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ORIGINAL ARTICLE

Unveiling the etiological impact of GST-M1, GST-T1, and P53 genotypic variations on brain carcinogenesis

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Abstract

Background Functional variants of glutathione-S-transferase (GST)-M1, GST-T1, p53 might modulate brain cancer risk by altering the rate of metabolism and clearance of carcinogens from the brain tissue. In this study, the role of GST-M1, GST-T1, p53 polymorphisms on brain tumor was investigated.

Methods and results Brain tumor tissues of 143 patients were obtained from the Gulhane Training and Research Hospital, Department of Neurosurgery between 2019 and 2020. In the xenobiotic mechanism, the null allele frequency in the GST-T1, GST-M1 gene regions of Phase II enzymes by qPCR method were investigated. Single nucleotide polymorphism encoding Arg/Pro conversion in the p53 gene region was analyzed in 120 cases by sequence analysis method. The data were analyzed statistically with patient's demographic and clinical data. GST-M1, GST-T1, p53 genotypes of the patient group were determined. The most frequent genotype was null genotype (0/0) for GST-M1 ($\chi^2 = 39.756$, $p < 0.001$). GST-M1 genotype frequencies were 30.8%, 23.1%, 44.3% for 1/1, 1/0, 0/0, respectively. The most frequent genotype was GST-T1 1/1 following by GST-T1 1/0 ($\chi^2 = 0.335$, $p = 0.846$). GST-T1 genotype frequencies were 64.3%, 30.8%, 4.9% for 1/1, 1/0, 0/0, respectively. GST-M1 null genotype might be associated with the development of brain tumors. Genotype distribution obtained in p53 exon 4 codon 72; Arg/Arg was determined as 31 (25.8%), Arg/Pro 70 (58.3%), and Pro/Pro 19 (15.8%) in the case group, while there were 18 (38.3%), 23 (48.9%), and 6 (12.8%) respectively in the control group. However, the genotype distribution of p53 exon 4 codon 72 among tumorous tissue did not significantly vary from healthy control tissues ($\chi^2 = 2.536$, $p = 0.281$).

Conclusion The null allele frequency encountered in the GST-M1, GST-T1 gene regions is consistent with the rates in the gene pool called Caucasian in the literature. GST-M1 gene polymorphism may play a crucial role in brain carcinogenesis in Turkish patients. This study based on clinical data is thought to help to understand the important epidemiological features of brain tumors.

Keywords Brain tumors · GST-T1 · GST-M1 · p53 · Polymorphism

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Introduction

Central Nervous System (CNS) tumors, originating in the brain or spinal cord tissues, pose a significant challenge as they disrupt the coordination and control of bodily functions governed by the CNS [1, 2]. These tumors can be primary, originating within the CNS, or secondary, resulting from metastasis of cancerous cells from other body parts [3]. Distinct types of CNS tumors can be classified based on the specific cell types affected, including Astrocytoma, Oligodendroglioma, Ependymoma, Medulloblastoma, Meningioma, and etc. [3].

Brain and other CNS tumors are among the most fatal cancers and account for substantial morbidity and mortality [4]. A single center pathology review of 21,622 cases showed that the proportion of CNS tumors was 63.8% [5]. Global incidence rates of CNS cancer reached 330,000 cases in 2016, with an age-standardized rate of 4.63 per 100,000 person-years [6]. A recent systematic review and meta-analysis reported a primary CNS tumor prevalence of 3.6 per 100,000 individuals [7]. In the year 2019, a staggering total of 347,992 documented incidences of CNS malignancies were recorded on a global scale. Concurrently, during this temporal span, the lamentable toll of 246,253 lives succumbed to the devastating impact of CNS cancers across the world [8]. The global age-standardized mortality rate in 2019 was 3.05 per 100,000 population [8]. Despite comparatively lower incidence rates in Turkey, CNS cancers still pose a significant threat, causing notable mortality [9]. According to a report by the esteemed international agency for research on cancer in the year 2020, Turkey bore witness to a total of 6,102 cases of afflicted patients, with an unfortunate corollary of 5,070 deaths ensuing from these dire circumstances. Furthermore, this same report expounded upon a five-year prevalence rate of 20.2 per 100,000 population [10].

The etiology of CNS cancers, while not yet comprehensively elucidated, manifests as a multifactorial phenomenon, characterized by an intricate interplay of genetic, environmental, and lifestyle factors [11, 12]. Genetic factors contribute to CNS cancer development through various mechanisms [13].

Glutathione S-Transferases (GSTs) proteins play a pivotal role in cellular detoxification and oxidative stress mitigation. When their integrity is compromised, they may contribute to carcinogenesis [14]. Similarly, impaired p53 function as a tumor suppressor gene hampers DNA repair and apoptosis induction [14]. These protein defects stem from genotypic variations in their regulatory gene regions [14]. Thus, we aim to examine the association between the null allele of GST-T1, GST-M1, arginine/proline (Arg/Pro) substitution in p53 exon4 codon72, and brain tumorigenesis.

Materials and methods

Study design and sampling

In 2019, clinical data from patients with intracranial tumors treated at a neurosurgery clinic were retrospectively evaluated. Inclusion criteria encompassed patients diagnosed with intracranial tumors, comprising both primary and secondary brain cancer types, and those possessing available tumor tissue specimens. Exclusion criteria were applied to ensure validity, excluding patients with unrelated malignancies, inadequate tumor samples, severe coexisting pathologies, prior targeted interventions, and inability to provide consent. The study included 149 subjects. A comprehensive checklist was used to collect demographic and clinical data, including age, gender, smoking and alcohol habits, radiotherapy or chemotherapy exposure, surgical history, lesion localization, and postoperative (exitus or alive) status. Tumor tissues that were appropriately embedded in paraffin for subsequent analysis were subjected to extract genomic DNA for further genotypic analysis. Finally, genomic DNA was obtained from 143 subjects for trimodal genotyping of the GST-M1 and GST-T1 gene regions using a melting-curve analysis-based qPCR method to identify gene deletions. This approach adhered to established practices in the field, which commonly eschew the inclusion of control groups for such analyses [15]. The consistency of this approach extends to sequence analysis techniques and is validated through gene region proliferation assessments, bioinformatics analyses, and data from publicly available databases like NCBI.

In our study, deviations in normalized qPCR values across different tissues or patient groups serve as indicators of gene loss, collectively referred to as "Gene Dosage," and are categorized based on predefined threshold criteria indicating the presence or absence of deletions.

Normalized mean values, as per Girault et al. (2005), offer insights into gene deletion's presence and impact for GST-M1 and GST-T1. For GST-M1, values between 1.00 and 0.80 or exceeding 1.00 denote no deletion (-/-), while values from 0.79 to 0.42 suggest some gene loss due to deletion, with a substantial effect observed as values decrease from 0.41 to 0.0. Similarly, for GST-T1, values within 1.00-0.80 or >1.00 indicate no deletion (-/-), whereas 0.79 to 0.36 suggest gene loss due to deletion,

with a pronounced effect observed when values fall from 0.35 to 0, expressed as (+/+), signifying gene deletion in this region [15].

Moreover, the genomic DNA of 120 brain tumor tissues and 47 normal tissues taken from the resection margin of the same group of patients were also used for sequence analysis to determine the SNP genotype of the p53 gene region exon4 codon72 (Fig. 1), where the Arg/Pro change associated with the Guanine/Cytosine base conversion occurs, affecting the phenotypic expression of the tumor suppressor p53 gene as a result of a point mutation in this gene region [16, 17].

Melting curve analysis by qPCR

In our study, qPCR method based on melting-curve analysis was applied to examine the deletion status of GST-M and GST-T gene regions. During this application, the Roche Lightcycler 480 qPCR system was used. Bio-Rad SSO Advanced Universal SYBR Green Supermix was used. GST-M and GST-T primer sequences used in the study; for GST-T1; 5-CAAGTCCCAGAGCACCTCACCTC-3' (NM_000853) Forward, 5-GTGTGCATCATTCTCATTGTGGCTT-3' (NM_000853) Reverse, for GST-M1; 5'-TGCATTCGTTCATGTGACAGTATTCT-3' (NM000561) Forward, 5'-GAGAGGAGACCGGGCACTCA-3' (NM000561) Reverse [15]. In addition, this primer sequence was synthesized in the laboratory in specialized columns with CPG (Controlled Pore Glass) using the oligosynthesis method and its purification was obtained from the C18 column and the sample collector with the reverse phase HPLC (Agilent) system. The controls were confirmed by the electrophoresis gel method in terms of both the graphs in the chromatographic system and the base sizes [18]. Mix ratios created in the pre-PCR stage before the qPCR system; SYBR Green PCR Master Mix (Power) 5uL; Forward primer 0.4uL; Reverse primer 0.4uL; cDNA 1uL(100ng/uL); Water (DNAse/RNAse free) 3.2uL; the total volume was 10µL. In addition, the melting curve analysis program used in the qPCR system; 3 min at 98ºC. 1 loop; Each cycle of the denaturation process was 10 s at 95ºC and 15 s at 60ºC, 40 cycles of amplification and finally 0.3ºC/second (Ramp Rate) from 65ºC to 95ºC.

SNPs analysis by sanger sequence

It is known that the Arg/Pro change that occurs with the Guanine/Cytosine base conversion located in the exon4 codon72 gene region, which is known to have an effect on the phenotypic expression of the tumor suppressor p53 gene, is caused by the point mutation occurring in this gene region. In order to reveal the situation of this point mutation in the patient group of our study, the position of the gene region that we amplified by polymerase chain reaction was analyzed in terms of point mutation by sequence analysis method (Applied Biosystems-3130XL, P53 primers = NM000546.6) [16, 17, 19].

Statistical analysis

Statistical analysis were performed using IBM SPSS Version 25.0. (Armonk, NY: IBM Corp). The categorizable variables were defined as the number of patients/controls (n) and percentage (%) with descriptive statistics. GST-M1 and GST-T1 gene doses of each participant in the patient groups were calculated, and genotypes and deletion statuse were expressed in the tables. The chi-square test investigated the GST-M1 and GST-T1 genotype frequencies deviation from the Hardy-Weinberg proportion. The relationships between demographic and clinical data and genotypes were evaluated with Chi-square test. If the chi-square test assumptions were not met, Fisher's exact test and Fisher-Freeman-Halton exact test were used by type of table. Differences at the $p < 0.05$ level were considered statistically significant.

Results

Descriptive data reveals the mean age of 49.44 ± 8.09 years. Out of the total number of patients, 85 were males (59.4%) and 58 were females (40.6%). Among the patients, 30% had a history of smoking, while 70% had never smoked. Only 9.8% reported alcohol use, with the majority (90.2%) abstaining from alcohol. In terms of treatment, 38.4% received radiotherapy and 22.3% underwent chemotherapy. Lesion analysis showed the highest frequency in the frontal Sect. (28%), followed by the temporal region (11.2%), cerebellar region (10.5%), and parietal region (2.8%). The remaining cases (47.5%) exhibited various tumor localizations. The overall postoperative survival rate was 65%. Table 1 provides a comprehensive overview of the patients' demographics, treatment history, and clinical profile.

Figure 1 presents various analytical components related to genetic analysis in brain tumor tissues. Deletion junction information, observed GST-M1 and GST-T1 genotypes and departure from Hardy-Weinberg proportion of the patients were described (Table 2) and distributions illustrated in Fig. 2. The GST-M1 genotype distribution was not in Hardy-Weinberg equilibrium in tumorous

Table 1 The demographic and clinical features distribution of participants

Characteristics	Total n (%)
Demographic characteristics	
Gender	
Female	58 (40.6%)
Male	85 (59.4%)
Age (year)	
< 60	93 (65%)
≥ 60	50 35%)
Smoking	
Yes	43 (30%)
No	100 (70%)
Alcohol consumption	
Yes	14 (9.8%)
No	129 (90.2%)
Clinical characteristics	
Radiotherapy	
Yes	55 (38.5%)
No	88 (61.5%)
Chemotherapy	
Yes	32 (22.3%)
No	111 (77.6%)
Lesion localisation	
Frontal	40 (28%)
Parietal	4 (2.8%)
Cerebellar	15 (10.5%)
Temporal	16 (11.2%)
Other	68 (47.5%)
Post-operation status	
Alive	93 (65%)
Exitus	50 (35%)

tissue ($\chi2 = 39.756$, $p < 0.001$) indicate GST-M1 null genotype may be associated with brain tumor development. The genotype frequencies were 30.8%, 23.1% and 44.3% for GST-M1 1/1, GST-M1 1/0 and GST-M1 0/0, respectively. However, the GST-T1 genotype distribution were in Hardy-Weinberg proportion ($\chi2 = 0.335$, $p = 0.846$) and the genotype frequencies were 64.3%, 30.8% and 4.9% for GST-T1 1/1, GST-T1 1/0 and GST-T1 0/0, respectively (Fig. 1). On the other hand, the most frequent genotype of p53 codon 72 polymorphism was Arg / Pro (Heterozygous) following by Arg /Arg (Wild Type) in both tumorous and healthy tissues (Table 3). Furthermore, the genotype distribution of GST-M1, GST-T1, and P53 exon 4 codon 72 did not exhibit statistically significant differences among patients concerning demographic factors such as age, gender, smoking, and alcohol habits, and clinical attributes including therapy received, lesion localization, and survival rates ($p > 0.05$).

Discussion

This study provides novel insights into the intricate relationship between GST-M1, GST-T1, and p53 genotypes with brain tumorigenesis. Numerous demographic factors, including age, gender, and substance abuse such as alcohol addiction and cigarette smoking, as well as several clinical features like therapy received, lesion localization, and survival rates have received attention due to their purported associations with cancer pathogenesis. Consequently, the present investigation examined the factors above within a cohort of brain tumor patients originating from the Turkish population.

The average age at diagnosis was different from previous studies conducted in Europe (mean age of 53.24 years) and the United States (mean age of 60.16 years) [20] but in line with study from Turkey (mean age of 46.72 years) [21]. These results indicate that brain tumors are frequently diagnosed in middle-aged individuals in Turkey and may reflect differences in epidemiology, risk factors, or healthcare practices compared to other regions.

According to the CBTRUS statistical report, women accounted for 42% of cases, while men accounted for 58% in all primary brain tumors [22]. Our study's gender distribution and sample selection align with this global rate.

Most intracranial tumors in adults are supratentorial, with the frontal and temporal regions being the most common locations, as supported by previous research [23–25]. Our study's resutls partially align with the existing literature in terms of tumor localization.

GST-M1 and GST-T1 variations have been extensively examined across various cancer types, yet a consensus regarding their role in carcinogenesis remains elusive. While a subset of studies support a significant correlation between the null genotypes of GST-M1 and GST-T1 and an elevated risk of cancer development [26–28], others do not propose a substantial contribution to cancer etiology [29, 30]. However, the impact of GST-M1 and GST-T1 on carcinogenesis may become evident when considering their interaction with other factors, such as lifestyle and the ethnic makeup of the population [27, 29]. Notably, the involvement of GST-M1 and GST-T1 in the etiology of brain cancer has received relatively little attention. Limited research exhibits contradictory evidence regarding the role of GST-M1 and GST-T1 in brain carcinogenesis.

Although certain studies have failed to demonstrate a significant association between homozygous deletion polymorphisms of GST-M1 and GST-T1 and the

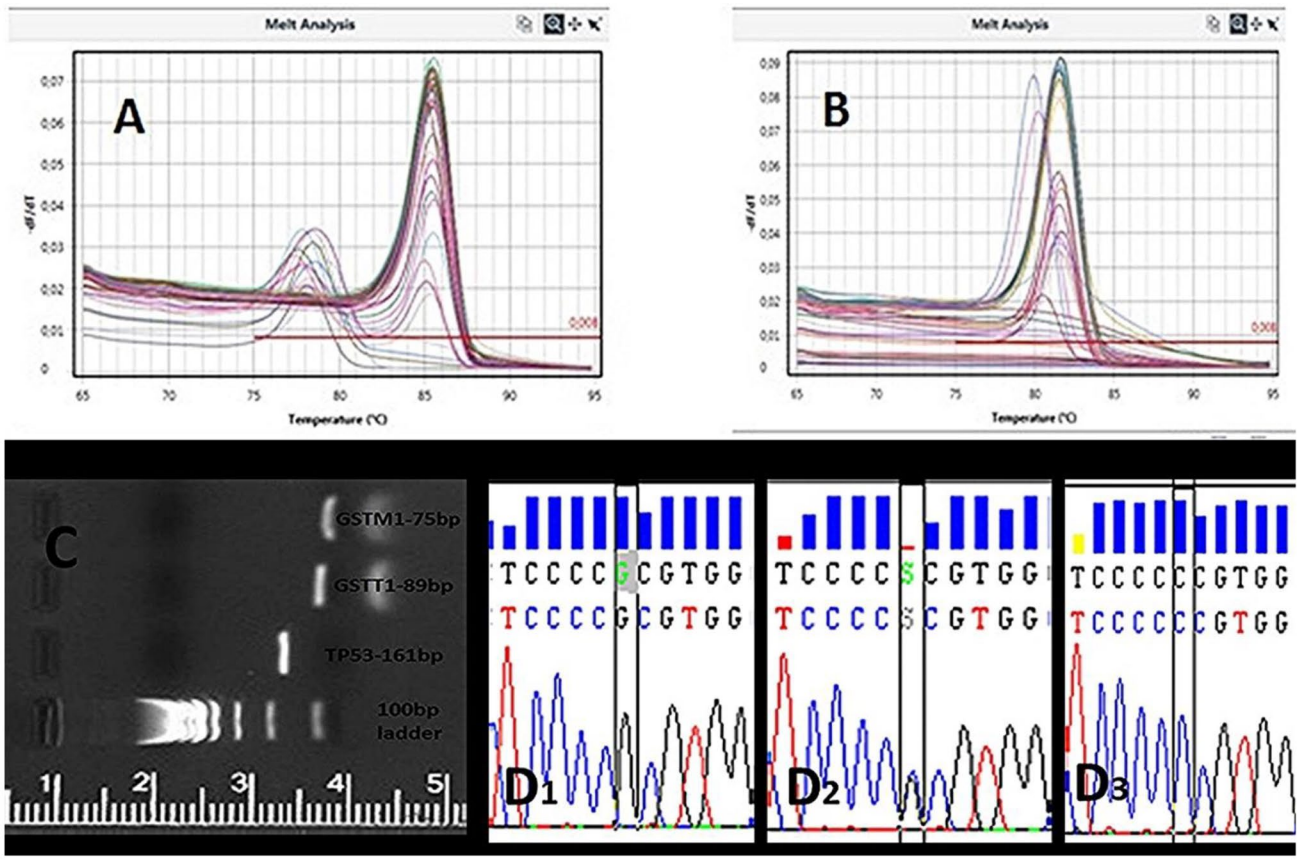

Fig. 1 **A**: General view of Melting-Curve graphs after analysis by qPCR in brain tumor tissues for GST-T1. **B**: General view of Melting-Curve graphs after analysis by qPCR in brain tumor tissues for GST-M1. **C**: Electrophoresis gel image obtained for the control of base sizes of the GST-M1, GST-T1 and TP53 gene regions. **D**: General view of the polymorphic state due to nucleotide change in the p53 exon 4 codon 72 gene region. **D1**: G/G (Arg/Arg-WT); **D2**: G/C (Arg/Pro-HT); **D3**: C/C (Pro/Pro-MT). WT: Wild Type, HT:Heterozygous Type, MT: Mutant Type

Table 2 Observed GST-M1 and GST-T1 genotypes and departure from Hardy-Weinberg proportion

Genotyping	n (%)	*p*-value
GST-M1 present (1/1)	44 (30.8%)	$p < 0.001$
GST-M1 present (1/0)	33 (23.1%)	$\chi 2 = 39.756$
GST-M1 null (0/0)	66 (44.3%)	
Total	143 (100%)	
GST-T1 present (1/1)	92 (64.3%)	$p = 0.846$
GST-T1 present (1/0)	44 (30.8%)	$\chi 2 = 0.335$
GST-T1 null (0/0)	7 (4.9%)	
Total	143 (100%)	

risk of brain tumors [31, 32], other investigations have provided evidence supporting the influence of the null genotype of GST-T1 on meningioma susceptibility [33]. Moreover, the deletion of GST-M1 and the dual deletions in GST-M1-GST-T1 loci have been associated with brain tumors in males [34]. Another study suggests that the deletion of GST-M1 may be linked to an earlier age at onset among female cases [35]. Notably, a study conducted via restricted fragment lengh polymorphism (RFLP) on the Turkish population with limited number of patients (n = 75), suggests a correlation between brain tumor incidence and the GST-M1 null genotype, while no such relationship was observed with GST-T1 or GST-P1 gene variants in the Turkish population [36]. Current study with higher number of patients (n = 143) and proven method (qPCR) approve the association between genotype of GST-M1 and cancer pathology in turkish population. On the contrary, the extensively studied tumor suppressor p53 has garnered substantial support for the significant involvement of p53 codon72 mutation in the formation of various tumor types, including brain tumors [37–41]. However, resutls from turkish population dose not support the association of p53 codon72 mutation with risk of cancer.

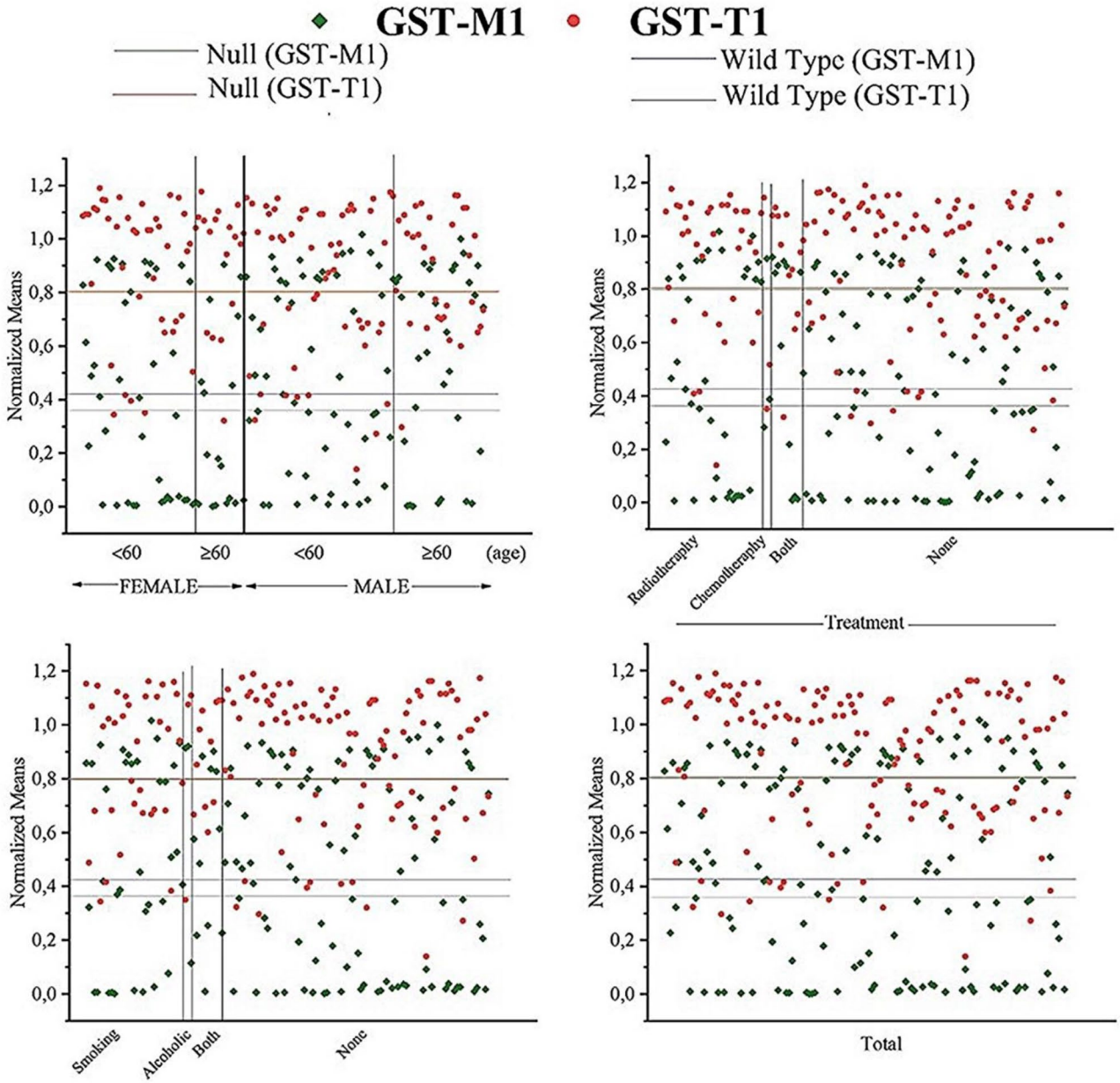

Fig. 2 Trimodal genotyping thresholds and distribution of GST-M1 and GST-T1 genotypic variations based on demographic, therapeutic, and lifestyle factors [15]

Table 3 Genotype and allel frequency of p53 codon 72 polymorphism in patients with brain tumor and healthy controls

	Patient group (n = 120)	Control group (n = 47)	*p*-value
Genotype			
Arg /Arg (Wild Type)	31 (25.8%)	18 (38.3%)	p = 0.281 χ^2=2.536
Arg / Pro (Heterozygous)	70 (58.3%)	23 (48.9%)	
Pro / Pro (Mutant Type)	19 (15.8%)	6 (12.8%)	
Allele			
Arg	0.55	0.63	p = 0.250 χ^2=1.323
Pro	0.45	0.37	

Conclusion

The present analysis posits that the contribution of GSTs to the pathogenesis of brain tumors exhibits heterogeneity across distinct populations. This investigation yields innovative perspectives on the intricate interplay between GSTM1 genotype and the process of brain tumor development in Turkish population.

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Data Availability The authors confirm that all data supporting the finding of the study are available within the article, and the raw data supporting the findings were generated and available at the corresponding author on request.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval and consent to participate Ethics committee approval was received for this study from the IRB Health Sciences University Keçiören Education and Research Hospital (No: 2012-KAEK-15/1810, date:27.02.2019). The participant received detailed explanations about the study, and written informed consents were obtained. The study was designed and conducted according to relevant ethical regulations and was performed with respect to the Declaration of Helsinki and its later amendments.

Consent for publication Not applicable.

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