed in July 2026). This package allows for the efficient querying, downloading, and preprocessing of TCGA data. To ensure consistency, only samples containing available PIK3CA mutation information were included in the study.

Mutation Analysis and Annotation

The downloaded mutation data were processed using R (v4.4.3) and annotated using the maftools R package(11). Consistent with standard maftools processing parameters, silent mutations were automatically filtered out; therefore, only non-silent variants (e.g., missense, nonsense, frame-shifts, and splice-site mutations) were retained for downstream analyses. No additional custom variant allele frequency (VAF) thresholds were applied. This package facilitates comprehensive mutation annotation, allowing for the identification of frequently mutated genes and their corresponding mutation types. To facilitate comparative analyses, PIK3CA mutant and wild-type groups were defined.

Co-Mutation and Confounding Analysis

For each cancer type, the top 20 most frequently mutated genes were determined using maftools. Initial co-occurrence and mutual exclusivity patterns were evaluated and visualized using the "somaticInteractions" function from the maftools package, which employs Fisher's exact test. To rigorously account for confounding effects driven by high background mutation rates, such as tumor mutational burden (TMB) and microsatellite instability (MSI) phenotypes, a multivariate logistic regression model was implemented using the base R "glm" function. In these models, the mutational status of PIK3CA was evaluated as the dependent variable, with the mutational status of each candidate gene serving as the independent variable. The total TMB (calculated as total mutations per sample, log10-transformed) was incorporated into the models as a continuous covariate. This approach allowed us to successfully distinguish genuine functional cooperativity from a shared dependence on global mutation burden. A significance threshold of $p < 0.05$ was established for the TMB-adjusted associations.

Visualization and Statistical Validation

Co-occurrence and mutual exclusivity relationships were visualized using heatmaps generated by the "somaticInteractions" function. To clearly represent the mutation patterns, oncoprint plots were generated using the ComplexHeatmap package(12). These plots

illustrate the distribution of PIK3CA mutations alongside the top 20 most frequently mutated genes across the samples, providing insights into potential interactions.

RESULTS

In COAD, after adjusting for tumor mutational burden (TMB), PIK3CA (30% prevalence) mutations demonstrated a robust and statistically significant co-occurrence with KRAS ($p < 0.001$, OR = 2.46). Furthermore, a strong mutual exclusivity between PIK3CA and TP53 was observed ($p = 0.006$, OR = 0.56) independent of mutational background **(Figure 1A)**. Oncoprint analysis revealed that PIK3CA mutations were predominantly missense mutations, with rare overlapping mutational events with TP53 **(Figure 1B)**.

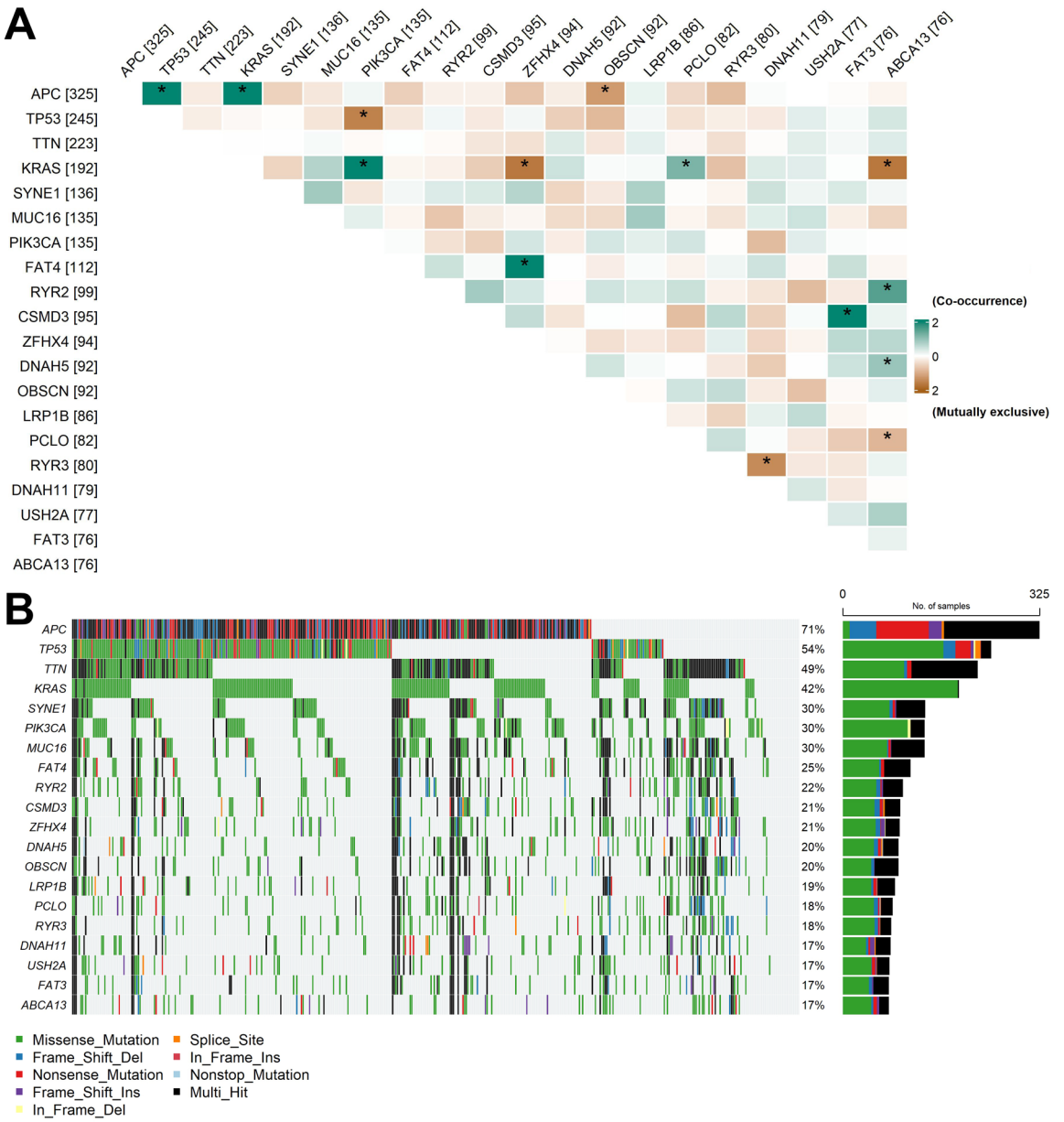

Figure 1. (A) Co-Mutation and Mutual Exclusivity Patterns of PIK3CA in COAD (green: co-occurrence; brown: mutual exclusivity) **(B)** Mutational Landscape of COAD.

In CESC, following TMB adjustment, PIK3CA (28% prevalence) mutations exhibited a highly significant mutual exclusivity with the mucin gene MUC17 (p = 0.009, OR = 0.21) and the calcium channel gene RYR2 (p = 0.048, OR = 0.35) **(Figure 2A)**. Oncoprint analysis revealed that PIK3CA mutations were distributed across the cohort without forming distinct clusters with classical structural driver mutations **(Figure 2B)**.

In STAD, TMB-adjusted logistic regression highlighted a distinct mutational landscape for PIK3CA (16% prevalence). The chromatin remodeling gene ARID1A showed a highly significant, functional co-occurrence with PIK3CA (p = 0.0004, OR = 3.30). Additionally, PIK3CA mutations exhibited strict mutual

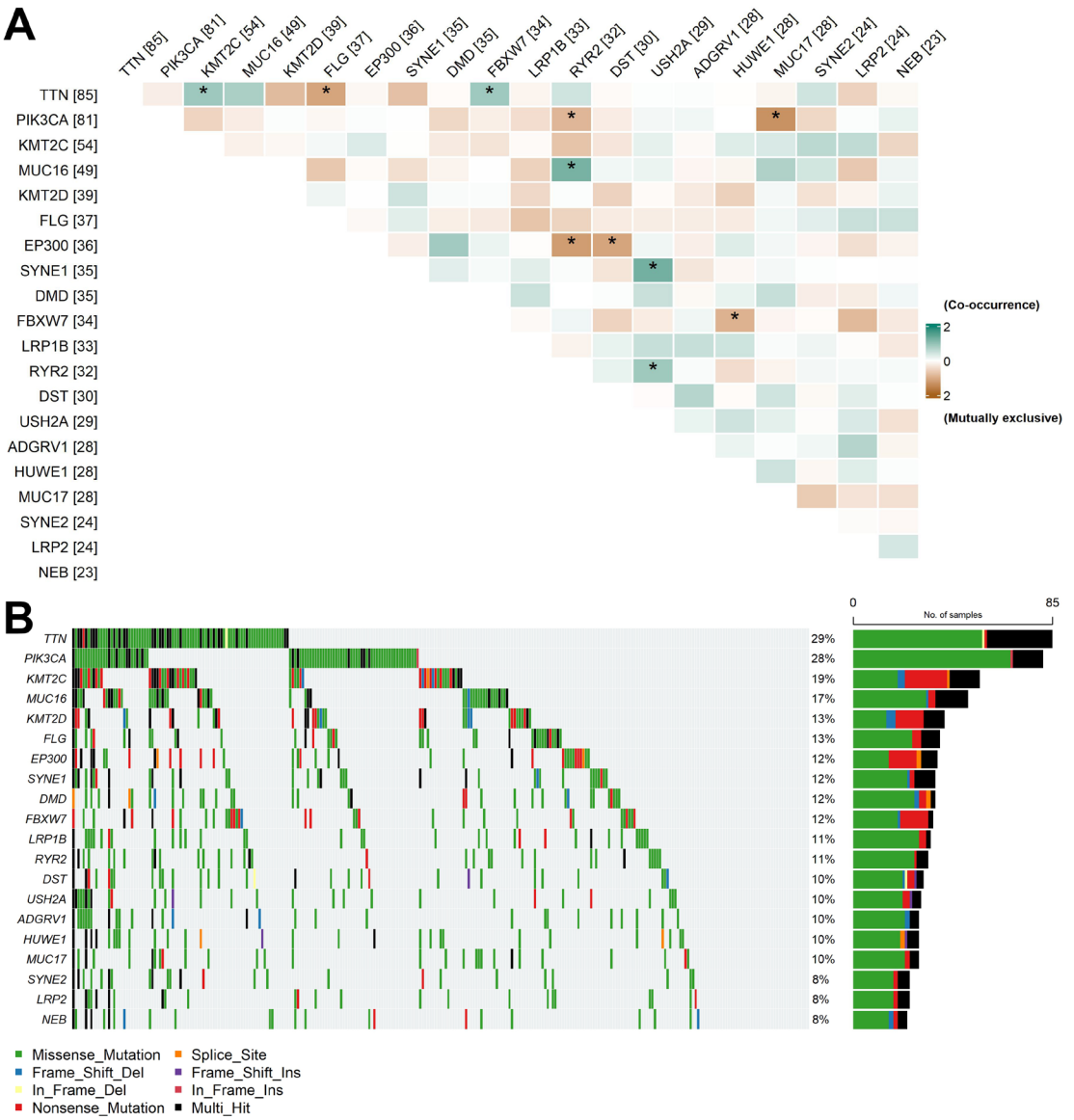

Figure 2. **(A)** Co-Mutation and Mutual Exclusivity Patterns of PIK3CA in CESC (green: co-occurrence; brown: mutual exclusivity) **(B)** Mutational Landscape of CESC.

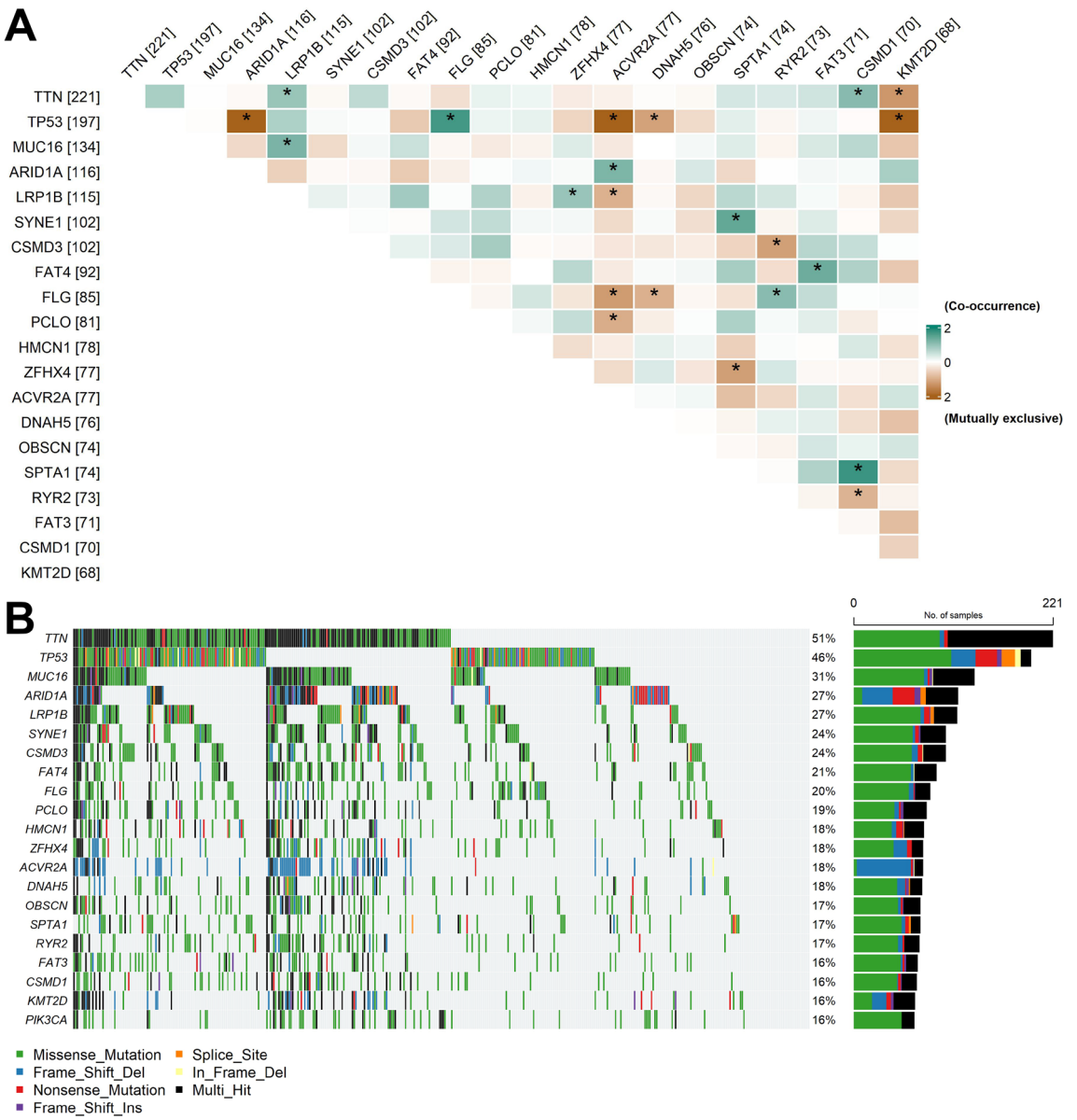

Figure 3. (A) Co-Mutation and Mutual Exclusivity Patterns of PIK3CA in STAD (green: co-occurrence; brown: mutual exclusivity) **(B)** Mutational Landscape of STAD.

exclusivity with TP53 (p = 0.001, OR = 0.36) and CSMD3 (p = 0.009, OR = 0.38) **(Figure 3A)**. Oncoprint analysis identified a distinct molecular subtype characterized by frequent PIK3CA/ARID1A co-mutations and rare TP53 alterations **(Figure 3B)**.

In LUAD, PIK3CA (5% prevalence) alterations showed a refined pattern of mutational exclusivity and co-occurrence. TMB-adjusted analysis revealed that PIK3CA maintained a robust and significant mutual exclusivity specifically with MUC17 (p = 0.037, OR = 0.11), while also demonstrating a significant co-occurrence with USH2A (p = 0.038, OR = 2.52) **(Figure 4A)**. Oncoprint analysis confirmed that PIK3CA mutations were distributed as independent events, exhibiting a pattern distinct from the mutational hotspots of TP53 or KRAS **(Figure 4B)**.

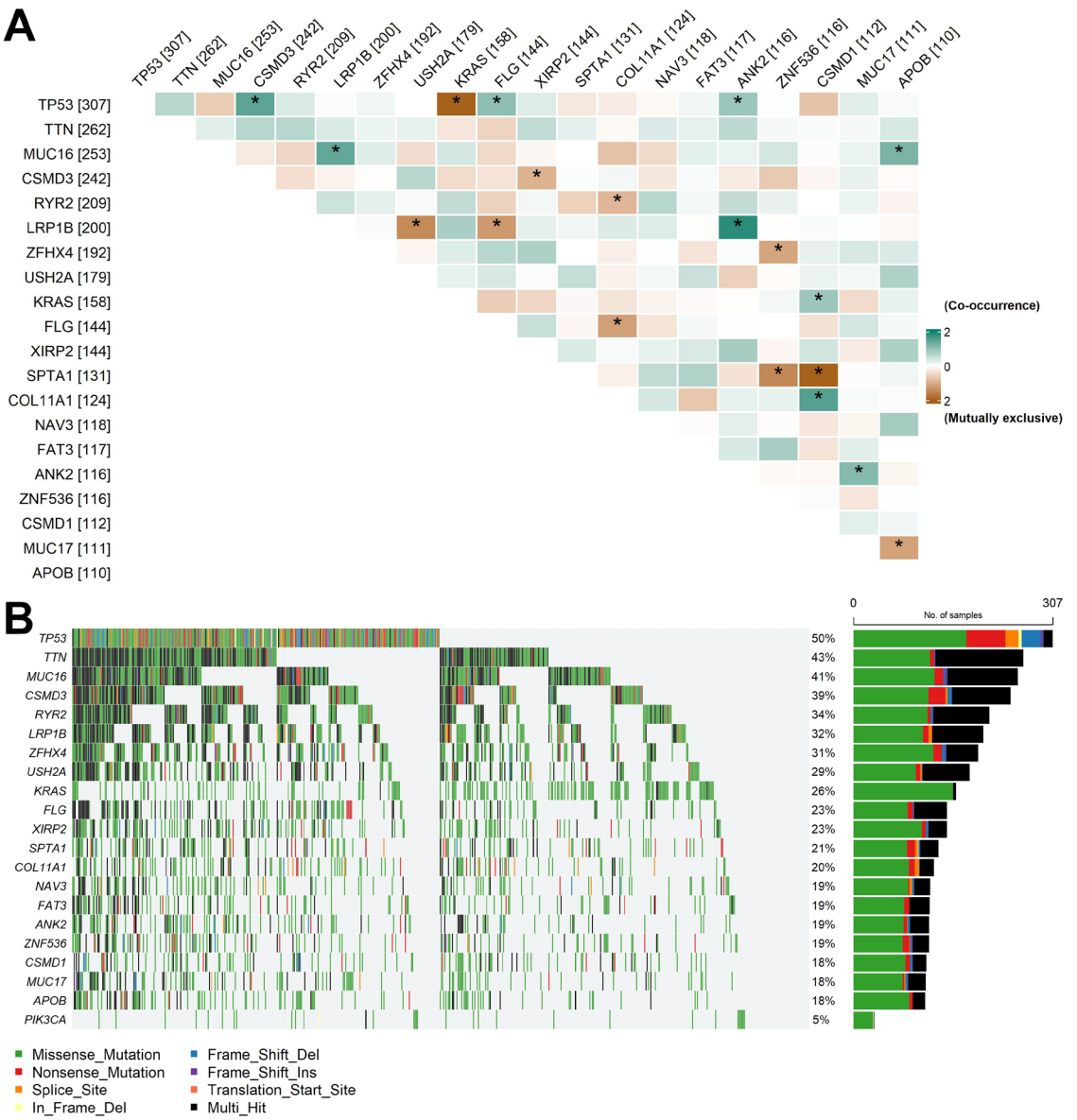

Figure 4. (A) Co-Mutation and Mutual Exclusivity Patterns of PIK3CA in LUAD (green: co-occurrence; brown: mutual exclusivity) **(B)** Mutational Landscape of LUAD.

DISCUSSION

In COAD, the PIK3CA mutational landscape is characterized by prominent co-occurrence with KRAS and strict mutual exclusivity with TP53. PIK3CA mutations (occurring in approximately 30% of samples) significantly co-occur with KRAS independently of global mutation burden. This relationship implies that concurrent activation of the PI3K/AKT and MAPK pathways is a selected evolutionary advantage in colorectal tumorigenesis, likely driving more aggressive phenotypes and contributing to broad resistance against EGFR inhibitors(13,14). Notably, the strong mutual exclusivity between PIK3CA and TP53, visualized with minimal overlap on the oncoprint, suggests that tumors in this subset follow distinct evolutionary trajectories. While TP53-mutated tumors heavily

rely on genomic instability, PIK3CA-driven tumors appear to be primarily sustained by constitutive PI3K pathway activation(6,9,15). The lack of significant correlation with APC (altered in 71% of cases) highlights that Wnt pathway dysregulation remains independent of PIK3CA-driven oncogenesis(16). Clinically, PIK3CA-mutated tumors without TP53 loss may constitute a highly specific, targetable subgroup for PI3Kα inhibitors(17). These findings underscore the necessity of integrating robust, TMB-corrected co-mutation profiles into the therapeutic stratification of colorectal cancer.

In CESC, TMB-adjusted analysis unveils a unique and highly specific mutational context for PIK3CA. PIK3CA mutations exhibited a profound mutual exclusivity with the mucin gene MUC17 and the calcium channel regulator RYR2. MUC17 is critical for maintaining epithelial barrier function, and alterations in mucins are deeply tied to tumor microenvironment interactions(18). The strong mutual exclusivity suggests that PI3K-driven cervical tumors may bypass the need for mucin-mediated microenvironmental disruption. Similarly, the exclusivity with RYR2 points towards alternative mechanisms of calcium signaling or cellular stress adaptation in PIK3CA-mutant tumors(19). Notably, PIK3CA has no significant association with TP53 or classical oncogenes in CESC, emphasizing its context-dependent role. Clinically, the mutual exclusivity with MUC17 and RYR2 may help in defining a distinct patient subgroup that could be particularly responsive to PI3K inhibitors, as these tumors lack confounding mutations in epithelial barrier or calcium regulation pathways(20).

In STAD, PIK3CA mutations exhibit a defining, true functional co-occurrence with the chromatin remodeling gene ARID1A, while maintaining mutual exclusivity with TP53 and CSMD3. The highly significant co-occurrence with ARID1A suggests a potent synergy between PI3K pathway activation and epigenetic dysregulation—a critical hallmark of gastric carcinogenesis(21). This robust interaction, sustained after rigorous TMB adjustment, implies that ARID1A loss may sensitize gastric tumor cells to PI3K dependence. Conversely, the strict mutual exclusivity with TP53 indicates that STAD tumors with PIK3CA activation can robustly progress without requiring the inactivation of p53, representing an alternative oncogenic route(22). The exclusivity with CSMD3 further separates PIK3CA-driven tumors from those relying on the dysregulation of large structural or adhesion-related tumor suppressors. Clinically, this positions PIK3CA as a central component of a distinct STAD su bgroup. These ARID1A-mutated/TP53-wild-type tumors present a unique therapeutic vulnerability, making the combination of epigenetic modulators and PI3K-targeted therapies a highly promising avenue for exploration(23).

In LUAD, the TMB-corrected co-mutation landscape of PIK3CA identifies significant interactions independent of the common mutational background typical of lung cancers. PIK3CA (altered in 5% of cases) showed a robust mutual exclusivity specifically with MUC17, mirroring the pattern observed in CESC, and a significant co-occurrence with USH2A. The mutual exclusivity with MUC17 reinforces the hypothesis that PIK3CA-mutated adenocarcinomas rely on intracellular metabolic and proliferative signals rather than structural barrier disruption(18). Furthermore, the co-occurrence with USH2A—a gene associated with cellular structural integrity—suggests potential

cross-talk between PI3K signaling and localized cytoskeletal dynamics, although the precise functional implications remain to be elucidated. Crucially, PIK3CA mutations rarely co-occur with major LUAD drivers like KRAS, reinforcing its role as an independent driver in a specific, narrow subset of tumors(24). The absence of complex confounding mutations suggests that this unique subset of PIK3CA-mutant LUADs may represent an ideal, uncluttered niche for targeted PI3K inhibitor monotherapy(25).

Limitations of the study

Although the findings of this study provide important, statistically robust insights for cancer research and personalized treatment strategies, they contain certain limitations. First, while TMB-adjusted logistic regression effectively mitigates false positives driven by global mutation burden, the biological roles and functional consequences of the observed true co-mutations (such as PIK3CA/ARID1A synergy or PIK3CA/MUC17 exclusivity) require rigorous in vitro and in vivo experimental validation to be fully confirmed. Second, because this research relies entirely on retrospective bioinformatics analyses of genomic data retrieved from the TCGA database, it lacks direct correlative data regarding patient responses to specific targeted therapies. Future studies must focus on providing functional evidence to successfully translate these identified, TMB-independent co-mutation relationships into actionable clinical applications and precision cancer therapies.

CONCLUSION

In conclusion, this study provides a comprehensive, TMB-adjusted analysis of the co-mutation landscape of PIK3CA across different cancer types, highlighting genuine molecular interactions that influence tumor progression and therapeutic responses. By integrating TCGA data with robust multivariate logistic regression, we successfully eliminated the confounding effects of background mutational noise, identifying key genetic associations—such as the synergy with KRAS in COAD and ARID1A in STAD, as well as the exclusivity with TP53 and MUC17. This refined molecular mapping offers critical insights into the evolutionary trajectories of PIK3CA-mutant tumors and provides a stringent, statistically sound framework for advancing more effective precision oncology approaches. Future studies should prioritize the functional validation of these interactions to translate these findings into improved combination therapies in the clinic.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

This study does not contain any clinical or experimental research data obtained directly from human participants or animal subjects by the author. All data in this study were obtained from publicly available databases. The author of this article declares that the materials and methods used in their research did not require ethics committee approval and/or any special legal permission

Author Contributions

Concept: PP, Design: PP, Supervising: PP, Data collection

and entry: PP, Analysis and interpretation: PP, Literature search: PP, Writing: PP, Critical review: PP

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