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Clinical Pathology & Research Journal
ISSN: 2642-6145

TERT Promoter Mutation is a Diagnostic and Differential Diagnostic Marker for Tumors with Urothelial Origin

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Mini Review

Volume 4 Issue 1

Received Date: July 21, 2020

Published Date: August 07, 2020

DOI: 10.23880/cprj-16000125

Abstract

Telomerase reverse transcriptase (*TERT*) promoter mutations have been found in approximately 60–80% of bladder urothelial cancers and its variants of all grades anywhere in the urinary tract. The *TERT* promoter mutations occur early in urothelial neoplasia and are biomarkers for neoplasm development, recurrence, diagnosis, differential diagnosis, and potentially a therapeutic target. This review highlighted the role of *TERT* promoter mutations in urothelial tumorigenesis, and the potential clinical implications.

Keywords: *TERT* promoter mutation; Urothelial carcinoma; Bladder cancer; Marker

Mini Review

Telomerase reverse transcriptase (*TERT*) promoter mutations have been found in approximately 60–80% of bladder urothelial cancers and its variants of all grades anywhere in the urinary tract [1-3]. *TERT* promoter mutations create a consensus E-26 transcription factor binding site, which up-regulate the TERT expression leading to urothelial transformation. The *TERT* promoter mutations reactivate telomerase conferring the hallmark of immortality on neoplastic cells. *TERT* promoter mutations frequently occur in cancers with low rates of self-renewal, suggesting that these cells acquired survival and growth advantages during tumorigenesis [4]. Current data suggested that *TERT* promoter mutations were not associated with clinical or pathologic parameters, and were found in variants of urothelial carcinomas. *TERT* promoter mutations were found in benign and malignant urothelial neoplasms and its variants such as small cell carcinoma, adenocarcinoma, squamous carcinoma, micropapillary urothelial carcinoma, plasmacytoid urothelial carcinoma, and sarcomatoid urothelial carcinoma [2,5-7].

Many studies reported that *TERT* promoter mutations with a comparable prevalence across the whole spectrum of urothelial carcinomas regardless the location, grade, stage and not associate with clinical outcome. Currently there is no consensus on the association of *TERT* promoter mutations and clinical behavior of the urothelial tumors. The ~80% *TERT* promoter mutation prevalence in tumors with urothelial origin make it a useful marker for diagnosis and surveillance, and may be a potential therapeutic target.

Bladder cancer patients need long term follow-up and surveillance after treatment. *TERT* promoter mutation detection from urine samples may provide a novel and non-invasive method to detect urothelial carcinoma from urine [8,9]. *TERT* promoter mutations were detected from urine samples of up to 80% of the urothelial carcinoma patients with a specificity of 90%. *TERT* promoter mutations from urine specimens are reportedly detectable up to 10 years prior to clinical diagnosis of bladder cancer further suggested its clinical surveillance utility [10].

A variety of glandular or pseudoglandular lesions may be seen in the urinary bladder, ranging from those that are

entirely benign to aggressive-behaving malignant primary and secondary tumors. Ectopic tissues of Müllerian origin may also be seen occasionally in the urinary bladder and their differentiation from a true glandular neoplasm is important to avoid improper treatment. *TERT* genotypes have been shown to be conserved across spatially, temporally, and morphologically distinct components of a single tumor, further supporting its use as a relatively stable and reliable molecular biomarker.

TERT promoter mutations showed organ specificity, which were found in malignant glandular urothelial lesions, but were not found from benign glandular urothelial lesions and glandular tumors from other organ sites [7]. *TERT* promoter mutation could potentially helpful in differential diagnosis between urachal and adenocarcinoma of bladder, since urachal adenocarcinoma possess very low *TERT* promoter mutation prevalence. The *TERT* promoter mutations occur early in urothelial neoplasia and are biomarkers for neoplasm development, recurrence, diagnosis, prognostication, and potentially a therapeutic target.

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