CANCER

The transcription factor GABP selectively binds and activates the mutant TERT promoter in cancer

Robert J. A. Bell,[1,2] H. Tomas Rube,[3,4] Alex Kreig,[4,5] Andrew Mancini,[1] Shaun D. Fouse,[1] Raman P. Nagarajan,[1] Serah Choi,[6] Chibo Hong,[1] Daniel He,[1] Melike Pekmezci,[7] John K. Wiencke,[8,9] Margaret R. Wrensch,[8,9] Susan M. Chang,[1] Kyle M. Walsh,[8] Sua Myong,[4,5] Jun S. Song,[2,3,4,5]*† Joseph F. Costello[1]*†

Reactivation of telomerase reverse transcriptase (*TERT*) expression enables cells to overcome replicative senescence and escape apoptosis, which are fundamental steps in the initiation of human cancer. Multiple cancer types, including up to 83% of glioblastomas (GBMs), harbor highly recurrent *TERT* promoter mutations of unknown function but specific to two nucleotide positions. We identified the functional consequence of these mutations in GBMs to be recruitment of the multimeric GA-binding protein (GABP) transcription factor specifically to the mutant promoter. Allelic recruitment of GABP is consistently observed across four cancer types, highlighting a shared mechanism underlying *TERT* reactivation. Tandem flanking native E26 transformation-specific motifs critically cooperate with these mutations to activate *TERT*, probably by facilitating GABP heterotetramer binding. GABP thus directly links *TERT* promoter mutations to aberrant expression in multiple cancers.

The human telomerase is an enzyme critical for maintaining telomere length and chromosomal stability in stem cells (*1*, *2*). The transcriptional regulation of the telomerase reverse transcriptase (*TERT*) gene, encoding the catalytic subunit of telomerase, is a rate-limiting step in modulating telomerase activity (*3*). Although normally silenced in somatic cells, *TERT* is aberrantly expressed in 90% of aggressive cancers, highlighting this event as a hallmark of tumorigenesis (*4*–*6*). Reactivating telomerase helps cells with a finite life span to achieve limitless proliferative potential and bypass cellular senescence induced by DNA replication–associated telomere shortening. Understanding the mechanisms of aberrant *TERT* expression is thus a crucial outstanding problem in cancer research.

Recently discovered noncoding mutations in the *TERT* promoter are among the most common genetic alterations observed across multiple cancer types, revealing a potentially causal biological mechanism driving increased telomerase activity in tumors (*7*–*9*). Specifically, one of two positions, G228A or G250A, is mutated in 21% of medulloblastomas (*10*), 47% of hepatocellular carcinomas (HCC) (*11*), 66% of urothelial carcinomas of the bladder (*12*), 71% of melanomas (*7*, *8*), and 83% of primary glioblastomas (GBMs) (*9*), making them the most recurrent single-nucleotide mutations observed in these cancer types. Both the G228A and G250A mutations are associated with increased *TERT* expression (fig. S1) and telomerase activity (*13*) and have prognostic power in bladder cancer and GBM (*14*–*16*). Both G>A transitions generate an identical 11–base pair (bp) sequence that is hypothesized to generate a de novo binding site for an E26 transformation-specific (ETS) transcription factor (*7*). Despite these compelling findings and the central importance of *TERT* in human cancer, the precise function of the mutations has remained elusive since their initial discovery in melanoma patients.

To determine whether the de novo ETS motif is necessary for mutant *TERT* activation, we performed site-directed mutagenesis of the core *TERT* promoter (*17*). The G228C, G250C, and G250T mutations did not increase promoter activity, highlighting the requirement for the G>A transition for *TERT* activation (Fig. 1A). Furthermore, removing the ETS motif while retaining the G228A mutation (A227T, G228A) resulted in a complete reduction of promoter activity to wild-type levels. The G228T mutation also partially increased promoter activity; this induction is consistent with the site being the second adenine position in an ETS motif, a position that is often degenerate for A/T (*18*). Mutating the second adenine position to thymine in the context of G250A (G250A, A251T) resulted in a similar intermediate level of promoter activity.

A small interfering RNA (siRNA) screen of 13 ETS factors expressed in GBMs revealed 5 ETS factors [ELF1, ETS1, ETV3, ETV4, and GA-binding protein, alpha subunit (GABPA)] whose knockdown reduced TERT expression in at least one of two GBM cell lines harboring *TERT* promoter mutations (Fig. 1B, fig. S2, and fig. S3) (*17*). Only three factors (ETS1, ETV3, and GABPA) consistently reduced TERT expression in both lines. GABPA knockdown reduced TERT expression by as much as 50% within the first 24 hours and sustained the largest effect on TERT expression among the ETS candidates throughout 72 hours (fig. S3). In contrast, knockdown of ETS1 and ELF1 resulted in a more modest reduction of *TERT* mRNA and only reached statistical significance at 72 hours, suggesting that their regulation of *TERT* is through indirect mechanisms. ETV3 is a transcriptional repressor in the ETS family and was thus not considered a candidate direct regulator of mutant *TERT* (*19*–*21*). Thus, the de novo ETS motif is critical for mutant *TERT* promoter activity in GBMs, and one or more candidate ETS factors may regulate TERT expression directly through the G228A and G250A mutations.

We next investigated whether regulation of *TERT* by ETS1, ETV3, ETV4, or GABPA depends on the *TERT* promoter mutation status by testing the effect of siRNA knockdowns on the activity of *TERT* promoter–driven luciferase reporters. Only GABPA knockdown significantly reduced mutant promoter activity without affecting wild-type promoter activity (Fig. 2A and fig. S4). Although ETV4 knockdown reduced mutant promoter activity, it also significantly reduced the activity of the wild-type promoter, indicating the potential of ETV4 to bind and regulate the wild-type *TERT* promoter sequence in this assay. Knockdown of ETS1 and ETV3 did not significantly reduce promoter activity (Fig. 2A and fig. S4). GABPA was thus the only ETS factor that reproducibly affected TERT expression in a mutation-specific manner. Furthermore, knockdown of GABPA did not significantly affect cell cycle or proliferation rate within this time frame (fig. S5).

To determine the in vivo binding specificity to the mutant *TERT* promoter sequence (CCGGAA) relative to the wild-type sequence (CCGGAG) among the candidate ETS factors, we analyzed publicly available ChIP-seq data for GABPA, ELF1, ETS1, and ETV4 (*22*, *23*). Although all factors display significant enrichment in the sequence found in the mutant *TERT* promoter relative to the wild-type sequence, we found that GABPA peaks contained significantly greater enrichment in the mutant motif as compared to ETS1 or ETV4 peaks (P value = 5.1×10^{-8} for ETS1 and 1.8×10^{-8} for ETV4, Wilcoxon rank-sum test) (Fig. 2B and fig. S6). This genome-wide analysis supports the binding specificity for the motif created by the *TERT* promoter mutations and suggests that GABPA binding may be more sensitive to these promoter mutations. Furthermore, this enrichment is not observed in DNase I hypersensitivity peaks in the same cells, demonstrating that the motif enrichment does not represent sequence biases in areas of open chromatin (fig. S6). Among the eight ENCODE (Encyclopedia of DNA Elements) Project cell lines with GABPA ChIP-seq, only HepG2 hepatocellular carcinoma cells and SK-N-SH neuroblastoma cells, both of

[1]Department of Neurological Surgery, University of California, San Francisco, CA. [2]Department of Biostatistics and Epidemiology, University of California, San Francisco, CA. [3]Department of Physics, University of Illinois, Urbana-Champaign, IL. [4]Institute for Genomic Biology, University of Illinois, Urbana-Champaign, IL. [5]Department of Bioengineering, University of Illinois, Urbana-Champaign, IL. [6]Department of Radiation Oncology, University of California San Francisco, San Francisco, CA. [7]Department of Anatomic Pathology, University of California San Francisco Medical School, San Francisco, CA 94143, USA. [8]Division of Neuroepidemiology, Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA 94158, USA. [9]Institute for Human Genetics, University of California, San Francisco, San Francisco, CA 94143, USA.
*Corresponding author. E-mail: songj@illinois.edu (J.S.S.); joseph.costello@ucsf.edu (J.F.C.) †These authors contributed equally to this work.

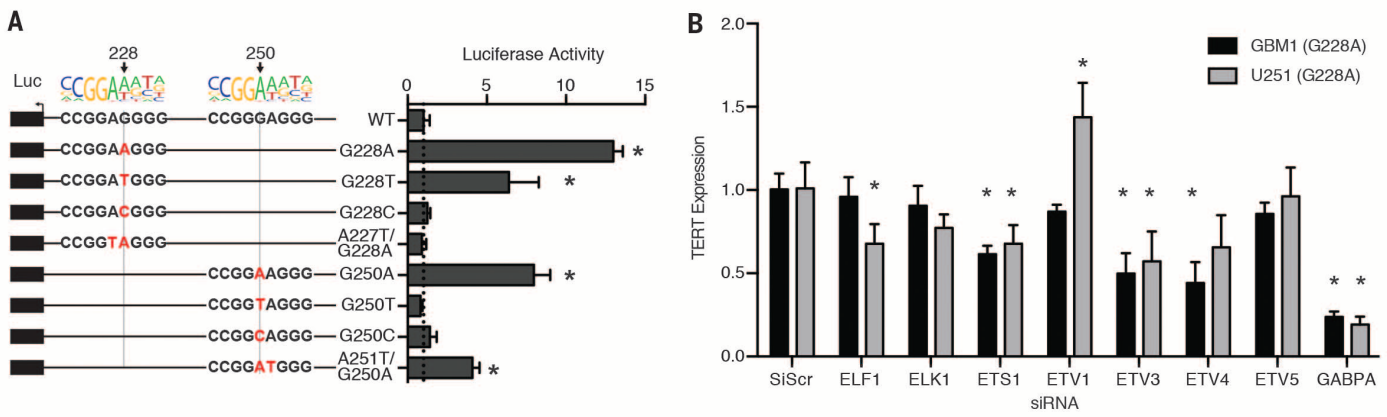

Fig. 1. The de novo ETS motif is critical for mutant *TERT* promoter activity in GBMs. (**A**) *TERT* promoter–luciferase reporter assays for wild-type, G228A, G250A, or targeted mutation sequences. *$P < 0.05$, Student's t test compared to wild-type (WT). (**B**) *TERT* expression relative to nontargeted siRNA (siScr) 72 hours after ETS factor siRNA knockdown. *$P < 0.05$, Student's t test compared to siScr. The results are an average of at least three independent experiments. Values are mean ± SD.

which harbor heterozygous G228A mutations, displayed significant GABPA binding at the *TERT* promoter (Fig. 2C). In contrast, none of the *TERT* mutant cell lines showed ELF1 binding at the *TERT* promoter (fig. S7). Likewise, ChIP of ETS1 and ETV4 did not show binding at the mutant *TERT* promoter in vivo (fig. S7). An in vitro single-molecule protein binding assay further confirmed that ETV4 does not stably bind the mutated sequence (fig. S8) (*17*). These results are consistent with the fact that only GABPA knockdown shows immediate reduction on TERT expression (fig. S3), and they implicate GABPA as the only ETS factor among the candidates to directly bind the mutant *TERT* promoter. All of the cell lines that did not show GABPA binding (K562, GM12878, A549, Hela, MCF-7, and HL-60) were derived from cancers in which *TERT* promoter mutations are absent or uncommon (*9*). Strikingly, 100% of the GABPA ChIP-seq reads covering the mutated site within the *TERT* promoter contained G228A, suggesting that GABPA selectively binds the mutant allele in vivo and that it cannot recognize and bind the wild-type sequence (Fig. 2C). Recruitment of GABP to the G250A mutant sequence was confirmed in vitro using a single-molecule protein binding assay. In contrast, no binding event of GABP was detected for the wild-type *TERT* sequence (fig. S8). Mutant allele–specific DNase I hypersensitivity and Pol II recruitment were also observed in these lines (fig. S9).

To confirm that GABPA is specifically recruited to the mutant allele, we performed GABPA ChIP in HepG2, SK-N-SH, two GBM lines, and three melanoma lines (table S1) (*17*). All cell lines harboring either the G228A or G250A mutation showed significant GABPA binding in the *TERT* core promoter (P value = 0.016, Wilcoxon rank-sum test, Fig. 2D). In contrast, the *TERT* wild-type melanoma line SK-MEL-28 showed no GABPA binding at the *TERT* promoter as compared to the other lines (P value = 0.007, Weisberg t test for outliers). Consistent with our findings of specificity for the mutant allele in the ENCODE ChIP-seq data, the GABPA-immunoprecipitated DNA from the heterozygous mutant cell lines HepG2, SK-N-SH, and GBM1 all showed significant bias toward the mutant allele as compared to input control DNA (P value = 1.264×10^{-5}, Fisher's exact test, Fig. 2E). Furthermore, we confirmed that both heterozygous mutations in the *TERT* promoter resulted in allelic deposition of H3K4me3 and allele-specific expression (fig. S10). Nucleosome positioning analysis from micrococcal nuclease–digested H3K4me3 ChIP-seq (*24*) data revealed that both mutation positions lie within a nucleosome-free region, with the upstream nucleosomes containing the H3K4me3 modifications (fig. S10). These data demonstrate that GABPA is selectively recruited to the mutant *TERT* allele across multiple cancer types and results in allele-specific activation of *TERT*.

GABPA is unique among the large ETS transcription factor family as it is the only obligate multimeric factor (*25*, *26*). GABPA dimerizes with GABPB, and the resulting heterodimer (GABP) forms a fully functional transcription factor that can both bind DNA and activate transcription (*27*). GABPA has a single transcript isoform that is widely expressed across tissue types, whereas GABPB is encoded by either the *GABPB1* or *GABPB2* gene, and GABPB1 contains multiple isoforms (*28*, *29*). A subset of GABPB isoforms contain leucine zipper–like domains, which allow two GABP heterodimers to form a heterotetramer complex capable of binding two GABPA motifs (core consensus CCGGAA) in proximity to each other, and further stimulating transcription (*30*). Consistent with this fact, genome-wide analysis of ENCODE GABPA ChIP-seq data showed that peaks containing two GABPA motifs have significantly higher binding enrichment scores as compared to peaks with just one or zero motifs (P value = 1.6×10^{-157}, Wilcoxon rank-sum test, figs. S11 and S12). Analysis of GABPA motif spacing within peaks containing two motifs revealed that strong peaks are more likely to have a separation distance shorter than 50 bp as compared to weak peaks (Fig. 3A and fig. S11). Moreover, this increase in likelihood occurred at discrete spacing that aligned well with the 10.5-bp periodicity of relaxed B-DNA, highlighting the importance of having two GABPA binding sites in phase and separated by full helical turns of double-stranded DNA. This periodicity was unique to GABPA and is not observed in ELF1 or ETS1 ChIP-seq data (fig. S11). The Fourier spectrum of the enrichment also spiked around the helical frequency in strong GABPA peaks, but not in weak peaks or the genomic background (fig. S13). This analysis suggested that two proximal motifs in helical phase act synergistically to recruit a GABP heterotetramer complex.

Investigation of the DNA sequence flanking the mutation sites revealed three native ETS binding motifs (ETS-195, ETS-200, and ETS-294) (Fig. 3B). To determine whether these flanking ETS motifs are required for mutant *TERT* activation, we performed site-directed mutagenesis of the flanking ETS sites with or without the G228A or G250A mutation. Mutating ETS-195 or ETS-200 alone reduced promoter activity from the relatively low level of the wild-type promoter and also significantly reduced activity in the context of G228A or G250A. In contrast, mutating ETS-294 had no effect on promoter activity in the context of G250A, despite being closer than ETS-195 or ETS-200 (Fig. 3C). These data demonstrate that both ETS-195 and ETS-200 are required for aberrant activity of the mutant *TERT* promoter. The GABPB1 isoforms required for GABP heterotetramer formation are the predominant isoforms expressed in GBM melanoma, hepatocellular carcinoma, and bladder urothelial carcinoma, all tumor types prone to *TERT* promoter mutations (fig. S14).

To test whether ETS motif spacing is essential for mutant TERT promoter activation, we performed a series of deletions in 2-bp increments between the native ETS site and the G250A mutation, effectively bringing G250A out of phase and back into phase with the native ETS motifs. Although the wild-type reporter construct displayed only noise level fluctuations in activity,

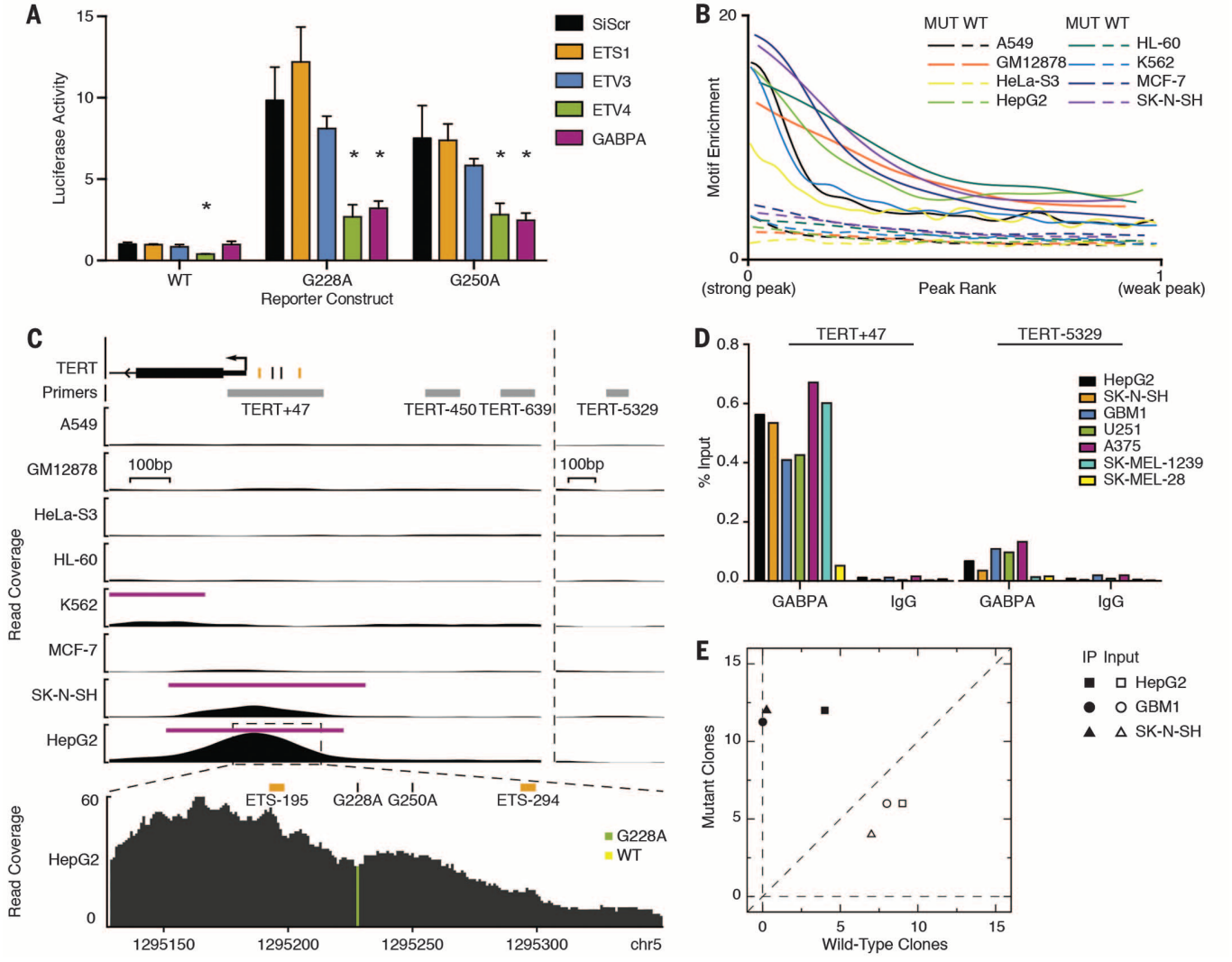

Fig. 2. GABPA selectively regulates and binds the mutant TERT promoter across multiple cancer types. (**A**) Wild-type, G228A, or G250A luciferase activity 72 hours after ETS siRNA knockdown in GBM1 cultured cells, scaled to WT-siScr. The results are an average of at least three independent experiments. Values are mean ± SD. *$P < 0.05$, Student's t test compared to siScr. (**B**) Enrichment of mutant (CCGGAA) or wild-type (CCGGAG) hexamer sequences in ENCODE GABPA ChIP-seq peaks relative to flanking regions. (**C**) ENCODE GABPA ChIP-seq data at the proximal TERT promoter and around distal quantitative polymerase chain reaction (qPCR) primers. Native ETS motifs and mutation positions are annotated by orange and black tick marks, respectively. The inset shows allelic read coverage at G228A in HepG2 cells. (**D**) GABPA ChIP-qPCR for the TERT promoter and a nearby control locus in seven cancer cell lines. Values represent the mean percent of input based on triplicate qPCR measurments. $n = 1$ for each cell line. (**E**) Allelic variant frequency in GABPA (IP) or input control DNA.

we observed clear periodic behavior in the G250A reporter, suggesting the recruitment of a GABP heterotetramer (Fig. 3D and fig. S11). However, G250A promoter activity peaked after deleting 6 bp, which brought the G250A site in phase with the ETS-200 site by a perfect four helical turns. Mutating ETS-195, although reducing the *TERT* activation level (Fig. 3C), did not change the periodic pattern, implying a preferential interaction of GABP with ETS-200 instead of ETS-195 (fig. S11). Repeating the experiment with a mutated ETS-200, however, led to a translation in 10.5-bp periodicity, which was now consistent with pairing between G250A and ETS-195 (Fig. 3D). These results strongly suggest that GABP may be able to bind and switch between both native ETS motifs in the context of G250A, consistent with the fact that both native ETS motifs are essential for robust *TERT* activation (Fig. 3C).

The critical role of two adjacent ETS motifs in aberrant *TERT* activation was further strengthened by our analysis of an oligodendroglioma tumor containing a unique heterozygous 41-bp tandem duplication within the core *TERT* promoter. This tumor sample also had the R132H IDH1 mutation and 1p19q co-deletion, genetic aberrations that often co-occur with *TERT* promoter mutations in oligodendroglioma (*31*). Although this sample was wild-type at G228A and G250A, we found that the junction of the duplication event generated a de novo ETS motif that is 41 bp away from the native downstream ETS-195 motif (Fig. 3B). The promoter sequence containing this duplication induced elevated promoter activity similar to the G228A and G250A mutant sequences, despite its wild-type status at these positions (Fig. 3C). Mutagenesis of either the native ETS-195 site or the de novo junction ETS site significantly reduced promoter activity, once again demonstrating that this duplication satisfies the prerequisite for GABP heterotetramer recruitment (Fig. 3C).

We have thus identified GABP as the critical ETS transcription factor activating TERT expression in the context of highly recurrent promoter mutations. Although many ETS transcription factors can bind similar DNA sequence motifs, GABP is unusual in that it can bind neighboring ETS motifs as a heterotetrameric complex. We showed that strong GABPA ChIP-seq peaks contain a periodicity of approximately 10.5 bp between neighboring ETS motifs, consistent with the binding of a GABP complex at two

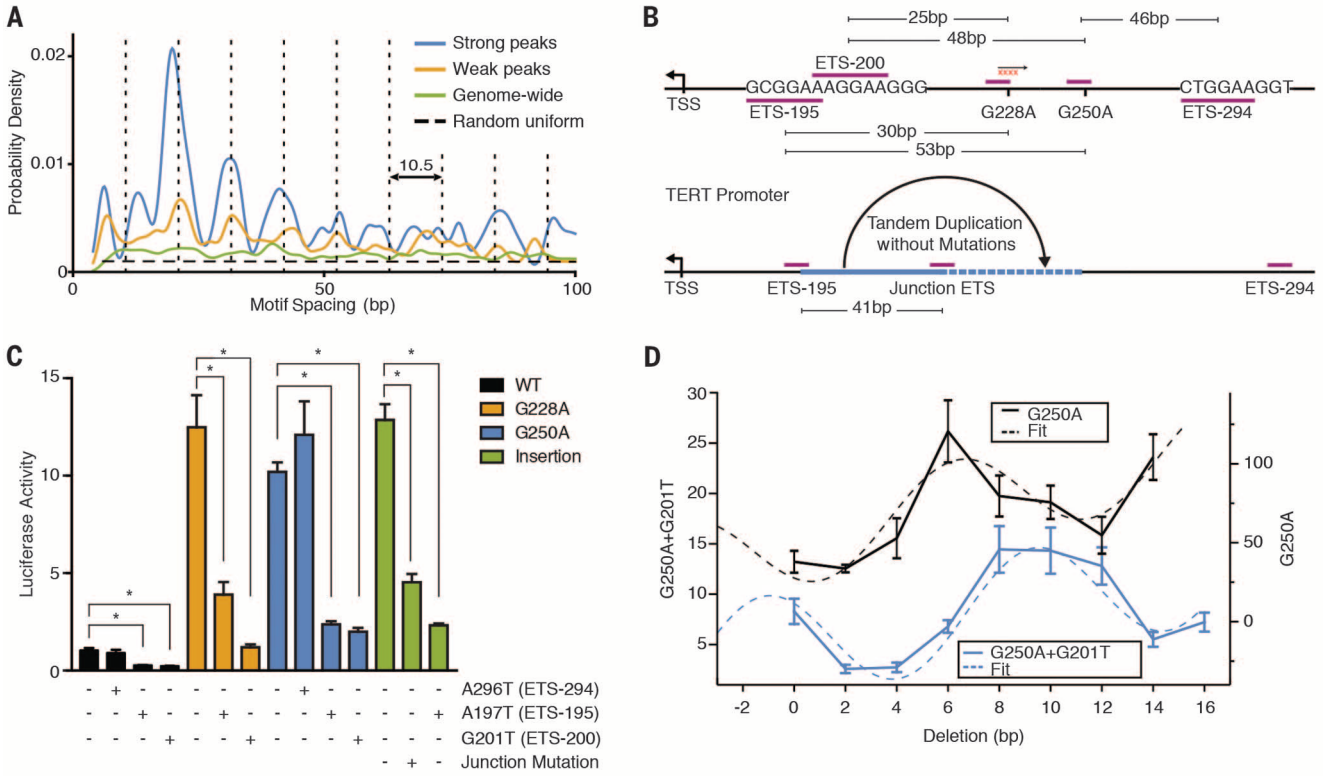

Fig. 3. G228A and G250A cooperate with the native ETS sites ETS-195 and ETS-200 and fall within spacing for GABP heterotetramer recruitment. (**A**) Distribution of motif separation in weak and strong GABP peaks. Vertical dotted lines denote periodicity of 10.5 bp. The horizontal dashed line indicates the theoretical null distribution. (**B**) Native and de novo putative ETS binding sites in the core *TERT* promoter. (**C**) Site-directed mutagenesis of the GABP heterotetramer motifs in the wild-type, G228A, G250A, or insertion *TERT* reporter constructs. Mutation of the ETS-195, ETS-294, or junction motif are indicated by "+." The results are an average of at least three independent experiments. Values are mean ± SD. *$P < 0.05$, Student's t test. (**D**) Site-directed mutagenesis deleting between 2 to 16 bp at the G228A site. Deletions were tested for promoter activity in a G250A or G250A+G201T background. The sinusoidal fits were obtained by using the model $a \sin[2\pi(x - b)/10.5] + cx + d$. The results are an average of at least three independent experiments. Values are mean ± SD.

locations separated by full helical turns of DNA. This genome-wide pattern is reproduced in the context of *TERT* promoter mutations, where both G228A and G250A are separated from two tandem proximal native ETS motifs by 2.9/2.4 (ETS-195/ETS-200) and 5.0/4.6 (ETS-195/ETS-200) helical turns, respectively. We propose that *TERT* promoter mutations cooperate with both of these native ETS sites to recruit GABP. Further work is necessary to elucidate which other transcription factors are interacting with GABP at the mutant *TERT* promoter in order to drive aberrant transcription. Additionally, both *TERT* promoter mutations fall within a GC-rich repeat sequence with potential to form a G-quadruplex, a DNA secondary structure that can regulate gene expression (*32*, *33*). A potential impact of *TERT* promoter mutations on this predicted secondary structure and on the complex relationship between secondary structure and GABP recruitment may also play a role in deregulating TERT expression. The cancer-specific interaction of GABP with the *TERT* core promoter mutations highlights a common mechanism used by many cancers to overcome replicative senescence.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/348/6238/1036/suppl/DC1
Materials and Methods
Figs. S1 to S14
Tables S1 to S6
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