# TERT Alterations Characterize a Subset of Progressive/Higher-grade Meningiomas with Poor Outcome

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CNS 2018 ANNUAL MEETING
HOUSTON, TEXAS
OCTOBER 6-10, 2018

## Introduction

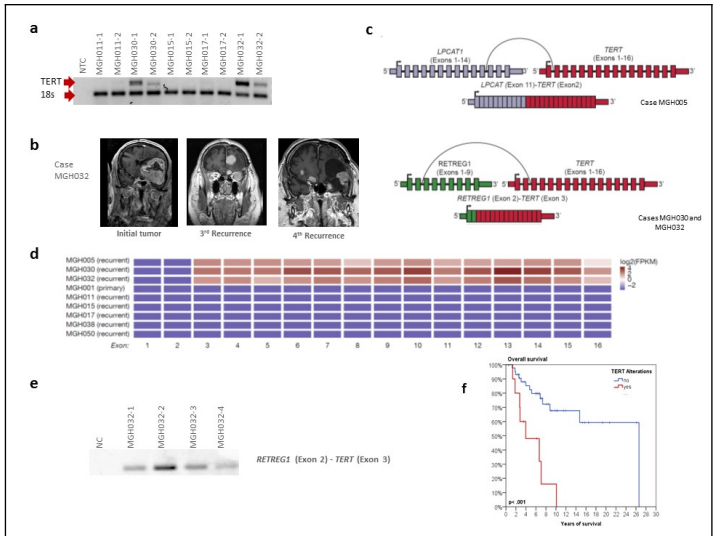
Although a significant proportion of aggressive meningiomas acquire *TERT* promoter (*TERT*p) mutations which drive TERT overexpression during progression, alternative mechanisms of telomere maintenance in meningioma are broadly unknown. *TERT* activating rearrangements are common in some aggressive cancers and associated with poor outcome. Therefore, we sought to assess *TERT* rearrangements in a large cohort of patients with progressive/high-grade meningiomas.

## Methods

We determined the frequency of TERT mRNA overexpression in 126 temporally- and regionally-distinct specimens from 55 WHO grades II/III meningioma patients using reverse-transcriptase PCR. Subsequently, RNA sequencing was performed in samples with TERT overexpression to detect rearrangements. Additionally, the *TERT*p region was sequenced in all patients to assess hotspot mutations.

## Results

- *TERT*p mutations were detected in seven patients (12.7%).
- In addition, highly amplified TERT mRNA expression was found in three patients (5%) (Figure 1A-C).
- RNA sequencing of samples with amplified TERT mRNA revealed a novel fusion *RETREG1-TERT* that was present in two patients, in addition to a *LPCAT1-TERT* fusion in a third case (Figure 1D).
- The *TERT* rearrangements began in either exon 2 or 3, upstream of the reverse transcriptase domain that begins in exon 4, consistent with a proposed activating mechanism-of-action (Figure 1D).
- In total, 10 patients (18.1%) harbored *TERT* alterations in our cohort: three *TERT* rearrangements and seven *TERT*p mutations.
- Patients whose meningiomas harbored *TERT* alterations had a significantly worse overall survival (5.1 years, 95%CI 3.1–7.2) compared to *TERT* wild-type patients (18.5 years, 95%CI 14.6–22.4, p<0.001) (Figure 1E).




(A) An example for a reverse transcriptase PCR demonstrating four samples from patients MGH030 and MGH032 with highly amplifiedTERT mRNA expression. (B) Representative MRIs of a patient with a progressive meningioma harboring TERT rearrangements (caseMGH032). (C) mRNA expression of TERT exons in FPKM confirming an amplified TERT expression in the same samples (MGH030,MGH032 and MGH005). (D) Schematic representation of the TERT rearrangement. Exons involved in the rearrangement arerepresented by colored boxes: LPCAT1 is reported in grey, RETREG1 in green, while TERT is reported in red. In all cases therearrangements began in either exon 2 or 3, upstream of the reverse transcriptase domain that begins in exon 4, consistent with aproposed activating mechanism-of-action. (E) Patients whose meningiomas harbored TERT alterations (n= 10) had a significantly worseoverall survival (5.1 years, 95%CI 3.1–7.2) compared to TERT wild-type patients (18.5 years, 95%CI 14.6–22.4, p<0.001).

## Conclusions

- We discovered novel *TERT* rearrangements in a subset of aggressive meningiomas (*RETREG1-TERT* and *LPCAT1-TERT*)
- Two distinct mechanisms for *TERT* activation, *TERT* rearrangements and *TERT*p mutations were associated with a particularly poor outcome, suggesting a central role of telomere lengthening in the pathogenesis of aggressive meningioma.
- Detection of *TERT* alterations offers a basis for a more precise identification of patients at-risk for developing early progression of meningioma.

## Learning Objectives

Understanding the mechanisms of *TERT* alterations in meningiomas

## References

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