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Research Article

# Detection of IL1β Gene in Sudanese Patients with Gliomas Tumor in Khartoum state, Sudan

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## Abstract

**Introduction:** Gliomas are the most prevalent type of primary intracranial tumors, representing 80% of all brain neoplasms.In Sudan Brain tumors have been as leading cause of mortality among children and as thirdcausative death among young adults.World Health Organization (WHO) classification2021, categorized gliomas into lower-grades gliomas (LGG,grades II and III) andglioblastoma (GBM, grade IV).Gliomas are surrounded by pool of pro inflammatory cytokines, chemokine and growth factor, particularly review the tumorigenic effects of central nervous system one of this inflammatory cytokines is Interleukin-1ß (IL-1ß ) which play a crucial role in gliomas pathophysiology.

**Aims of the study:** This study aimed to amplify IL-1ß gene and detect -5511, rs371339015 and rs376341819 SNPs in gliomassubtypes among Sudanese patients using PCR and Sanger sequencing.

**Material and methods:** The study was conducted at the National Center for Neurological Sciences during the period from May to September 2022, Khartoum Sudan. From all gliomas patientsduring the above mentioned period, tissue samples were collected and processed for DNA extraction, PCR and further Sanger sequencing

**Results:** In this study, the most common affected agegroup was 31- 40 years, supratentorial location was seen in more than half of the patients and the astrocytoma grade 1 was detected in 80.9%.

In astrocytoma grades I, the most frequent mutation was C >A in 28.7% and A > C in 19%.

C>T mutation was present in gliomasgrade I, II and III.

**Conclusions:** In this study, C>T was the most encountered mutation in astrocytoma grades.

**Key words:** Interleukin-1ß, DNA, PCR

## INTRODUCTION:

Gliomas are the most prevalent type of primary intracranialtumors, representing 80% of all brain neoplasms,[1]Internationally Approximately 1,000,000 new patients are diagnosed with gliomas[2]Although gliomas constitute less than2% of all new cases of diagnosed cancers, these are often associatedwith substantial mortality rates in patients, [3].

More than 250 000 new cases of primary malignant brain tumors are diagnosed annually worldwide, 77% of which gliomasare more common.Little is known about the etiology of brain neoplasm which is usually in curable, Gliomas account for >70% of all primary brain tumors, the most common (65%) and most malignant type are gliomas, but no underlying cause has been identified for the majority of primary brain tumors, the only established risk factor being exposure to ionizing radiation [4].

Gliomas is more common localized in the supratentorial compartment, the rest location of gliomasin the brainstem and cerebellum. Macroscopically gliomas are quit heterogeneous featuring multifocal hemorrhage, necrosis, cystic and gelatinous areas[5]. The main types of gliomas are: astrocytoma,oligodendrogliomas and pilocystic astrocytoma[6]. reported that, gliomas cells without self-renewal capability in standard conditions could also contribute to gliomas malignancy when cytokines, such as IL-1β and TGF-β, are present in the tumor environment.

Interleukin-1ß gene is a major pro-inflammatory cytokine that triggers a number of malignant processes by activating various cells to up-regulate key molecules that drive oncogenic events. Elevated levels of IL-1ß were observed in a panel of GBM cell lines, including CCF3 and U87MG, and in human GBM tumour specimens [7]. Significant association of the IL-1B –511C/T polymorphism with cancer was detected in IL-1β -511T allele showed liability include increased cervical

cancer risk, established a protective role in the development of hepatocellular carcinoma and also observed improved blood cancers [8,9].

## MATERIAL AND METHODS

This was cross sectional study, done at the National Center for Neurological Sciences, Khartoum Sudanduring the period from May to September 2022. This study included 21 gliomaspatients operated at the National Center of Neurological Sciences during the period of this study.The diagnosis was confirmed radiologically and histologically as having gliomas, all tissue samples were classified according to WHO guidelines (2017 of Central Nerves System). The tissue sample were taken in sterile containers, and then processed for DNA extraction and Sanger sequencing.

The clinical and demographic data wereanalyzed using Statistical Package for Social Sciences (SPSS) version 16, frequencies and cross tabulations were obtained by using descriptive statistical methods. The sequencing data was analyzed using different bioinformatics programs and online databases (BioEdit, NCBI, Ensemble and Mutation Taster).BioEdit program was used for sequence multiple alignments, the reference sequence of IL1ßgene was retrieved from NCBI and Ensemble databases.

The ethical approval was obtained from the National Center for Neurological Sciences; personal data were collected from database office at NCNS by using standardized non self-questionnaire as well as hospital and medical record.

### DNA extraction

Genomic DNA was extracted according to guanidine chloride method. Each tumor tissue was minced using surgical blade into small pieces, then incubated in a mixture of 20µl of proteinase K, 100µl of 10% SDS, and 800 µl of STE buffer, then the tubes were incubated at 65ºC overnight.After incubation, protein was precipitated by adding 6 M sodium chloride, after this step, the tubes were placed in the refrigerator at 4ºC for 15 minutes and then centrifuged at 18000 rpm for 20minutes,following this step, 500µl of the supernatant wastransferredto a new clean and dry eppendrofftube. After that, 350µL of 8M of guanidine chloride and 150µl of 0.49 M ammonium acetate were addedand then incubated at room temperature for 90 minutes, after incubation,500µl from pre-chilled chloroform was added, and then the tubes werecentrifuged at 12000 rpm for 5 minutes. After centrifugation, the upper layerwhich contains DNAwas transferred to new clean tube, and then 800µl of chilled ethanol was added, the tubes were incubated at -20ºCforovernight to precipitate DNA.The next day the tubeswere centrifuged at 12000 rpm for 5minutes. The supernatantwas discarded and washed with 400µl of 70% ethanol, vortex and centrifuged at 7000rpmfor 5 minutes, then the supernatant was pour off and the pallet was allowedto dry by air.Finally, 50 µl of deionized water was added to elute DNA.The extraction step was followed by PCR, which was performed to amplify the target sequences of IL1ß gene using 5`- CCCTTTCCTCCTCTCTGAGC-3`forward and 5`-GCCTTCTTTGTTTTGTCTC-3` reverse primers

### PCR and Sanger Sequencing

The polymerase chain reaction was used to amplify the specific segment of IL1ß (434 bp). For each 2µl of DNA, 4µL PCR master mix, 1.5µl from each primer, 0.2µl magnesium chloride, 0.2µl taq polymerase and 14µl distilled water were added, and then PCR reaction was initiated by denaturation step at 95ºC for 10 minutes, followed by 30 cycles of 95ºC for 30 seconds, 58ºC for 30 seconds, 72ºC for 1.5 mint and final elongation step at 72ºC for 7 minutes.

The PCR products were then separated in 2.5% agarose gel electrophoresis and visualized under UV light. Furthermore, five PCR products (10 reactions) were sent to MacrogenEuropCompany (Amsterdam 1105 BA) for Sanger sequencing.

## RESULTS

### Demographic results

In this study, the distribution of gender showed that, male were 13constituted 61.9 % and female were 9 constituted 38.1%, (Table : 1). The most common age group was ranging from 31- 40 years (28.5%), followed by age group 21-30 years in 23.6%, while the age group >60 years was detected in 4.67%, P-value of goodness of fit test =0.000 (Table: 1).

Regarding the tumor site, supratentorial was detected in 57.1%, intratentorial in 42.6% (Table: 2).

### Subtypes results

The distribution of gliomas subtype showed that, Astrocytoma was detected in 81.0% of the patients, followed by GBM in14.2%. (Table: 2).

In this study, Astrocytoma grade I was detected in 57.1% of the patients followed by Astrocytoma grade IIandIII (14.3% each) (Table: 2).

The distribution of astrocytoma was found higher in male, pilocytic astrocytoma present only in female, (Table: 2).

Table 1: the frequency of gender and age groups in gliomas patients

| Demographic result | | Frequency | Percent |
|---|---|---|---|
| Gender | Male | 11 | 52.4 |
| | Female | 10 | 47.6 |
| | Total | 21 | 100.0 |
| Age groups in gliomas | <10 | 2 | 9.5 |
| | 11-20 | 3 | 14.3 |
| | 21-30 | 5 | 23.8 |
| | 31-40 | 6 | 28.6 |
| | 51-60 | 4 | 19.0 |
| | >60 | 1 | 4.8 |
| | Total | 21 | 100.0 |

Table 2: the frequency of tumor site, gliomas subtypes and grades in gliomas patients

| Clinical result | | Frequency | Percent |
|---|---|---|---|
| Tumors site | Supratentorial | 12 | 57.1 |
| | International | 9 | 42.9 |
| | Total | 21 | 100.0 |
| | Astrocytoma | 17 | 81.0 |
| Gliomas subtype | Pilocystic astrocytoma | 1 | 4.8 |
| | GBM | 3 | 14.3 |
| | Total | 21 | 100.0 |
| Gliomas grades | astrocytoma I | 12 | 57.1 |
| | astrocytoma II | 3 | 14.3 |
| | astrocytoma III | 3 | 14.3 |
| | IV | 3 | 14.3 |
| | Total | 21 | 100.0 |

**Molecular results**

In this study, positive PCR results and sequence alignment were displayed in figures 1 and 2, and distributions of IL-1ß gene mutations in gliomas were displayed in table 3.

Cross tabulation betweengliomas subtypes and mutationsshowed that, C>T was detected in 42% of astrocytoma followed by A>C in 19%, deletion Cin 14% and G>Ain 4.7%.In this study Pilocystic astrocytoma revealed only one mutation G>A in 4.7%, T>G was detected only in GBM 14.2%, (Table: 4).In astrocytoma grades I the most common mutation was C>A in 28.7% followed byA>C in 19%. C>T mutationwas detected in all types of astrocytomagrades (I, II and III), while grades IV (GBM) revealed only one mutations T>G (Table: 5).

Figure 1: show 434 bpof IL1ß gene detected with gel electrophoresis

Figure 2: shows multiple sequence alignment using Bio-Edit.

Table 3: Distribution of IL-1ß gene mutations in gliomas

| Mutation | Frequency | Percent |
|---|---|---|
| C > T | 9 | 42.9 |
| Deletion C | 3 | 14.3 |
| G > A | 2 | 9.5 |
| T > G | 3 | 14.3 |
| A > C | 4 | 19.0 |
| Total | 21 | 100.0 |

Table 4: cross tabulation between glioma subtypes and mutations result

| | | Distribution of the Mutation | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | C > T | Deletion C | G > A | T > G | A > C | |
| Distribution of Gliomas subtype | Astrocytoma | 9 | 3 | 1 | 0 | 4 | 17 |
| | Pilocystic astrocytoma | 0 | 0 | 1 | 0 | 0 | 1 |
| | GBM | 0 | 0 | 0 | 3 | 0 | 3 |
| Total | | 9 | 3 | 2 | 3 | 4 | 21 |

Table 5: cross tabulation between astrocytoma grades and mutations

| | | Distribution of the Mutation | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | C > T | Deletion C | G > A | T > G | A > C | |
| Distribution of Gliomas grades | astrocytoma I | 6 | 2 | 0 | 0 | 4 | 12 |
| | astrocytoma II | 2 | 1 | 0 | 0 | 0 | 3 |
| | astrocytoma III | 1 | 0 | 2 | 0 | 0 | 3 |
| | IV | 0 | 0 | 0 | 3 | 0 | 3 |
| Total | | 9 | 3 | 2 | 3 | 4 | 21 |

## DISCUSSION

Populations based studies consistently demonstrate that incidence of gliomas varies significantly by sex, and most gliomas histology occur with a 30–50% higher incidence in males, and this male preponderance of glial tumors increases with age in adult gliomas,[10]. In addition to this, several studies have attempted to estimate the influence of lifetime estrogen and progestogen exposure on gliomas risk in women. Of these one concluded that, male predominance in incidence occurs broadly across multiple cancer types and is also evident in cancers that occur in pre-pubertal children and in post-menopausal adults[11].

It is known that, the hormonal factors play important role in the increase the incidence of gliomas is present about 1.5 times greater in men than women. In the United States the male excess of gliomas deceptive even during childhood and adolescence rises with age, And the persistence of sex difference across the ethnic groups and in international comparisons suggests that intrinsic rather than environmental factors that differ in men and women, protective effect of female hormone to deleterious effect mediated by male hormones. In the present study, our finding that males were more affected by gliomas than females. Moreover, Gliomas can occur at any age,with different incidence and grading at several ages the lowgrade gliomas present in the mostcommon brain tumor in children, while the high grade gliomas morecommon in the adults[12].In this current study, which agree with the fact thatCancer incidence generally increases with age, regarded as important factor related to the prognosis of gliomas patient.

Brain tumor represent in the regions of the world in Central and South America at different countries with incidence and mortality was prominent in Brazil, Colombia, Cuba and Uruguay than in the remaining countries[13]. and this highlight the distribution of gliomas among these countries, our results in this current study, dente the distributions of gliomas among different Sudanese states, despite most of our patients are coming from the capital of Sudan, however, big data may be needed for analysis. Gliomas is found in the supratentorial areas of the brain (cerebral hemispheres and midline structures above the tentorium) were most frequent in adult, while subtentorial (brainstem and cerebellum) tumors were more common inyoung children than in adolescents and adult [14].On this current study mostof the tumors were located in the supratentorial site of the brain.

The Word Health Organization guideline for classifying malignant gliomas were based on histologic feature and more subtypes are classified according to grades and molecular characteristics, in which several morphologic subtypes corresponded to the general appearance of the tissue origin: astrocytoma, oligodendroglioma and mixed oligodendroglioma.

On histologic a criterion WHO grades I and II gliomas are recognized as low- grade gliomas and III and IV are considered high grade gliomas in individual [15]. On this current study which shown the most frequent sub type of gliomas is astrocytoma and grade I. Moreover, the mechanism of IL-1ß secretion can be might by several pathways like primary cellsor cell lines, and cell types (macrophage, fibroblast, neutrophils); activation that induced cell death [16].

Interleukin-1 beta was released through the vesicles or membrane permeability,Pro-IL-1ß and

IL-1ß are localized in the cytoplasm and a fraction is sequestered in vesicles identified as endosomes/ lysosome through unidentified mechanism, part of lysosomal IL-1ß is targeted for degradation, while a fraction is saved for further exocytosis and secretion through fusion with the plasma membrane [17].Interleukin-1 beta play vital role for autophagosomes fuse with lysosomes to proteotickallydegrade their content. In this context it has been reported that IL-1ß can localize between the two layers of autophagosomes, [18]. Autophagosomes also fuse with IL-1ß contenting endosomes toundergo exocytosis and IL-1ß release out of cell, lysosome for degradations of their content withplasma membrane to form and release exosomes, [19].The most important enzymeinvolved in IL-1ß maturationremains caspase-1 is the most proteases that can fully activate IL-1ß, caspase-1activations occurs via employment to multi protein complex calledinflammasome the intracellular composed of receptor and adapter [20].Interleukin-1 beta hasbeen shown play a role in unregulated in many solid tumors including melanoma, in melanomakeratinocyte secrete IL-1ß,[21]. in Colon Cancer the high amount of IL-1beta and IL-1alphawere detected in murineadenomatous polyposis, colon cancer model by using the disruption of IL1-R1on different cell type due to Autophagosomes process, [22].

in lung cancer IL-1ß, was shown to promote carcinoma by repressing miR-101 expressionthrough a cyclooxygenase 2(COX2)/HIF1 pathway[23].In Breast Cancer IL-1 is up regulated in breast neoplasm initiation and development[24].while IL-1R and IL-1β variations have also been related to breast tumorigenesis[25].

Furthermore, in the response of gliomas IL-1ß is produced and secreted by different cell types like the immune cells, fibroblasts, or cancer cells ,However the mechanisms of IL-1ß production most widely in immune cells particularly in myeloid cells such as macrophages [26]. The production of IL-1ß requires two signals specifically priming and cleavage [27].Priming resembles to the transcription of IL-1ß gene, and induced mainlyby activation of the toll-like- receptors (TLRs),

namely lipopolysaccharides. TLRs and IL-1receptor 1(IL-1R1) adaptor protein and differentiation primary response, [28].

The intracellular domain which go to activates interleukin-1 receptor associated kinase and the tissue necrotic factor receptors (TNFR) associated factor 6(TRAF6) Pathway,TNFR workers TNFR1 associated death domains (TRADD) which activate the TRF2\5 andreceptor interacting protein 1 (RIP1) Pathway, All these signal cascades able to activate a nuclearfactor kappa light chain which is enhancer activate B-cells (NF-Kb). Hypoxia is important event within the tumor; because the hypoxia induced factor -1 (HIF1) was shown to regulate IL-1ß transcription.

Finally single nucleotide polymorphisms (SNPs) in IL-1ß gene or promoter can affect IL-1ß transcription by inhibiting the fixation of transcription factor described above by allowing the fixation of repressor factor,After the transcription/ translation the pro- IL-1ß is produced as an inactive 31kDa protein thatneed to cleaved in to 17kDa IL-1ß to become active [29].Polymorphisms on the IL-1ß gene can be associate with variation in IL-1ß expression for

example IL-1ß-511 C > T (rs16944) , [30].IL-1ß-31 C > T (rs1143627) associate with cervical and gastric cancer [31].IL-1ß-1464 G > C (rs114623) associate with renal carcinoma[32].in Lung Cancer The level of IL-1β in bronchoalveolar lavage is higher in patients with lung cancer than in patients with benign lung diseaseIL-1β was shown to promote carcinoma by repressing miR-101 expression through a cyclooxygenase 2 (COX2)/HIF1α pathway [33].

Ovarian cancer cells communicate with cancer-associated fibroblasts (CAFs) through IL-1β to downregulate p53 expression in these cells to generate a pro-tumorigenic inflammatory microenvironment[34]. in Prostate Cancer High-score values for IL-1β or low-score values for interferon (IFN)β (both measured by immunohistochemistry (IHC)) were significantly associated with biochemical recurrence of prostate cancer ,[35].InBRCA1 (breast cancer 1) 185delAG mutation in ovarian epithelial cells allows IL-1βexpression [36], and For IL-1β-1464 G > C (rs1143623), the G allele has decreased binding ability, suggesting weaker promoter activity[37].

In our results present the deletion C, C >T, G > T, T > G and A > C effect protein. See the effect of protein in inflammatory response.

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## Conflict of interest:

No conflict of interest.

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## Author contribution:

All authors were equally contributed.

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