TERT Promoter Mutation Status in Glioma

- Rapid diagnosis of TERT promoter mutation using Terahertz absorption spectroscopy in glioblastoma
- Characterization of MRI findings by pTERT mutation status and the prognostic significance in GBM patients with recurrent lesions
- Diffusion imaging in gliomas: how ADC values forecast glioma genetics
- Cortical Origin-Dependent Metabolic and Molecular Heterogeneity in Gliomas: Insights from (18)F-FET PET
- A dual-genotype IDH-mutant infiltrating glioma, a real oligoastrocytoma in cerebral hemisphere
- Research Progress in Imaging Investigation of TERT Promoter Mutations in Gliomas
- Predicting telomerase reverse transcriptase promoter mutation status in glioblastoma by whole-tumor multi-sequence magnetic resonance texture analysis
- High p16^{INK4A} expression in glioblastoma is associated with senescence phenotype and better prognosis

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The presence of the TERT Promoter Mutation Status in Glioma is associated with a better prognosis.

Mutation in the telomerase reverse transcriptase promoter (TERTp)is commonly observed in various malignancies, such as central nervous system (CNS) tumors, malignant melanoma, bladder cancer, and thyroid carcinoma. These mutations are recognized as significant poor prognostic factors for these tumors. In this investigation, a total of 528 cases of adult-type diffuse gliomas diagnosed at a single institution were reclassified according to the 2021 WHO classifications of CNS tumors, 5th edition (WHO2021). The study analyzed clinicopathological and genetic features, including TERTp mutations in each tumor. The impact of known prognostic factors on patient outcomes was analyzed through Kaplan-Meier survival and Cox regression analysis. TERTp mutations were predominantly identified in 94.1% of oligodendrogliomas (ODG), followed by 66.3% in glioblastoma, IDH-wildtype (GBM-IDHwt), and 9.2% of astrocytomas, IDH-mutant (A-IDHm). When considering A-IDHm and GBM as astrocytic tumors (Group 1) and ODGs (Group 2), TERTp mutations emerged as a significant adverse prognostic factor ($p = 0.013$) in Group 1. However, within each GBM-IDHwt and A-IDHm, the presence of TERTp mutations did not significantly impact patient prognosis ($p = 0.215$ and 0.268, respectively). Due to the high frequency of TERTp mutations in Group 2 (ODG) and their consistent prolonged survival, a statistical analysis to evaluate their impact on overall survival was deemed impractical. When considering MGMTp status, the combined TERTp-mutated and MGMTp-unmethylated group exhibited the worst prognosis in OS ($p = 0.018$) and PFS ($p = 0.034$) of GBM. This study confirmed that the classification of tumors according to the WHO2021 criteria effectively reflected prognosis. Both uni- and multivariate analyses in GBM, age, MGMTp methylation, and CDKN2A/B homozygous deletion were statistically significant prognostic factors while in univariate analysis in A-IDHm, grade 4, the Ki-67 index and MYCN amplifications were statistically significant prognostic factors. This study suggests that it is important to classify and manage tumors based on their genetic characteristics in adult-type diffuse gliomas [1)]

Patients with IDH and TERTp glioma mutations have the best prognosis, and only IDH mutation patients and only TERTp mutation patients have the worst prognosis. Moreover, the molecular classification of gliomas by mutations of IDH and TERTp is not suitable for pediatric patients [2].

A study aimed to investigate the TERT mutation in patients with glioma using machine learning (ML) algorithms on radiographic imaging.

This study was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The electronic databases of PubMed, Embase, Scopus, and Web of Science were searched from inception to August 1, 2023. The statistical analysis was performed using the MIDAS package of STATA v.17.

Results: A total of 22 studies involving 5371 patients were included for data extraction, with data synthesis based on 11 reports. The analysis revealed a pooled sensitivity of 0.86 (95% CI: 0.78-0.92) and a specificity of 0.80 (95% CI 0.72-0.86). The positive and negative likelihood ratios were 4.23 (95% CI: 2.99-5.99) and 0.18 (95% CI: 0.11-0.29), respectively. The pooled diagnostic score was 3.18 (95% CI: 2.45-3.91), with a diagnostic odds ratio 24.08 (95% CI: 11.63-49.87). The Summary Receiver Operating Characteristic (SROC) curve had an area under the curve (AUC) of 0.89 (95% CI: 0.86-0.91).

The study suggests that ML can predict TERT mutation status in glioma patients. ML models showed high sensitivity (0.86) and moderate specificity (0.80), aiding disease prognosis and treatment planning. However, further development and improvement of ML models are necessary for better performance metrics and increased reliability in clinical practice [3].

Human hotspot TERT promoter gene (TERTp) mutations may cause increased expression of telomerase and are found in over 50 cancer types [4].

TERT promoter mutations are one of the most common genetic alterations in adult-type diffuse gliomas and show specific patterns compared with other genetic alterations according to glioma subtypes. This mutation has variable impacts on patient outcomes in association with other genetic alterations, including IDH1/2 mutations or histological types. Arita et al. reviewed the knowledge on the values of TERT promoter mutations in the diagnosis and prognostication of adult-type diffuse gliomas. Although its impact on prognosis is somewhat complicated and enigmatic, the mutational status of the TERT promoter provides highly useful information for predicting patients' outcomes in the conventional classification of gliomas defined by IDH1/2 and 1p/19q co-deletion status [5].

TERTp mutations commonly occur concomitantly with 1p/19q co-deletion [6] and are mutually exclusive in gliomas with TP53 mutations.

TERT is proven to confer poor prognosis in high-grade gliomas, independent of IDH and MGMT [7].

With the advance of genomics research, there have been a new breakthrough in the molecular classification of gliomas. Glioblastoma (WHO grade Ⅳ) could be subtyped to proneural, neural, classical, and mesenchymal according to the mRNA expression. Low-grade gliomas (WHO grade Ⅱ and Ⅲ) could be divided into 5 types using 1p/19q co-deletion, isocitrate dehydrogenase(IDH) mutation, and TERTp (promotor region) mutation. In 2016, a new classification of tumors of the central nervous system was proposed, and some new markers such as IDH1 mutation were introduced into the diagnosis of gliomas. Genotype and phenotype were integrated to diagnose gliomas. In the meantime, precision treatment for gliomas has also been vigorously developed [8].

Telomerase reverse transcriptase (TERT) activity is up-regulated in several types of tumors including glioblastoma (Glioblastoma).

In a study, 128 primary glioblastoma patients were examined for single nucleotide polymorphisms of TERT in blood and in 92 cases for TERT promoter mutations in tumors. TERT promoter mutations were observed in 86% of the tumors and of these, C228T (-124 bp upstream start codon) was detected in 75% and C250T (-146 bp) in 25% of cases. TERT promoter mutations were associated with shorter overall survival (11 vs. 20 months p = 0.002 and 12 vs. 20, p = 0.04 for C228T and C250T, respectively). The minor alleles of rs2736100 and rs10069690 SNP's, located in intron 2 and the promotor regions, respectively, were associated with an increased risk of developing Glioblastoma (p = 0.004 and 0.001). Glioblastoma patients having both TERT promoter mutations and being homozygous carriers of the rs2853669 C-allele displayed significantly shorter overall survival than those with the wild type allele. The rs2853669 SNP is located in a putative Ets2 binding site in the promoter (-246 bp upstream start codon) close to the C228T and C250T mutation hot spots. Interleukin-6 (IL-6) expression regulated by TERT promoter status and polymorphism, what leads us to think that TERT and IL-6 plays a significant role in Glioblastoma, where specific SNPs increase the risk of developing Glioblastoma while the rs2853669 SNP and specific mutations in the TERT promoter of the tumor lead to shorter survival [9].

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