Original Article

Prevalence of *TERT* Promoter Mutations in Thai Patients with CNS WHO Grade 2 Meningiomas

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Abstract

OBJECTIVES: To determine the prevalence of telomerase reverse transcriptase *(TERT)* promoter mutations in Thai patients with atypical meningiomas and assess associations with clinical and histopathological features.

MATERIALS AND METHODS: A retrospective review was conducted. Demographic, clinical, and histopathological data were collected. *TERT* promoter mutations were identified and analyzed for associations with features such as chordoid or clear cell variants, mitosis ≥ 4, brain invasion, necrosis, and hypercellularity.

RESULTS: The cohort comprised 92 patients, 29 males and 63 females (median age 58). *TERT* promoter mutations were present in 5.43% of cases, most commonly C250T (60% of mutated cases). No significant associations were found between the mutation status and the assessed pathological features.

CONCLUSION: *TERT* promoter mutations were detected in a small proportion of Thai WHO Grade 2 meningiomas. While no significant correlations with pathological features were observed, these mutations may contribute to tumor biology, warranting further study on their prognostic and therapeutic relevance.

Keywords: atypical meningioma, WHO grade 2 meningioma, *TERT* promoter mutation, Thailand

Meningiomas are neoplasms arising from meningothelial cells of the arachnoid mater, representing approximately 30% of all primary intracranial tumors.[1,2] The 2021 World Health Organization (WHO) classification categorizes meningiomas into three grades based on histological and molecular features. Grade 2 (atypical) meningiomas exhibit intermediate biological behavior, with higher recurrence rates and more aggressive growth patterns compared to Grade 1 tumors.[1,3]

Clinical presentation varies depending on tumor location, with common symptoms including headaches, seizures, and focal neurological deficits due to compression of adjacent neural structures. Tumor location is linked to specific genetic profiles: convexity meningiomas frequently harbor chromosome 22q deletions and NF2 mutations, whereas skull-base meningiomas more often carry AKT1, TRAF7, SMO, or PIK3CA mutations.[4-9] Higher-grade meningiomas, including Grade 2 tumors, are more often found in convexity or non–skull-base sites and exhibit broader genomic abnormalities, including frequent *TERT* promoter mutations.[1,10]

TERT encodes the catalytic subunit of telomerase, essential for telomere maintenance and cellular immortality.[10] In the current WHO classification, *TERT* promoter mutation is also one of the molecular markers for anaplastic meningioma (CNS WHO Grade 3).[1] While substantial evidence from Western populations highlights the prognostic significance of *TERT* promoter mutations, data in Asian populations remain scarce, particularly in Thailand.

This study aimed to determine the prevalence of *TERT* promoter mutations in WHO Grade 2 meningiomas among Thai patients.

Materials and Methods

This retrospective study only included patients diagnosed with WHO grade 2 meningiomas, as assessed by board-certified pathologists according to the current WHO classification.[1] WHO grade 2 meningiomas include atypical, chordoid, and clear cell subtypes. Atypical meningioma, as defined by WHO, is diagnosed when **at least one** of the following criteria is present:

1. a mitotic count of **≥ 4 and < 20 mitoses per 10 high-power fields;**
2. **brain invasion;** or
3. the presence of **at least three** of the following five histopathological features: **hypercellularity, small-cell change, necrosis, sheet-like growth, and macronucleoli.**

Eligible cases were required to have available clinical data, pathological specimens, and *TERT* promoter mutation results. Clinical data and pathological diagnoses were obtained from the Chulalongkorn GenePRO Center, Faculty of Medicine, Chulalongkorn University, Thailand. Patients diagnosed between July 2021, and July 2024 were included. All clinical and histopathological data were reviewed. The study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University (IRB No. 0007/66; COA No. 0049/2023, 0135/2024, and 0116/2025).

Histopathological Assessment

All available pathology slides and formalin-fixed, paraffin-embedded (FFPE) tissue blocks were retrieved from participating institutions. Histological parameters evaluated included mitotic count (≥ 4 and < 20 mitoses per 10 high-power fields), brain invasion, hypercellularity, small cell formation, necrosis, sheeting architecture, macronucleoli, chordoid pattern, and clear cell features.

TERT promoter mutation analysis

Genomic DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) tumor tissue using the cobas® DNA Sample Preparation Kit (Roche Diagnostics). DNA concentration and purity were assessed with a NanoDrop™ 2000 Spectrophotometer (Thermo Fisher Scientific). Pyrosequencing was employed to detect *TERT* promoter mutations C228T and C250T. The target region encompassing these loci was amplified using primers 5′-CGTCCTGCCCCTTCACCT-3′ and biotinylated 5′-GCGCTGCCTGAAACTCGC-3′, as previously described.[11] PCR was carried out with 100 ng template DNA, 10 µM of each primer, and the PyroMark® PCR Kit (Qiagen, USA), according to the manufacturer's protocol. PCR Cycling conditions included an initial denaturation at 95 °C for 15 minutes, followed by 45 cycles of 95 °C for 20 seconds, 64 °C for 30 seconds, and 72 °C for 20 seconds, with a final extension at 72 °C for 5 minutes. PCR product quality was evaluated by 8% polyacrylamide gel electrophoresis. Pyrosequencing was then performed on the PyroMark Q24 System using the PyroMark Gold Q24 Reagents (Qiagen, USA) and 0.3 µM sequencing primer 5′-CCCGCCCCGTCCCGA-3′, as previously described.[11]

Statistical Analysis

Associations between *TERT* promoter mutation status (positive vs. negative) and clinicopathological variables were evaluated using Fisher's exact test. Continuous variables (e.g., age) and categorical variables (e.g., sex, mitotic count, brain invasion, necrosis, histological subtype) were included in the analysis. All statistical analyses were conducted using STATA software, with a p-value < 0.05 considered statistically significant.

Results

A total of 92 patients met the inclusion criteria (Table 1). The mean age was 57.24 years (range, 27–81 years), comprising 29 males (31.5%) and 63 females (68.5%). *TERT* promoter mutations were identified in 5.43% of cases (5/92).

Fisher's exact test revealed no statistically significant associations between *TERT* promoter mutation status and histopathological features, including mitotic activity ≥ 4/10 HPF, brain invasion, necrosis, hypercellularity, small cell change, sheeting architecture, and chordoid meningioma (all $p > 0.05$). No cases of clear cell meningioma were observed in this cohort, and none of the mutation-positive cases exhibited sheeting architecture; therefore, potential associations with these subtypes could not be assessed. Analysis of gender distribution showed a higher proportion of *TERT* promoter mutations among males (3/29, 10.3%) compared to females (2/63, 3.2%), although the difference did not reach statistical significance (OR 3.52, $p = 0.32$). Similarly, patient age did not correlate significantly with mutation status. All cases positive for *TERT* promoter mutation are summarized in Table 2.

Table 1: Demographic and Histopathological Data of the Study Population (n = 92).

Variable	n (%)
Total patients	92 (100)
Gender	
Male	29 (31.5)
Female	63 (68.5)
Age (years)	
Mean ± SD	57.24 ± 12.11
Median	58
Range	27 – 81
TERT Mutation	
Positive	5 (5.43)
C228T	2 (2.17)
C250T	3 (3.26)
Negative	87 (94.57)
Histopathological Features	
Mitosis ≥4	40 (43.5)
Brain Invasion	34 (37.0)
Hypercellularity	63 (68.5)
Small Cell Change	39 (42.4)
Necrosis	46 (50.0)
Sheeting architecture	3 (3.3)
Macronucleoli	40 (43.5)
Chordoid Meningioma	4 (4.3)
Clear Cell Meningioma	0 (0.0)

Table 2: Summary of Cases with *TERT* Promoter Mutation.

	Age	Sex	*TERT*mut	Mitosis ≥4	Brain Invasion	Hypercell	Small cell	Nec	Sheet	Macro	Chordoid	Clear Cell
1	43	M	C250T	+	-	+	+	+	-	-	-	-
2	48	F	C250T	-	-	-	-	-	-	-	+	-
3	63	F	C228T	+	-	+	-	-	-	+	-	-
4	68	M	C250T	-	-	+	+	+	-	+	-	-
5	79	M	C228T	-	+	+	+	+	-	-	-	-

M = male, F = female, mut = mutation pattern, Hypercell = Hypercellularity, Small cell = Small cell formation, Nec = Necrosis, Sheet = Sheeting architecture, Macro = Macronucleoli, Chordoid = Chordoid meningioma, Clear cell = Clear cell meningioma

Discussion

This study is the first to report the prevalence and clinicopathological correlations of *TERT* promoter mutations in CNS WHO Grade 2 meningiomas in 92 Thai patients. We found a mutation rate of 5.43%, closely matching previous reports from other populations (0.9%–7.7%).[10,12-16] The number of patients previously reported in different series varied from 26 to 220 (mean, 88.5).[10,12-16] The most common alteration was C250T, accounting for 60% of mutation-positive tumors.

TERT promoter mutations have been identified in several aggressive and recurrent malignancies, including glioblastomas, melanomas, bladder cancer, thyroid cancer, and meningiomas.[17,18] In meningiomas, these mutations are strongly linked to complex genomic alterations such as chromosome 22q deletions and NF^2 loss and are recognized as adverse prognostic markers with potential therapeutic relevance.[1] Their inclusion in the current WHO classification as one of the molecular markers for anaplastic meningioma underscores their clinical importance.[1]

No statistically significant associations were found between *TERT* promoter mutation status and histopathological features—including chordoid or clear cell variants, mitotic count ≥ 4, brain invasion, necrosis, and hypercellularity. This lack of significance may be due to the small number of mutation-positive cases (n = 5) and the underrepresentation of rare histological variants; notably, no clear cell meningiomas were identified, limiting subgroup analyses.

The consistent prevalence of *TERT* promoter mutations observed in our series and prior studies, [10,12-16] suggests that these alterations may represent a conserved molecular feature across populations. A key strength of this study is its focus on a Thai cohort, addressing a geographic gap in the literature where most research has been conducted in Western populations. Given the possible influence of ethnicity and geographic factors on molecular profiles, our findings provide valuable regional data.

Future studies should include larger, multicenter cohorts and incorporate comprehensive molecular profiling to better define the prognostic and therapeutic roles of *TERT* promoter mutations. Long-term follow-up will also be crucial to assess their impact on recurrence and survival outcomes.

Conclusion

In conclusion, **promoter mutations were identified in 5.43% of CNS WHO grade 2 meningiomas** in this Thai cohort, a prevalence comparable to that reported in other populations. The mutations were infrequent and showed **no statistically significant association with histopathological features, patient age, or sex,** likely reflecting the small number of mutation-positive cases and the rarity of certain histological subtypes. These findings suggest that ***TERT* promoter mutations represent a conserved but uncommon molecular alteration in WHO grade 2 meningiomas,** independent of conventional pathological criteria. Larger multicenter studies with long-term follow-up and integrated molecular analyses are warranted to clarify the prognostic significance and potential clinical utility of *TERT* promoter mutations in this tumor group.

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Conflict of interest

The authors declare no conflict of interest.

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