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Prevalence of TP53 Gene Mutation in GBM Patients in Egyptian Population

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Abstract

Background: Glioblastoma Multiforme (GBM) is one of the most fatal of all brain tumors. TP53 mutation is the hallmark genetic mutation of GBM, because these tumors have a high incidence of mutation in this gene (>65%), suggesting that p53 pathway has an important role in the development of the tumors.

Aim of Study: This study aimed to assess the prevalence of TP53 gene mutation in Glioblastoma multiforme patients and its correlation to the clinical pictures of this tumors in Egypt.

Patients and Methods: This retrospective cross-sectional study included 59 patients pathologically confirmed of having GBM after surgical excision, underwent further immunological analysis of presence of TP53 gene mutation.

Results: Patients with TP53 presented with DCL (*p*-value =0.703), fits (*p*-value=0.677), weakness (*p*-value=0.212) were statistically insignificant.

Conclusion: Patients diagnosed with TP53 gene mutation didn't present with significantly different clinical picture from other patients.

Key Words: *Glioblastoma Multiforme – TP53 – Gene Mutation and Astrocytomas.*

Introduction

GLIOMAS are the tumors that arise from the brain's glial cells, which are the non-neuronal cells of the central nervous system. Neurons function in synaptic interactions, whereas glial cells are supportive cells which provide protection and structural support to the neurons. According to the Global cancer statistics (GLOBOCAN) 2020, brain cancer and central nervous system tumors are the 19th and 12th, respectively **[1].**

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Biomarkers are important tools for diagnosis, monitoring disease progression, prognosis, and therapeutic response prediction.

TP53 tumor suppressor gene is the most commongene mutation in human tumors and one of the most analyzed in different types of tumors. Advanced or aggressive tumors have a higher frequency of TP53 gene mutations in their genomes **[2].**

Patients and Methods

This is a cross sectional analytical study involved 59 Egyptian patients of both sexes and at any age who were diagnosed Radiologically and pathologically with Glioblastoma multiforme after surgical excision and histopathological analysis of the specimen. Further histopathological analysis of the specimens indicated the presence of TP53 gene mutation and was correlated with the clinical picture of the patients.

The study was conducted at Cairo University Hospitals in Egypt from December 2020 to May 2021.

The study included patients with Glioblastoma Multiforme (de novo or recurrent).

Ethical approval and consent to participate:

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institution and approved by the ethics committee of Cairo University.

Methodology in details:

All patients were subjected to thorough history taking, clinical examination and radiological examination.

All the patients underwent surgical excision, followed by histopathological analysis of the specimen at Pathology department, Faculty of Medicine,

Cairo University, with analysis of TP53 marker presence in the tumor specimens with correlation to clinical picture of the patients.

Postoperative period included medical treatment with antiepileptics in the form of epanutin according to the body weight and Corticosteroids in the form of Decadron and brain dehydrating measures prescribed to all patients, Prophylactic intravenous antibiotics were given and stopped after removal of the drain and the patient continued oral antibiotics for a week. Analgesics, gastric protecting drugs were also prescribed.

Patients were followed-up for 2 weeks after discharge with neurological and radiological assessments. Referral to Oncology Department based on pathological result.

Sample size:

Based on evidence from previous similar studies and by considering the TP53 mutation gene in Glioblastoma patients' percent as a primary outcome. Epi-calc 2000 was used to calculate the sample size of this cross-sectional analytical study. Assuming 80% power, 0.05 level of significance, 16% null hypothesis value and estimated proportion of 31%, Sample size will be = 54 participants. Considering the drop-outs rate of 10%, therefore the final sample size will be 59 participants.

Statistical analysis:

- Microsoft excel 2013 will be used for data entry and the statistical package for social science (SPSS version 24) will be used for data analysis.
- Arithmetic mean and standard deviation will be used for summary of normal quantitative data, median and interquartile range will be used for summary of abnormal quantitative data, and frequencies will be used for qualitative data.
- Bivariate relationship will be displayed in cross tabulations and comparison of proportions will be performed using the chi-square and Fisher's exact tests where appropriate.
- *t*-independent will be used to compare normally distributed quantitative data and Mann-Whitney for skewed data.
- *p*-value will be calculated to assess statistical significance, a value less than 0.05 will be considered statistically significant.

Results

1- *Age:* Around 25% of patients were in the 5th decade of life, 23% in the sixth decade, 20% in the 4th decade, 18% in 7th decade, 7% in the 8th decade and 3% in the 3rd and 2nd decades.

Average age was 46 years with range of 15-72 years.

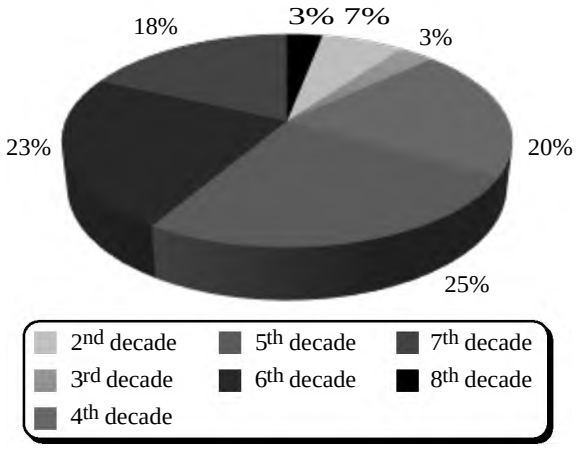

Fig. (1): Age distribution.

2- Gender: Of the 59 patients, 42 patients (72%) were males while 17 patients (28%) were females.

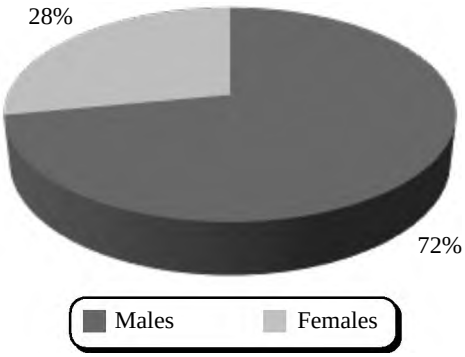

Fig. (2): Gender distribution.

3- Anatomical tumor location: Of all 59 patients, 18 patients (32%) had temporal, 19 patients (33%) had parietal, 8 patients (12%) of patients had frontal, 4 patients (7%) had occipital, 4 patients (7%) had thalamic, 3 patients (5%) had posterior fossa, 3 patients (5%) had callosal GBM.

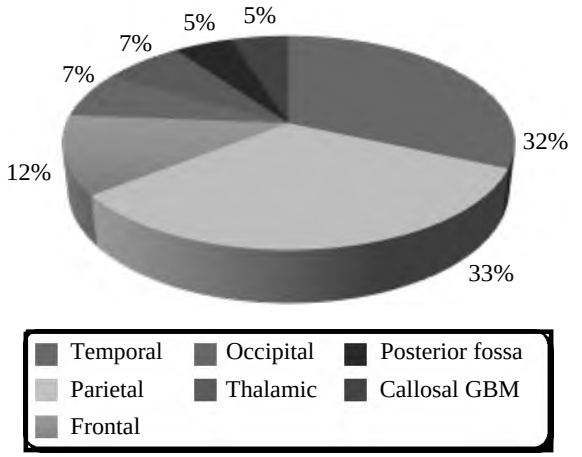

Fig. (3): Anatomical distribution.

4- *Clinical picture:* Of all 59 patients, 55% presented with fits, 22% presented with weakness, 23% presented with DCL.

5- *Presence of TP53 Gene Mutation:* Of All 59 patients included in our study; 61% of the patients had TP53 Gene mutation.

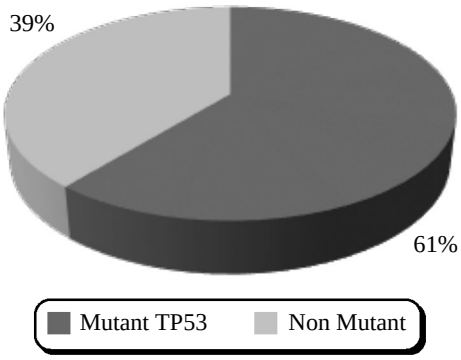

Fig. (4): Gene mutation distribution.

6- *TP53 Gene Mutation with Age:* Statistical analysis shows significant correlation between TP53 mutant gene and advancing age of patients.

Table (1): Statistical analysis of TP53 against age.

	Age
TP53 marker %:	
Correlation Coefficient	0.441
p-value	<0.001
N	59

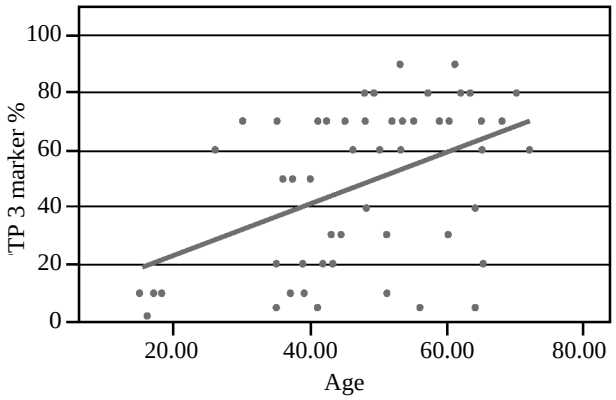

Fig. (5): TP53 against advancing age.

7- *TP53 Gene Mutation with Gender:* No statistical difference was identified regarding the correlation between gender and gene mutation.

Table (2): Gene mutation against gender.

	TP53 marker %					*p*-value
	Mean	Standard Deviation	Median	Mini-mum	Maxi-mum	
Sex:						
F	50.12	27.56	60.00	2.00	80.00	0.722
M	46.07	28.17	55.00	5.00	90.00	
No	43.93	28.60	45.00	2.00	90.00	

8- *TP53 Gene Mutation with tumor location:* Also, no statistical difference was identified regarding the correlation between tumor location and gene mutation.

Table (3): TP53 against tumor location.

	TP53 marker %					*p*-value
	Mean	Standard Deviation	Median	Mini-mum	Maxi-mum	
Tumor location:						
Thalamic	18.00	14.24	20.00	2.00	30.00	0.177
Temporal	49.17	30.59	60.00	5.00	90.00	
Posterior fossa	25.00	30.41	10.00	5.00	60.00	
Parietal	57.37	23.24	70.00	5.00	80.00	
Occipital	40.00	28.28	30.00	20.00	80.00	
Frontal	46.88	27.64	60.00	5.00	80.00	
Callosal	43.33	30.55	50.00	10.00	70.00	

9- *TP53 Gene Mutation with clinical presentation:* Patients diagnosed with mutant genes didn't present with significantly different clinical picture from other patients.

Table (4): Gene mutation against clinical picture.

	TP53 marker %					*p*-value
	Mean	Standard Deviation	Median	Mini-mum	Maxi-mum	
DCL:						
Yes	49.10	30.90	60.00	2.00	90.00	0.70
No	46.28	26.48	60.00	5.00	80.00	3
Fits:						
Yes	46.24	27.74	50.00	2.00	90.00	0.67
No	50.77	28.93	70.00	5.00	80.00	7
Weak ness:						
Yes	54.21	25.40	70.00	5.00	80.00	0.21
No	43.93	28.60	45.00	2.00	90.00	2

Discussion

Many studies have investigated the predictive value of TP53 gene mutation for tumor response to treatment and patient outcome in various cancers. Different clinical and methodological techniques have been used and the results have often been inconsistent and contradictory [3].

In this Study, prevalence of TP53 gene mutation among patients diagnosed with GBM was 61% of total of 59 patients.

Martha L. Simmons et al., in their study, of a total 110 patients diagnosed with GBM underwent TP53 immunohistochemical analysis; TP53 was positive in 51.8% of patients [4].

Sherise D. Ferguson et al., in their study of 375 adult GBM samples comprised the data set conducting molecular profiling. TP53 gene mutation was found in 56.6% of cases [5].

In this study we found around 25% of patients were in the 5th decade of life with average age of 46 years (range: 15-72 years), Statistical analysis shows significant correlation between TP53 gene mutation and advancing age of patients. (p<0.001).

Sherise D. Ferguson et al., in their study found younger patients (<45 years) were more likely than older ones (>70 years) to have a mutation in TP53 (56.6% versus 25.8%, respectively; p<0.0001) [5].

Stark et al., in their study of 143 patients diagnosed with GBM underwent retrospective analysis for TP53 mutation, patients were separated into three groups (1. <40 years, 2. 40-60 years 3. >60 Years). 11 patients were younger than 40 years, 33 patients were from 40-60 years, 28 patients were older than 60 years. They concluded that TP53 protein expression was significantly decreasing with advanced age (p<0.05) [6].

Martha L. Simmons et al., in their study found TP53 was positive in 30 of 53 younger patients <55 years and 24 of 57 of older patients >55 years. They concluded that an age interaction was not identified [4].

We found that TP53 gene mutation was increasing with advancing age of patients, especially in 5th decade of life, in contrast with Ferguson and Stark et al., while Simmons et al., found no statistically significant correlation.

In this study, we found 42 cases (72%) were males while 17 cases (28%) were females. No statistically significant difference was identified regarding the correlation between gender and TP53 gene mutation (p 0.722).

Maryam Rahman et al., [7] in their study of 50 patients of primary (38 patients) and recurrent (12 patients) GBM patients, immune marker expression between primary and recurrent GBM were not significantly different, in addition; no statistically significant differences in gender regarding TP53 gene mutation.

Colen et al., [8] in their study on 99 patients (30 female patients, 69 male patients) they found that results suggest sex-specific molecular mechanisms for cell death in patients with GBM in male patients is associated with TP53 activity. Male patients had higher volumes of necrosis than female patients. The results of this study suggest that cell death in GBM may be driven by sex-specific molecular pathways.

We found that no significant statistical difference found regarding relation between TP53 gene mutation and gender of the patients.

In our study, Tumor location was detected in 18 patients (32%) in temporal region, 19 patients (33%) in parietal region, 8 patients (12%) in frontal region, 4 patients (7%) in occipital region, 4 patients (7%) in thalamic region, 3 patients (5%) in posterior fossa region, and 3 patients (5%) in callosal region. No statistically significant difference was identified regarding the correlation between tumor location and TP53 gene mutation. (p 0.177).

Melike Mut et al., [9] in their study on 85 patients diagnosed with GBM and underwent TP53 histopathological analysis found that 15% (13 patients) of tumor presented in non-eloquent areas (Frontal or temporal polar lesion, parietooccipital lesions, cerebellar hemisphere lesions), while 36% (31 patients) of tumor presented near eloquent areas (Near motor orsensory cortex, near calcarine fissure, near speech center, corpus callosum, near dentate nucleus, or near brain stem), while 49% (41 patients) of tumor presented in eloquent areas (Motor/sensory cortex, visual center, speech center, internal capsule, basal ganglia, hypothalamus/thalamus, brain stem, or dentate nucleus). No statistically significant difference was identified regarding the correlation between tumor location and TP53 gene mutation.

We found that no significant statistical difference found regarding relation between TP53 gene mutation and tumor location.

In this study, of all 59 patients, 55% presented with fits (p-value=0.677), 22% presented with weakness (p value =0.212), 23% presented with DCL (p-value=0.703). Patients diagnosed with TP53 gene mutation (61%) didn't present with significantly different clinical picture from other patients.

Chitra Sarkar et al., [10] in their study on 58 patients diagnosed with GBM and underwent TP53 gene mutation screening, duration of symptoms at presentation and clinical picture ranged from 0.5 to

12 mouths, with the shortest duration of 1.4 months noted in elderly patients (61-80 years). They concluded that no difference was observed among cases in the mean duration of symptoms and clinical presentation that can be correlated to gene mutation.

Shoji Shiraishi et al., **[11]** in their study on 55 patients with GBM underwent TP53 gene mutation screening, TP53 was found in 31% of supratentorial GBMs. The ages of GBM patients with and without TP53 mutations were 53.2 (+or-) 4.6 and 54.9 (+or-) 2.3 years, respectively. The median survival of GBM patients carrying the mutation was 69.7 (+or-) 16.2 weeks; it was 71.2 (+or-) 3.4 weeks for GBM patients with normal TP53. They concluded that the difference between the two groups regarding survival was not statistically significant.

We found that no significant statistical difference found regarding relation between TP53 gene mutation and clinical picture of the patients.

Limitations of the study:

1- Small sample size as compared to other similar studies.
2- Limited resources and foundation.
3- Long time of histopathological analysis of samples due to COVID-19 pandemic and its safety measures.

Conclusion:

TP53 tumor suppressor gene is the most common mutated gene in human cancers and one of the most studied on different kinds of tumors, including GBM. Patient diagnosed with mutant genes didn't present with significantly different clinical picture from other patients. Also, there was a significant correlation between TP53 mutant gene and advancing age of patients, and no significant correlation found between gender or tumor location and TP53 mutation.

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انتشار طفرة الجين TP53 فى مرضى (GBM) الورم الأرومى الدبقى متعدد الأشكال فى السكان المصريين

يعد الورم الأرومى الدبقى متعدد الأشكال (GBM) واحدًا من أكثر أورام الدماغ فتكًا. طفرة TP53 هى الطفرة الجينية المميزة لـ GBM، لأن هذه الأورام لديها نسبة عالية من الطفرة فى هذا الجين (< ٦٥٪)، مما يشير إلى أن مسار p53 له دور مهم فى تطور الأورام.

هدف البحث إلى تقييم مدى انتشار طفرة الجين TP53 فى مرضى الورم الأرومى الدبقى متعدد الأشكال وارتباطه بالصور السريرية لهذا الأورام فى مصر.

شملت هذه الدراسة المقطعية بأثر رجعى ٥٩ مريضًا تم تأكيد إصابتهم بمرض GBM بعد الاستئصال الجراحى، وخضعوا لمزيد من التحليل المناعى لوجود طفرة جينية TP53.

المرضى الذين تم تشخيص إصابتهم بطفرة جين TP53 لم تظهر لديهم صورة سريرية مختلفة بشكل كبير عن المرضى الآخرين.