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Review Article

Prevalence and clinical significance of FGFR3 genomic alterations in Asian bladder urothelial carcinoma: A systematic review

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ABSTRACT

Bladder urothelial carcinoma is a common malignancy with distinct genetic variations across populations. Fibroblast Growth Factor Receptor 3 (FGFR3) mutations and structural variants play a critical role in its pathogenesis and represent important therapeutic targets. This systematic review was conducted using the repositories such as large genomic data repositories (including cBioPortal and GENIE) and PubMed (from inception to July 2024) to assess FGFR3 alterations in Asian patients. This review reveals at least 14.6% (average of 18.4%) of patients harbored FGFR3 genomic alterations (mutations or structural variants), with the S249C mutation being the most prevalent. Notably, these alterations were primarily mutually exclusive with TP53 mutations. The findings emphasize the clinical importance of FGFR3-targeted therapies, such as the U.S. Food and Drug Administration(FDA)-approved pan-FGFR inhibitor *erdafitinib* and underscore the necessity of molecular profiling to enhance treatment outcomes in bladder urothelial carcinoma.

Keywords: Bladder urothelial carcinoma, Asian patients, Fibroblast growth factor receptor 3

INTRODUCTION

Bladder urothelial carcinoma is one of the most prevalent malignancies worldwide, characterized by significant variability in incidence and genetic alterations across different populations.[1-4] In 2022, the World Cancer Research Fund reported that over 614,298 new cases of bladder cancer were diagnosed globally. Among these:

- India: 22,548 cases
- Japan: 34,568 cases
- China: 92,883 cases

These statistics highlight the global impact of bladder cancer and the varying incidence rates across different regions. Recently, the Fibroblast growth factor receptor 3 (FGFR3) gene has been identified as a key contributor to the pathogenesis of bladder urothelial carcinoma.[5,6] Mutations and structural variants of FGFR3, particularly in hotspot regions, are increasingly recognized for their oncogenic potential and as promising therapeutic targets.[5,6]

The incidence and genetic landscape of bladder urothelial carcinoma can vary significantly among Asian populations, making the prevalence and implications of FGFR3 alterations particularly noteworthy in this group.[7] Understanding the frequency and nature of these alterations in Asian patients is crucial for developing effective treatment strategies and improving clinical outcomes.[8]

This systematic review study focuses on analyzing the prevalence of FGFR3 mutations and structural variants in bladder urothelial carcinoma among Asian patients. By conducting a systematic review of genomic data, the research aims to elucidate the significance of these alterations and their potential as targets for FGFR3-directed therapies[9], such as the FDA-approved pan-FGFR inhibitor *erdafitinib*. The findings of this study are expected to enhance the growing body of evidence supporting the use of precision medicine in the treatment of bladder urothelial carcinoma.

MATERIAL AND METHODS

This systematic review was conducted using the following repositories:

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1. Large genomic data repositories, including cBioPortal and American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE)
2. PubMed, from inception to July 2024

The inclusion criteria combined the keywords "Bladder Urothelial Carcinoma," "Bladder Cancer," "Asian," "Primary," and "Genomic." From the large-scale genomic repositories, we identified three relevant datasets out of 11 after applying the inclusion criteria and removing duplicates.

From the PubMed search, 132 records were identified after applying the inclusion criteria. Several of these records overlap with the three datasets identified in large-scale genomic repositories, with only one additional relevant record found. Table 1 summarizes the studies on primary bladder urothelial carcinoma used to determine the prevalence of FGFR3 mutations in the Asian population. The datasets from large-scale genomic repositories were retrieved and analyzed using cBioPortal[10-12] and GENIE Cohort v16.0,[13] both open-access cancer genomics databases. The additional dataset from PubMed was retrieved from Peak *et al*.[14] The analysis focused on genomic alterations, including mutations, copy number variants, and structural variations/fusions.

RESULTS

Table 2 presents the mutation and structural variants of FGFR3 identified in the primary bladder urothelial carcinoma studies analyzed. Figure 1 illustrates the FGFR3 gene alterations in the three selected datasets of Asian bladder urothelial carcinoma patients. FGFR3 is the most frequently altered gene in Asian bladder urothelial carcinoma patients.[7] FGFR3 alterations predominantly include mutations and structural variants.

Figure 2 illustrates landscape of FGFR3 mutations in the three selected datasets of Asian bladder urothelial carcinoma patients. The TCGA bladder urothelial carcinoma study reports a few patients with FGFR3 copy number amplifications; however, these amplifications co-occur with mutations or structural events. Notably, mutations and structural events are

Table 1: Summary of bladder urothelial carcinoma studies used to assess FGFR3 prevalence in the Asian population.

Dataset ID	Studies	Ethnicity	No. of Asian patients of the total number of patients in the dataset
Bladder_Dataset1	TCGA Bladder urothelial carcinoma[1,15]	Asian	43 of 411 patients (10.46%)
Bladder_Dataset2	Bladder urothelial carcinoma[16]	Asian-far east/Indian subcontinent	35 of **1,014** patients **(3.45%)**
Bladder_Dataset3	AACR Project genomics evidence neoplasia information exchange (GENIE) cohort v16.0 public (https://genie.cbioportal.org/)[13]	Asian	104 of **2,845** patients **(3.65%)**
Bladder_Dataset4	Urothelial carcinoma of the bladder[14]	Asian	279 of **8,728** patients **(3.19%)**

TCGA: The cancer genome atlas, AACR: American association for cancer research

Table 2: Mutation rates and structural variants of FGFR3 in bladder urothelial carcinoma studies.

Dataset_ID	FGFR3 mutation in Asian patients	FGFR3 Structural variants/fusions in Asian patients	FGFR3 Copy number variants in Asian patients	Total FGFR3 genomic alterations in Asian patients	Total FGFR3 genomic alterations in Asian patients
Bladder_Dataset1	28% (12/43)	14% (6/43)	9% (4/43)	44% (19*/43)	19% (77/411)
Bladder_Dataset2	20% (7/35)	3% (1/35)	0% (0/35)	23% (8/35)	28% (280/1014)
Bladder_Dataset3	14% (15/104)	2% (2/104)	0% (0/104)	16% (17/104)	24% (671/2845)
Bladder_Dataset4	14.6% (41/279	NA	NA	14.6% (41/279)	18.3% (1605/8728)
FGFR3 genomics alterations (in summary)				18.4% (85/461)	20.3% (2633/12998)

**includes 3 samples with multiple alterations in the same patient.*
NA – Data not available, FGFR3: Fibroblast growth factor receptor 3.

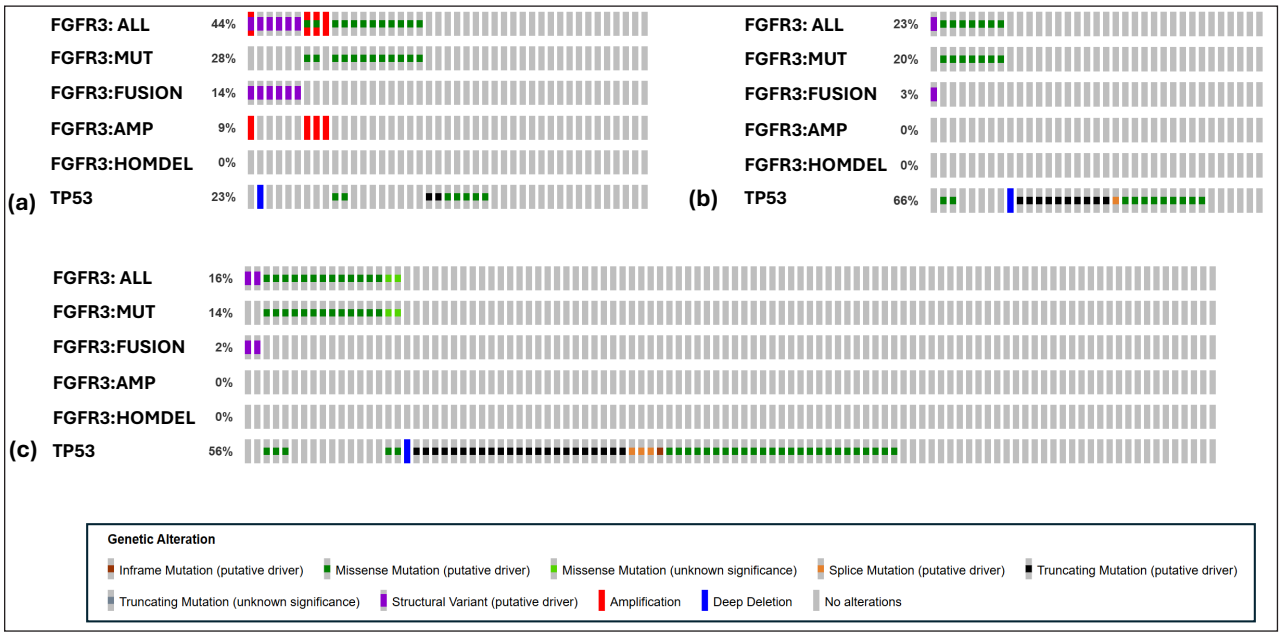

Figure 1: FGFR3 genomic alterations assessed in Asian patients. This figure was generated using cBioPortal web tools. (a) FGFR3 alterations in Bladder_Dataset1 (b) FGFR3 alterations in Bladder_Dataset2(c) FGFR3 alterations in Bladder_Dataset3

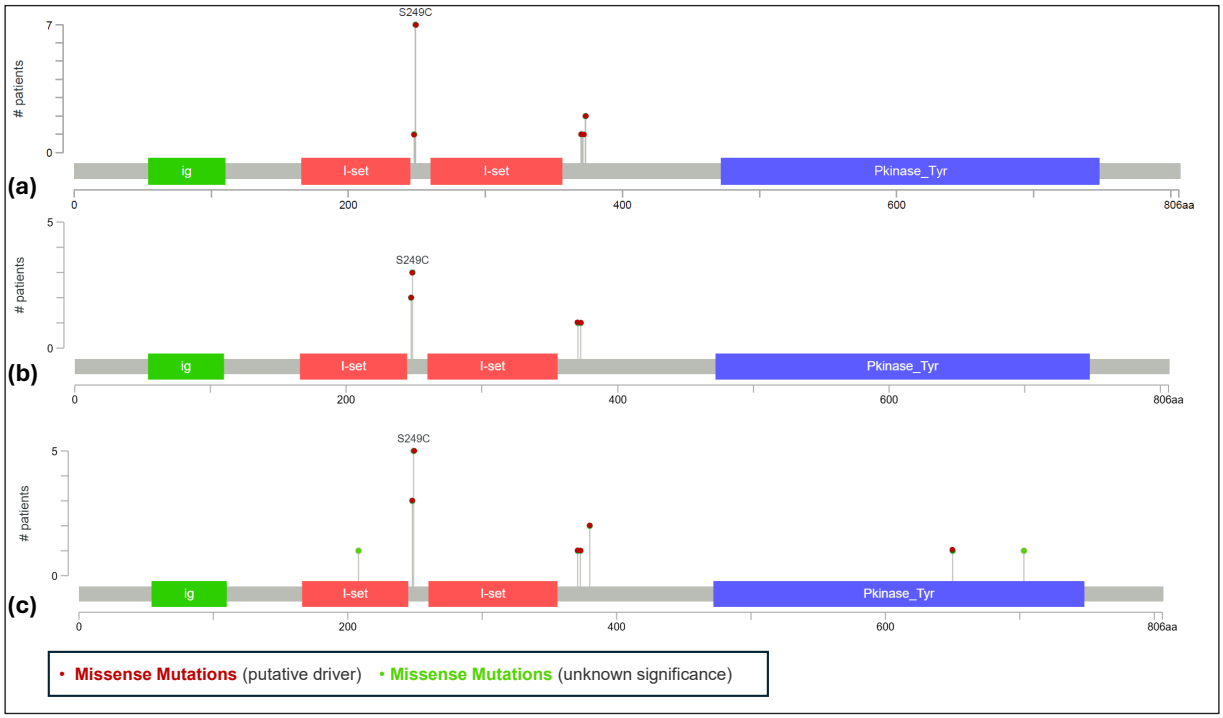

Figure 2: Landscape of FGFR3 mutations in bladder urothelial carcinoma patients. This figure is generated using cBioPortal web tools. (a) Lollipop schemes for FGFR3 in Bladder_Dataset1(b) Lollipop schemes for FGFR3 in Bladder_Dataset2 (c) Lollipop schemes for FGFR3 in Bladder_Dataset3

mutually exclusive FGFR3 mutations, frequently identified in bladder urothelial carcinoma studies, are predominantly driver mutations and account for a significant portion of oncogenic events. In addition, the FGFR3-TACC3 fusion is recognized for its strong oncogenic potential. FGFR3 genomic alterations are observed in at least 14.6% (average of 18.4%) of Asian patients. The overall frequency of FGFR3 alterations (including mutations, copy number variations, and structural variants in all ethnicities) is 19%, 28%, 24%, and 18.3% in Bladder_dataset1 to Bladder_dataset4, respectively.

Table 3 highlights the prevalence of FGFR3 genomic alterations across different ethnic groups in Bladder_Dataset1, revealing statistically significant differences:

- Between Asian vs. White patients: p = 0.0001 (Fisher's exact test).
- Between Asian vs. African American patients: p = 0.0047 (Fisher's exact test).

In contrast, no statistically significant differences were observed in other datasets, indicating that these findings may be specific to Bladder_Dataset1 or influenced by datasetspecific factors.

Table 4 presents the prevalence of FGFR3 genomic alterations alongside other recurrent molecular alterations, including TP53, KMT2D, KDM6A, ARID1A, PIK3CA, KMT2C, RB1, EP300, E2F3, PPARG, MDM2, and CDKN2A.[17] In addition

Table 3: Comparison of FGFR3 genomic alteration frequencies among ethnicities in bladder urothelial carcinoma across studies

Dataset_ID	Ethnicity comparison	Fischer's exact test P-value *(FGFR3 genomic alteration frequencies between ethnicities)*
Bladder_Dataset1	*Asian (vs) White*	**0.0001 (19/43 vs 53/327)**
	Asian (vs) African American	**0.0047 (19/43 vs 2/23)**
Bladder_Dataset2	*Asian-Far East/Indian Subcontinent (vs) White*	0.5677 (8/35 vs 245/849)
	Asian-Far East/Indian Subcontinent (vs) African American	1.0 (8/35 vs 8/38)
Bladder_Dataset3	*Asian (vs) White*	0.0614 (17/104 vs 578/2374)
	Asian (vs) African American	0.3674 (17/104 vs 21/95)
Bladder_Dataset4	*Asian (vs) European genomic ancestry*	0.1332 (41/279 vs 1368/7447)

FGFR3: Fibroblast growth factor receptor 3

Table 4: Prevalence of FGFR3 genome alterations and other recurrent molecular alterations in Asian bladder urothelial carcinoma patients

Frequently altered genes	Bladder_Dataset1 (n = 43)	Bladder_Dataset2 (n = 35)	Bladder_Dataset3 (n=104)	Bladder_Dataset4 (n=279)
FGFR3	44%	23%	16%	14.6%
TP53	23%	66%	56%	61%
KMT2D	21%	20%	30%	NA
KDM6A	28%	31%	30%	NA
ARID1A	12%	26%	25%	22%
PIK3CA	12%	14%	17%	14%
KMT2C	23%	26%	27%	NA
RB1	14%	34%	25%	18%
EP300	9%	14%	13%	NA
E2F3	9%	11%	15%	NA
PPARG	9%	7%	7%	NA
MDM2	12%	14%	10%	9%
CDKN2A	35%	14%	15%	39%

n=*size of the patient population*
NA: Data not available, FGFR3: Fibroblast growth factor receptor 3

to FGFR3 genomic alterations, TP53 and CDKN2A exhibit the highest frequency of genomic alterations.

DISCUSSION

FGFR3 mutations, frequently identified in bladder urothelial carcinoma studies, are predominantly driver mutations and account for a significant portion of oncogenic events. In addition, the FGFR3-TACC3 fusion is recognized for its strong oncogenic potential. Notably, mutations in FGFR3 and TP53 are typically mutually exclusive across all datasets.

Current treatment strategies in Asian patients vary depending on the stage of the cancer. Different treatment modalities for the treatment of bladder cancer include intravesical instillation of Bacillus calmette-Guerin (BCG), transurethral resection of bladder tumor radical cystectomy with urinary diversion, immunotherapy, *neoadjuvant* chemotherapy and chemoradiation. Given that a subset of bladder cancer patients harbors FGFR3 mutations, it is crucial to identify these alterations prior to initiating treatment, especially in Asian populations. Several FGFR inhibitors have been developed in recent years for various cancers, including bladder cancer. FGFR inhibitors such as *infigratinib* and *futibatinib* (used in cholangiocarcinoma), and *pazopanib* (used in renal cell carcinoma) are among the therapies that target FGFR pathways.

In 2019, The U.S. FDA granted accelerated approval to *Balversa* (*erdafitinib*) for treating adult patients with locally advanced or metastatic bladder cancer that has FGFR3 or FGFR2 genetic alterations.[17] Common side effects include increased phosphate levels, dry skin, anemia, and eye problems. *Balversa* also requires further clinical trials to confirm its benefits and is used alongside an FDA-approved diagnostic tool such as the therascreen Fibroblast growth factor receptor rotor-gene Q real-time reverse transcription polymerase chain reaction (FGFR RGQ RT PCR) Kit.[17] *Balversa* is the first personalized treatment targeting these specific genetic mutations. In the Janssen Pharmaceutical clinical trial, patients selected in the trail had progressed following treatment with chemotherapy. In the same clinical trial, it achieved a 32.2% overall response rate (with 2.3% having a complete response and almost 30% having a partial response), with responses lasting about 5.5 months.[18] This highlights the critical role of identifying these genomic alterations in the management and treatment of bladder urothelial carcinoma.

CONCLUSION

This study highlights the significant prevalence of FGFR3 mutations and structural variants in bladder urothelial carcinoma among Asian patients. The systematic review revealed that at least 16% of the patients exhibited FGFR3 alterations, with the S249C mutation being the most frequent hotspot. These findings underscore the importance of molecular profiling in managing bladder cancer and identifying actionable mutations for targeted therapy.

The clinical relevance is further emphasized by the FDA-approved pan-FGFR inhibitor *erdafitinib*, which targets FGFR3 mutations and recurrent fusions. The mutual exclusivity observed between mutations and structural events suggests distinct oncogenic pathways, informing future therapeutic approaches. Continued research and development of FGFR-targeted therapies could significantly improve outcomes for bladder urothelial carcinoma patients, especially within the Asian demographic.

Author contributions

RP: Conceptualization, formal analysis, methodology, reviewing, writing and editing; CSP: Visualization, data curation, supervision, reviewing, writing and editing; AO: Methodology, writing, reviewing and editing.

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Declaration of patient consent: Patient's consent is not required as there are no patients in this study.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of AI-assisted technology for assisting in the writing of the manuscript and no images were manipulated using AI.

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