Understanding TERT Promoter Mutations: a Common Path to Immortality

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Abstract

Telomerase (TERT) activation is fundamental step in tumorigenesis. By maintaining telomere length, telomerase relieves a main barrier on cellular lifespan, enabling limitless proliferation driven by oncogenes. The recently discovered, highly recurrent mutations in the promoter of TERT are found in over 50 cancer types, and are the most common mutation in many cancers. Transcriptional activation of TERT, via promoter mutation or other mechanisms, is the rate-limiting step in production of active telomerase. While TERT is expressed in stem cells, it is naturally silenced upon differentiation. Thus, the presence of TERT promoter mutations may shed light on whether a particular tumor arose from a stem cell or more differentiated cell type. It is becoming clear that TERT mutations occur early during cellular transformation, and activate the TERT promoter by recruiting transcription factors that do not normally regulate TERT gene expression. This review highlights the fundamental and widespread role of TERT promoter mutations in tumorigenesis, including recent progress on their mechanism of transcriptional activation. These somatic promoter mutations, along with germline variation in the TERT locus also appear to have significant value as biomarkers of patient outcome. Understanding the precise molecular mechanism of TERT activation by promoter mutation and germline variation may inspire novel cancer cell-specific targeted therapies for a large number of cancer patients.

Telomeres are composed of 'TTAGGG' repeats at the end of chromosomes, and telomere length plays a critical role in multiple human diseases including cancer (1,2). Telomere length is regulated by telomerase, the large multicomponent reverse transcriptase that recognizes, binds, and elongates the telomere ends using its intrinsic RNA template (3,4). The *TERT* gene encodes the catalytic subunit of telomerase, and its transcriptional regulation is usually the limiting step in telomerase activity(*5-8*). Telomerase activity is silenced in the majority of normal tissues, causing telomeres to shorten with each successive round of cell division (9,10). Eventually, a critical telomere length is reached(9,11-13), and cells enter replicative senescence(*14-16*). In contrast, cells that require high rates of self-renewal such as cells in the ovary(*10*), intestinal epithelium(*17*), and hematopoietic stem cells(*18*) have telomerase activity and can maintain telomere length over many cell divisions. The expression of telomerase is considered a hallmark of tumorigenesis, as over 90% of human cancers express the enzyme (10,19,20). The cancers found to be telomerase negative use an alternative mechanism of telomere lengthening termed ALT(21-23). Furthermore, germline variation in genes involved in telomere regulation such as *RTEL1, POT1, TERC, TERT,* and genes of the CST complex underlies increased risk of glioma (24-27), melanoma(28), and cancers of the lung(29,30), bladder(28), and pancreas(31).

In 2013, two hotspot point mutations were found in the *TERT* promoter in 71% of melanomas (32,33). The mutations were located 124bp and 146bp upstream of the translation start site and referred to as C228T and C250T, respectively, based on their hg19 genomic coordinates. The mutations are typically heterozygous, occur in a mutually exclusive fashion, and both create an identical 11bp sequence 'CCCGGAAGGGG'. The mutated sequence has an increased similarity to an ETS binding motif, leading to the hypothesis that the mutations generate a de-novo binding site for an activating ETS family transcription factor (TF). Soon after their initial discovery, the *TERT* promoter mutations were found to be the most common point

mutations in several tumor types including 83% of glioblastoma(34), 71% of melanoma(32,33), 66% of bladder cancer(35), and 47% of hepatocellular carcinoma(34,36). To date, the hotspot mutations have been identified in over 50 distinct cancer types (figure 1). Both mutations activate *TERT* promoter activity and *TERT* gene transcription (32,33). In bladder cancer, Borah and Xi et al. have also demonstrated that the promoter mutations are associated with increased telomerase activity and stable telomere length(37). Less commonly, *TERT* can be activated by other genetic mechanisms including rare point mutations at other promoter positions(38), rearrangements(39,40), duplication(41), or amplification(42,43). *TERT* promoter mutations were not detected in other common cancer types, such as breast and prostate cancer (figure 1 legend).

The high frequency of *TERT* promoter mutations in just two nucleotide positions strongly implicates them as driver events, arising upon tumor initiation or potentially later in tumor evolution(44). However, recent studies suggest *TERT* promoter mutations are among the earliest genetic events in bladder cancer(35), hepatocellular carcinoma(45), thyroid carcinoma(46), cutaneous melanoma(47-49), basal cell and squamous cell carcinoma(50), and oligodendroglioma(51). *TERT* promoter mutation may be the second genetic event following the activation of an oncogenic signaling pathway, such as MAP kinase signaling in melanoma (47) or Wnt signaling in hepatocellular carcinoma(45). It is unclear whether reactivation of telomerase through *TERT* promoter mutation is required only for early stages of tumorigenesis or is also necessary for sustained neoplastic growth(37).

Stem cells have been proposed as the cell of origin in multiple types of cancer. Because these cells express *TERT*, tumors originating from stem cells may not require *TERT* promoter mutations to activate telomerase and maintain telomere function. Interestingly, *TERT* promoter mutations occur most frequently in cancers with low rates of self-renewal, such as cancers of

the brain, liver, and melanocytes(34). In human embryonic stem cells genetically engineered to contain the hotspot mutations, there was little effect on *TERT* expression, but these cells failed to silence TERT upon differentiation(52). These observations raise the possibility that cells with low rates of self-renewal and lack of *TERT* expression acquire a *TERT* promoter mutation to avoid replicative senescence during early carcinogenesis. In contrast, transformation of *TERT*-expressing stem cells such as hematopoetic stem cells may not require promoter mutation to maintain *TERT* expression through tumorigenesis. As an alternative to mutation, TERT promoter activation may occur through an epigenetic switch(53). Stern et al. 2015 has additionally suggested that *TERT* promoter mutations can convert the silent *TERT* promoter into an active chromatin state(54).

Germline variation near or within the TERT gene is associated with telomere length in peripheral blood leukocytes and risk of *TERT* promoter mutant (25,55) and non-mutant (56-58) cancer. Notably, the *TERT* promoter polymorphism rs2853669 modulates the prognostic value of *TERT* promoter mutations across a variety of tumor types. The rs2853669 common allele is thought to create a binding site for the ETS/TCF factor Ets2 99bp and 121bp upstream of the C250T and C228T hotspot mutations, respectively(59). In the presence of a somatic *TERT* promoter mutation in the tumor, patients with the rs2853669 common allele showed decreased overall survival and increased tumor recurrence rate in bladder cancer(59,60) and decreased mean survival in glioma (61). Additionally, gliomas bearing the common allele of rs2853669 and a hotspot promoter mutation have significantly increased *TERT* expression compared to tumors with the rs2853669 minor allele, suggesting a possible molecular link between the hotspot mutation sites and the rs2853669 site in the *TERT* promoter(62). However, other studies reported the minor allele to associate with decreased overall survival in *TERT* mutant glioma(63) or have no prognostic effect with either allele(64). Thus, determining the precise

prognostic value of rs2853669 may require larger sample sizes and cohorts with more extensive treatment information.

The prognostic power of *TERT* promoter mutations highlights their potential use as clinical biomarkers. In addition to bladder cancer and glioma, the presence of *TERT* promoter mutations is associated with decreased overall survival in medulloblastoma(65), thyroid cancer(66-68), urogenital cancer(59,69), melanoma(70,71), and laryngeal tumors(72). Furthermore, *TERT* promoter mutations may serve as biomarkers to distinguish subtypes of urological malignancies(35,73-75). They also predict malignant transformation of premalignant nodules in HCC(76) and meningiomas(77), and associate with the anatomical origin of squamous cell carcinomas(78). A new and powerful molecular classification of glioma subtypes is based on three common genetic alterations in the tumors, including *TERT* promoter mutations(79-81), that predicts overall survival with higher accuracy than traditional classification based on histology. The molecular classification will be useful in clinical trials to enable improved interpretation of patient response to therapy (81,82).

Based on the identical 11bp DNA sequence motif created by the *TERT* promoter mutations, the mechanism of promoter activation was hypothesized to involve recruitment of an ETS family transcription factor. Indeed, site-directed mutagenesis of the hotspot positions in a promoter-reporter plasmid revealed the generated ETS motif was necessary for promoter activation(41). There are 27 ETS factors however, and most bind a very similar DNA sequence in vitro, suggesting extensive redundancy(83). It was therefore surprising that GABPA but not other ETS factors was identified to be the transcription factor responsible for mutant *TERT* activation(41). GABPA is the only ETS factor of those expressed in glioblastoma (GBM) to selectively regulate the mutant *TERT* promoter without affecting wild-type promoter activity. Single molecule binding assays, chromatin immunoprecipitation and sequencing (ChIP-seq) and

ChIP-qPCR analysis revealed that GABPA is exclusively recruited to the mutant allele *in vitro* and *in vivo*. GABPA binding to the mutant *TERT* promoter was conserved across cell lines from multiple cancer types including GBM, melanoma, hepatocellular carcinoma, and neuroblastoma. This finding was later corroborated in bladder cancer(54). While the other ETS factors are active as a monomer GABPA is unique in that it can only function as a heterodimer or heterotetramer with GABPB(84-86). Analysis of the sequence content of GABPA binding sites at the *TERT* promoter and genome wide from GABPA ChIP-seq data, suggested that the promoter mutations create the second in a pair of binding motifs that are optimally spaced to recruit the heterotetramer complex. This work begins to explain how the mutant *TERT* promoter is activated, though factors binding to the sequences up and downstream of the mutation sites may cooperate (figure 3). This study also provided supporting evidence as to why GABPA is a key, mutation-selective activating factor across multiple cancer types. It also raised a new, testable hypothesis as to why the mutations occur in the same two nucleotides in nearly all TERT-mutant tumors

Li et al. have suggested that the C228T and C250T mutations may be subject to differential regulatory mechanisms in glioma(87). Utilizing a cell culture system of non-canonical NF-kB activation, p52 is recruited to the C250T mutation but not to C228T. Furthermore, p52 cooperated with ETS1/2 to induce *TERT* expression specifically in the context of C250T. That C228T and C250T are not functionally identical is independently supported by the fact that the two mutations do not occur at equal frequency within a given tumor type. For example, in one study of glioma, while 48% of patients were found to harbor the C228T mutation, only 22% contained the C250T mutation(51) (figure 2). Whether these biases in mutation prevalence reflect differences in upstream regulatory factors or significant differential effects on downstream *TERT* expression remains to be determined.

The mechanism of mutant *TERT* promoter activation has just begun to be revealed. It will be critical to elucidate the similarities and differences of all the proteins bound to the mutant promoter compared to the active wild-type *TERT* promoter. For example, Myc(88), Sp1(89), USF1/2(90), Id2(91), and Ets2(92) have all been reported to regulate *TERT* promoter activity. Analysis of ENCODE ChIP-seq in HepG2 and SK-N-SH cells shows binding of the MAX transcription factor downstream of GABPA in the *TERT* promoter. However, this is also observed in the MCF7 breast cancer cell line that is wild-type at the *TERT* promoter, implying that MAX could be involved in regulation from the mutant and wild-type *TERT* promoter (figure 3).

It remains unclear how GABPA is regulated by upstream signaling pathways within the context of *TERT* promoter mutant cancer cells. GABPA function is primarily regulated by its transport to the nucleus. Both the MAPK and Hippo signaling pathways modulate GABPA activity through post-translational modification and nuclear localization in different cell contexts (93,94). *EGFR* amplification and $BRAF^{V600E}$ mutation, both MAPK activating events, significantly co-occur with *TERT* promoter mutations in GBM and melanoma, respectively (32,34).

An increased mechanistic understanding of both germline variation and somatic mutation at the *TERT* promoter could help inform newer strategies to therapeutically target telomerase. Several attempts have been made to block telomerase activity in cancer patients, but thus far none are standard of care. Past strategies have included the use of small molecules, immunotherapy, gene therapy and G-quadruplex stabilizers(95). One promising approach is the antisense oligonucleotide therapy GRN163L from Geron. By hybridizing and inhibiting the RNA template of telomerase, GRN163L reduced tumor growth in preclinical models of breast cancer (96,97), GBM(98,99), and pancreatic(100) and liver cancer(101). The preclinical success has not translated to clinical benefit in cancer patients, as trials in breast,

lung, and pediatric CNS cancers were discontinued(102-104). In each trial, frequent grade III/IV hematopoietic toxicities were observed, potentially resulting from telomerase inhibition in healthy hematopoietic stem cells. As a result, trials with GRN163L have been restricted to myeloproliferative diseases. Promising results have been reported in Myelofibrosis patients treated with GRN163L(105). Determining whether *TERT* promoter mutations can act as a biomarker to predict patient response to existing telomerase inhibitor trials, or foster the creation of new telomerase inhibitors will be an exciting area of research in the future.

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Figures

Figure 1: Prevalence of TERT promoter mutations in human cancers.

The frequency of *TERT* promoter mutations is plotted for all tumor types in which at least 20 samples have been tested. Horizontal lines indicate Wilson score confidence intervals. In contrast to these tumor types, no *TERT* promoter mutations were found in the following cancers: oral mucosal melanoma (n=39 (106)), pilocytic astrocytoma (n=111 (107)), medullary thyroid carcinoma (n=24 (34), n=28 (44), n=37 (67)), metastatic bladder adenocarcinoma (n=30 (108)), colorectal adenocarcinoma (n=22 (34)), gastric cancer (n=74 (109)), breast carcinoma (n=88 (34)), cholangiosarcoma (n=28, (34)), dedifferentiated liposarcoma (n=61 (110)), leiomyosarcoma (n=27 (110)), undifferentiated pleomorphic sarcoma (n=40 (110)),myeloid leukemia (n=48 (34)), pancreatic cancer (n=46 (109)), pancreatic acinar carcinoma (n=25 (34)), pancreatic ductal adenocarcinoma (n=24 (34)), prostate carcinoma (n=34 (34)), endometrioid carcinoma (n=43 (111)), leiomyosarcoma (n=22 (111)), endocervical adenocarcinoma (n=25 (111)), endometrial cancer (n=24 (111)), intrahepatic cholangiocarcinoma (n=52 (37)), thymoma (n=47 (109)), head and neck paraganglioma (n=37 (112)), lung squamous cell carcinoma (n=25 (78)).

Figure 2: Percentage of C228T mutations within tumor types harboring high *TERT* promoter mutation frequency.

Each oval indicates the percentage of C228T mutations observed within *TERT* mutant tumors (aggregated across studies) for a specific cancer type. A value of 50% means there is equal occurrence of C228T and C250T within that cancer type. Only studies with 20 or more samples and only cancer types with 20 or more observed mutations were included. The cancers types were grouped as in figure 1.

Figure 3: GABPA and MAX binding at the *TERT* promoter in ENCODE cell lines.

ChIP-seq coverage for GABPA and MAX is displayed at the *TERT* promoter for MCF-7 (WT), HepG2 (C228T), and SK-N-SH (C228T) cells respectively. MAX binding is observed in all three cell lines while GABPA binding is specifically associated with *TERT* promoter mutation status.

Figure 4: A model for the activation of the mutant *TERT* promoter by GABP recruitment as a heterotetramer.

The GABP heterotetramer is made up of two GABPA(green) and two GABPB(blue) subunits. GABPA is responsible for direct DNA binding, and one subunit is hypothesized to bind to the promoter mutation (stars in blue sections) while the other binds to a native ETS binding site further downstream (red highlighted section).

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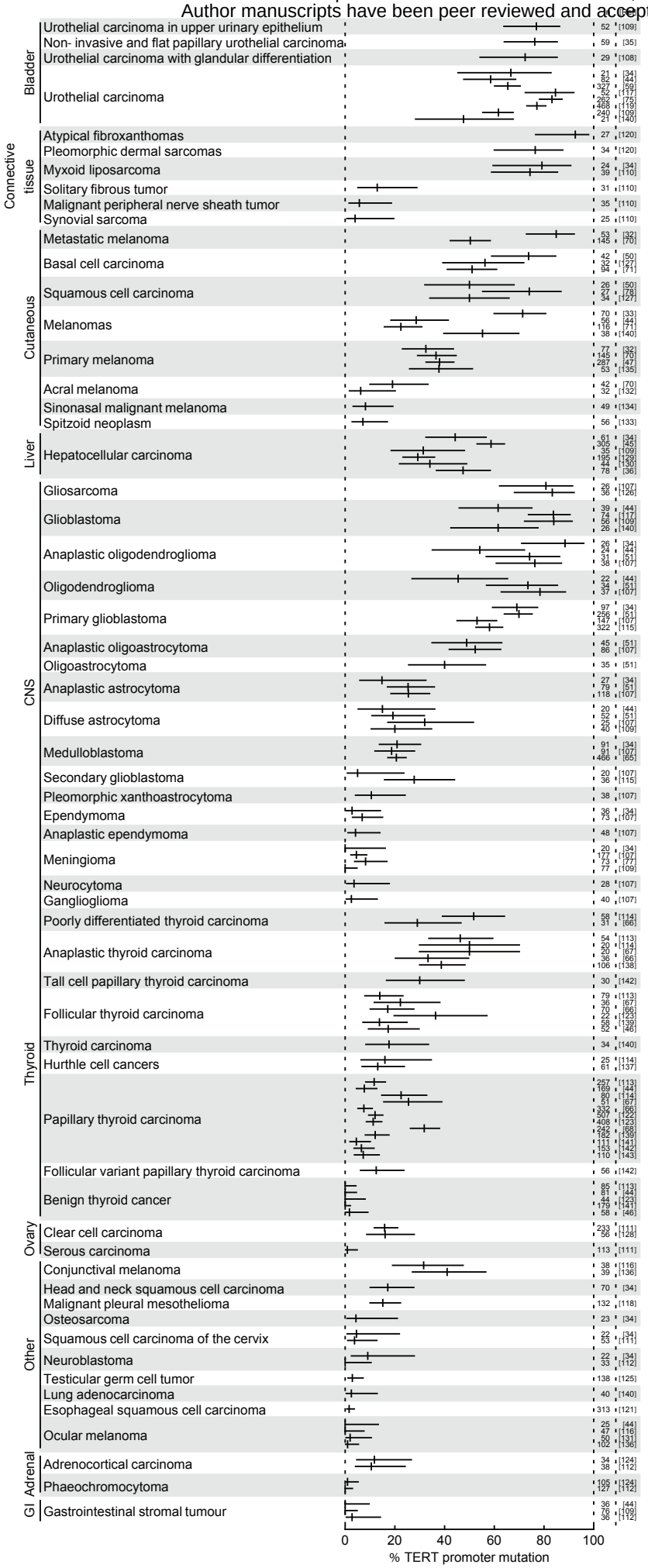

Figure 1

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Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

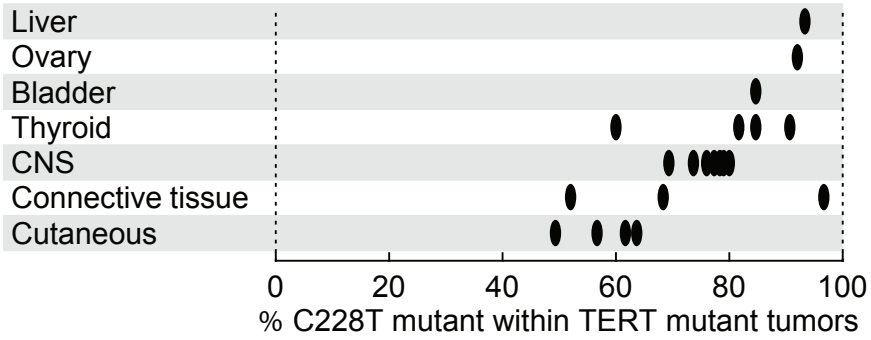

Figure 2

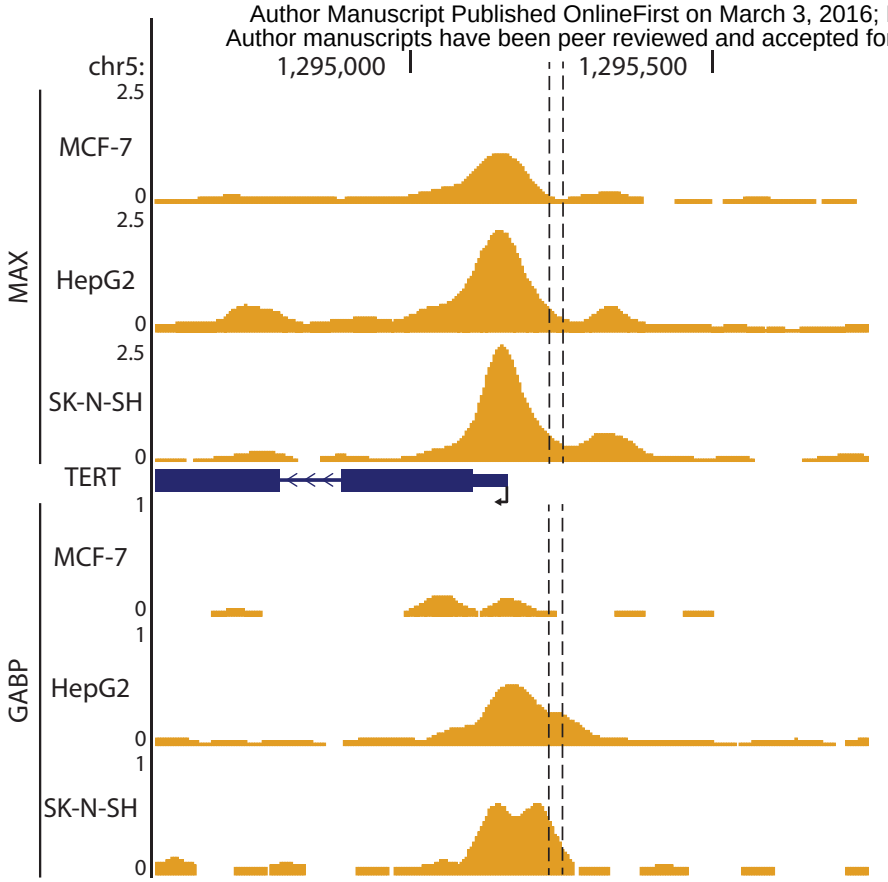

Figure 3

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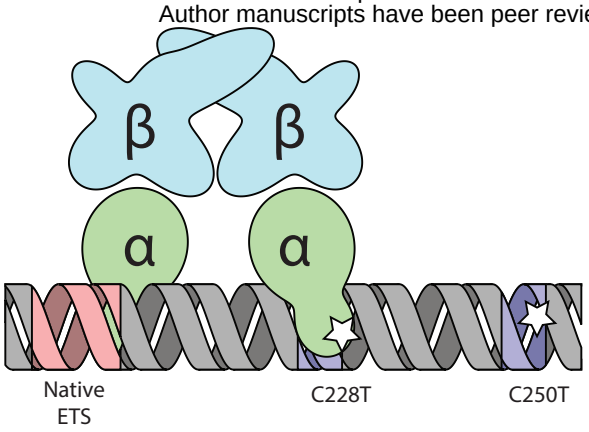

Figure 4

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Molecular Cancer Research

Understanding TERT Promoter Mutations: a Common Path to Immortality

Robert J. A. Bell, H. Tomas Rube, Ana Xavier-Magalhães, et al.

Mol Cancer Res Published OnlineFirst March 3, 2016.