Original Article

Molecular Study of Iraqi Patients with Brain Tumors Infection with *HTLV-1*

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Abstract

Background: *HTLV-1* is associated with the chronic, persistent infection of T cells, which can result in neoplastic or inflammatory diseases; *HTLV-1* indirectly damages the central nervous system to cause associated neuropathies starting with the virus crossing the blood–brain barrier, then enters and infects the cells of the central nervous system. **Objectives:** The study aimed to determine the percentage of *HTLV-1* and estimate the genetic polymorphism of tumor necrosis factor-alpha (TNF-α), Killer-cell immunoglobulin-like receptor (KIR), and interleukin-1 receptor antagonist (IL-1Ra) genes in Iraqi patients with brain tumors and control groups. **Materials and Methods:** Case–control research has been carried out on (100) brain tissues enrolled in the current research, including (75) randomly selected brain tumors with different types and grades and (25) autopsies included as baseline control obtained from dead cases. The specimens were collected during the period from January 2022 to September 2022. Each participant provided tissue samples, which were then stored frozen at −80°C for RNA extraction and used in quantitative real-time polymerase chain reaction (PCR) and conventional PCR tests to detect the *HTLV-I*, TNF-α, KIR, and IL-1Ra genes. **Results:** Of 75 brain tumor specimens, 50 (66.7%) had a viral infection, whereas 25 (33.3%) specimens without a viral genome were detected in this study. According to the real-time PCR result for the (50) specimens with viral genome, the rate of *HTLV-I* infection was 42% (21 of 50). In contrast, the percentage of negative results was 58% (29 of 50). Gene polymorphisms of the TNF-α-G>T (rs1800629) and *KIR2DS2*-A>T (rs78713511) genes have been associated with risk in the Iraqi patient with brain tumors, with significant differences ($P < 0.05$) in the frequency of genotype distribution of the polymorphism between patients and the control group. While the genotype distribution of the *IL-1RN* gene polymorphism between the patient and control groups was statistically nonsignificant for the 329C>G (rs2234679) and 376C>T (rs16065) variants, respectively. **Conclusion:** Polymorphism of TNF-α and KIRs in Iraqi patients with brain tumors could point to that act as a risk factor in the pathogenesis of idiopathic brain tumors. Also, indicate that IL-1Ra might be a protective factor in Iraqi patients with brain tumors. The following conclusion leads to the idea that *HTLV-1* acts as a cofactor in patients with brain tumors.

Keywords: Brain tumor, gene polymorphism, *HTLV-1*, KIR, RNA–RT-PCR

Introduction

Brain tumors are made up of abnormal growth of tissue due to the uncontrolled multiplication of cells, and this tissue has no physiological function inside the brain.[1] In addition to tumor cells, the microenvironment of brain tumors includes nonneoplastic cells such as astrocytes, microglial cells, macrophages, endothelial cells, and lymphocytes. Moreover, tumorigenesis and tumor invasion depend on communications between cancer and nonneoplastic cells.[2]

HTLV-1 is a highly oncogenic virus that possesses regulatory proteins that can alter host cellular signaling pathways and cell cycle checkpoints to promote clonal proliferation and the long-term persistence of infected cells. Additionally, *HTLV-1* evades immune defenses by limiting its replication by regulating viral gene expression.[3] The oncogenic

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potential of *HTLV-1* is mediated by viral gene products that interact with host proteins to alter their function and promote viral infection and persistence. Several mechanisms involving Tax and *HTLV-1* basic leucine zipper factor (HBZ), the viral regulatory proteins, are crucial for *HTLV-1*-induced oncogenesis.[4] Regardless of viral transcription, Tax is a transactivator of oncogenic pathways, and HBZ can change the immunophenotype of infected immune cells, enhancing their proliferation.[5] During the infection, Tax has an essential role in the transformation process induced in *HTLV-1*–infected cells. Tax-induced alters in gene expression, dysregulated genes involved in cell cycle regulation, cell survival, and cell proliferation, as well as cytokines and cytokine receptors, and exploit host cellular signaling pathways through interaction with multiple cellular factors.[6] In addition, HBZ is crucial for the cellular transformation and oncogenesis of *HTLV-1* by regulating viral transcription and modulating multiple host factors and cellular signaling pathways that contribute to cancer progression.[7] The low immunogenicity of HBZ probably facilitates *HTLV-1*–infected cells to avoid host immune system surveillance by suppressing the classical nuclear factor-κB pathway, which decreases the expression of some genes associated with innate immunity and inflammatory responses and then contributes to *HTLV-1*–mediated oncogenesis.[8] With a focus on their potential significance in survival, numerous studies have investigated the impact of single nucleotide polymorphisms (SNPs) in genes associated with inflammation on the risk of developing glioma.[9]

Killer-cell immunoglobulin-like receptors (KIR) play an essential role in the signaling of natural killer (NK) cells; moreover, they are involved in the activity of CD8+ T cells.[10] Due to the importance of NK cells in tumor immunity and their role in human leukocyte antigen (HLA) recognition, genetic differences in KIR and HLA have been hypothesized to interfere intensely with the risk of developing cancer.[11]

Interleukin-1 receptor antagonist (IL-1Ra) is a naturally occurring competitive inhibitor of IL-1–induced pro-inflammatory activity.[12] IL-1Ra has been identified in neurons that can block pro-inflammatory actions by competing with IL-1β for IL-1R binding. Thus, IL1Ra exerts potent anti-inflammatory and neuroprotective actions in the brain and other tissues.[13]

Tumor necrosis factor-alpha (TNF-α) is a principal player among pro-inflammatory cytokines and has both tumor-promoting and suppressing roles in the tumor microenvironment; endogenous TNF-α is continually produced by the tumor cell, promoting tumor angiogenesis and progression. In the central nervous system, "neuro-inflammation" refers to cellular and inflammatory reactions of vascularized neuronal tissue involving activation of resident brain cells (astrocytes, microglia, and endothelial cells), recruitment of blood-derived leukocytes such as neutrophils, lymphocytes, and macrophages, as well as a wide range of humoral factors.[14-16].

Materials and Methods

Study design

In this case–control study, 100 tissue specimens were obtained from 75 confirmed patients with brain tumors in Teaching Hospital in Baghdad Medical City from January 2022 to September 2022. The autopsies used in this study were obtained from deceased individuals who had non-neurological reasons of death. These individuals were selected as control cases due to their normal brain histology. The patient's brain tumor was diagnosed by an oncologist. From various brain regions, a piece with (0.8 mm) in diameter was taken and frozen at (−80°C) until the nucleotides were extracted. The tissue is cut into small pieces and gridding to achieve quick lysis and high yields. Next, the proper amount of tissue is measured and placed in a 1.5 mL microfuge tube to prepare for the genome.

Extraction of human genomic DNA from the specimens

Genomic DNA was extracted and purified using (G-spin Total DNA Extraction Mini Kit, Intron/Korea) according to company instructions.

Extraction of the viral nucleic acid from the specimens

RNA was extracted from tissue samples using a specific viral RNA extraction kit (Patho Gene-spin DNA/RNA Extraction Kit, Intron/Korea), as a preliminary step to amplify the target *HTLV-1*–RNA, according to the manufacturer's instructions.

Detection of *HTLV-1* by real-time polymerase chain reaction

Real-time PCR (qPCR) is based on two major processes: Firstly, isolation of viral genome (DNA\ RNA) from specimens, and secondly, real-time amplification for each sample. PCR amplification was performed with SYBR Green PCR Mix, GoTaq 1-Step RT-qPCR System (Promega, Madison, WI, USA). The primers sequence was mentioned in Table 1 to detect the *HTLV-1* genome as described previously.[17] The conditions of amplification reactions were initiated with reverse transcription at 45°C for 15 min, followed by GoTaq DNA polymerase activation at 95°C for 10 min, 40 cycles of denaturation at 95°C for 10 s, annealing at 60°C for 10 s, and extension at 72°C for 30 s.

Detection of genes polymorphism by polymerase chain reaction

PCR amplification was done using a conventional thermal cycler and was made according to the conditions in Table 2.

The sequences of the specific primers are illustrated in Table 1.

Table 1: Primer sets used to detect *HTLV-1*, TNF-alpha, KIR, and IL-1Ra genes polymorphism

Gene	Sequence (5′-3′)	Product size (bp)	Source/origin	References
HTLV-1 LTR-gag	F-ACAGTTCAGGAGGGGGCTC	438 bp	IDT\USA	Van Tienen *et al*.[17]
	R-TAGGGAATAAAGGGGCGCTC			
TNF-alpha	F-GCTCATGGGTTTCTCCACCA	528 bp	IDT\ USA	Designed
	R-AGGGGAAATGGAGACGCAAG			
KIR	F-GAGACAGACACCAGCAAGGG	530 bp	IDT\ USA	Designed
	R-AGACTGACTTGCTGAGGTTTGT			
IL-1Ra	F-CCCAGCTCAGTTCTCTGCAT	477 bp	IDT\ USA	Designed
	R-AAATGTCAAGCGCATGGAGC			

Table 2: PCR amplification conditions for detecting TNF-alpha, IL1Ra, and KIR genes

Gene	Initial denaturation	Denaturation	Annealing	Extension	Final extension	No. of cycles
TNF-alpha	95C0/5 min	95C0/1 s	57 C0/45 s	72 C0/1 min	72 C0/5 min	40
KIR	95C0/5 min	95C0/1 min	56.5 C0/45 s	72 C0/ 2min	72 C0/5min	40
IL1Ra	95C0/5 min	95C0/1 s	58 C0/45 s	72 C0/1 min	72 C0/5min	40

Ethical approval

The study was conducted according to the ethical principles in the Declaration of Helsinki. It was done with the patient's verbal and analytical approval before taking the sample. To get this approval, the study protocol, subject information, and consent form were reviewed and approved by a local ethics committee according to document number M221205 on December 6, 2022.

Result

Of 75 brain tumor specimens in this study, 50 (66.7%) were found to have a viral infection. A total of 25 brain tumor specimens without a viral genome were detected in this study, accounting for 33.3% of the total number of patients, according to the protocol of viral genome extraction intron/Korea company. CAT.NO 17151, as well as Nanodrop, to estimate the concentration and purification of the viral genome.

The positive result according to q RT-PCR shows 42% (21 of 50 cases) as positive, whereas 58% (29 of 50 cases) as negative, as in Figure 1A and B and Table 3. The difference between patient groups was statistically significant.

TNF-α gene PCR detection was performed under optimal conditions using a specific primer as shown in [Figure 2]. KIR gene PCR detection was performed under optimal conditions using a specific primer as shown in [Figure 3].

Genotyping of TNF-alpha polymorphism

To summarize the results obtained from the sequenced 528 bp fragments, the detailed positions of the observed variations are described in the NCBI reference sequences. Results showed that TNF-α gene polymorphism appeared in three genotypes, which were G\G, G\T, and T\T. The distribution of different genotypes was 40%, 53.3%, and 6.7%, respectively, in patients with brain tumors and 10%; 80%, and 10%, respectively, in the control group. The difference in the frequency of genotype distribution of the polymorphism between patients and the control group was statistically significant [Table 4].

Moreover, by reviewing the dbSNP details of the identified 349G>T, it was found that this detected SNP was previously known as it was deposited as rs1405990400. In the most recent update of this SNP, it is known that this SNP is a missense SNP located in the coding sequences of the targeted *TNF-alpha* (*TNF-α*) gene, as detailed in Table 4. This SNP caused an amino acid substitution of glycine to glutamine in position 22 (NP_000585.2:p.Gly22Glu).

In addition, nucleotide sequences of TNF-α of our outcome for 10 samples were submitted in NCBI as a new recording, with the following accession numbers: BankIt2620154 Seq1 OP380425, BankIt2620154 Seq2 OP380426, BankIt2620154 Seq3 OP380427, BankIt2620154 Seq4 OP380428, BankIt2620154 Seq5 OP380429, BankIt2620154 Seq6 OP380430, BankIt2620154 Seq7 OP380431, and BankIt2620154 Seq8 OP380432.

Genotyping of KIRs polymorphism

To elucidate the results obtained from the sequenced 530 bp fragments, the exact positions of the observed variations are detailed in the NCBI reference sequences. The results revealed that DNA polymorphism distribution according to A\T, A\A, and T\T was 56.7%, 40%, and 3.3%, respectively, in patients with brain tumors and 15%, 75%, and 10%, respectively, in the control group. Statistical comparison of these polymorphisms revealed significant differences ($P < 0.05$) in Table 5.

Moreover, by reviewing the dbSNP details of the identified 225A>T, it was found that this detected SNP was previously known as it was deposited as rs78713511. In the most recent update, this SNP, known as a missense

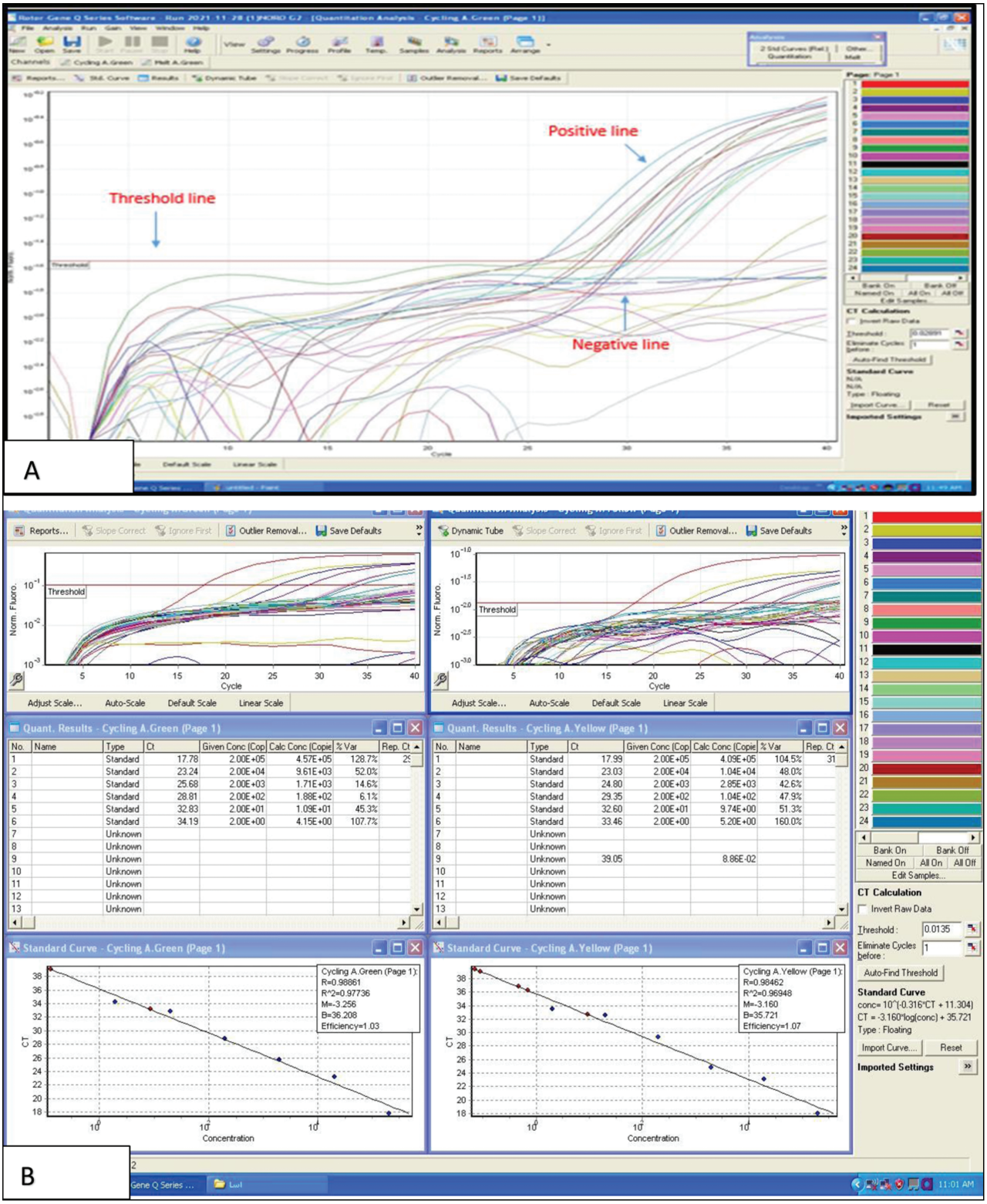

Figure 1: Detection of the *HTLV-1* genome by real-time PCR. (A) Cycle threshold of *HTLV-1 genome* that showing in many colored lines after 45 cycles in real-time PCR. (B) Qualtatiative and standard curve for detection of *HTLV-1* by RT-PCR

SNP, located in the coding sequences of the targeted *KIR2DS2* gene, as detailed in Table 5. This SNP caused an amino acid substitution of phenylalanine to tyrosine in position 66 (NP_056952.2:p.Phe66Tyr).

Additionally, nucleotide sequences of KIR of our results for eight samples were submitted in NCBI as a new recording, with the following accession numbers: BankIt2619196 Seq1 OP373670, BankIt2619196 Seq2 OP373671,

BankIt2619196 Seq3 OP373672, BankIt2619196 Seq4 OP373673, BankIt2619196 Seq5 OP373674, BankIt2619196 Seq6 OP373675, BankIt2619196 Seq7 OP373676, and BankIt2619196 Seq8 OP373677.

Genotyping of IL-1Ra polymorphism

To summarize the results obtained from the sequenced 477 bp fragments, the detailed positions of the observed variations are described in the NCBI reference sequences. The results of IL1Ra gene (rs2234679) showed that the genotype distribution according to C\C, C\G, and G\G was 70%, 6.7%, and 23.3%, respectively, in patients with brain tumors, while in the control group was 85%, 5%, and 10%, respectively. The results of IL1Ra gene (rs16065) showed that the genotype distribution according to C\C, C\T, and T\T was 83.3%, 13.3%, and 3.4%, respectively, in patients with brain tumors, while in the control group was 80%, 15%, and 5%, respectively. The difference in frequency of genotype distribution of the polymorphism between patients and control groups was statistically nonsignificant in Table 6.

Moreover, concerning the 329C>G and 376C>T, the dbSNP details showed that the identified SNP was found to be previously known as rs2234679 and rs16065, respectively. The detected SNPs were located in the intronic sequences of the targeted *IL1RN* gene, as detailed in Table 6.

Additionally, nucleotide sequences of IL-1Ra of our results for 10 samples were submitted in NCBI as a new recording, with the following accession numbers: BankIt2618097 Seq1 OP351527, BankIt2618097 Seq2 OP351528, BankIt2618097 Seq3 OP351529, BankIt2618097 Seq4 OP351530, BankIt2618097 Seq5 OP351531, BankIt2618097 Seq6 OP351532, BankIt2618097 Seq7 OP351533, BankIt2618097 Seq8 OP351534, BankIt2618097 Seq9 OP351535, and BankIt2618097 Seq10 OP351536.

Table 3: Positive signals of *HTLV-1* using qRT-PCR in samples from patients with brain tumors

HTLV-1 genome	No.	%	Chi-square (P value)
Positive	21	42	P = 0.04 Sign. (P > 0.05)
Negative	29	58	
Total	50	100	

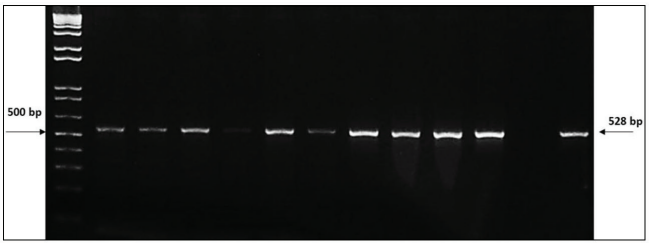

Figure 2: PCR amplification with specific primers for *TNF-α* gene on 1.5% agarose gel electrophoresis, Tris/Borate/EDTA (TBE) 1×, at voltage 75 for 60 min

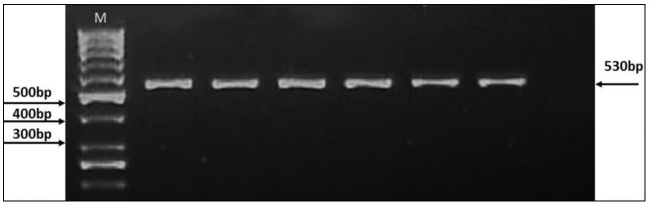

Figure 3: PCR amplification with specific primers for *KIR* gene on 1.5% agarose gel electrophoresis, TBE 1×, at voltage 75 for 60 min

Spearman's rho statistical testing of age, types of brain tumors, *HTLV-1*, and SNPs of TNF-α KIRs and IL-1Ra to evaluate the studied markers in study population groups

The relationship between *HTLV-1* and SNP of TNF-α, KIRs, and IL-1Ra in brain tumors showed a highly significant correlation ($r = 0.739$*, $P = 0.04$; $r = 0.834$*, $P = 0.03$, and $r = 0.969$**; $P = 0.02$), respectively as illustrated in Table 7.

Table 4: Genotyping of *TNF-alpha* gene (528 bp) in comparison with the NCBI referring sequences (GenBank acc. no. NC_000006.12)

Zygosity status	Brain tumors	Control	Position in PCR fragment	Position in the reference genome	OR (95%)	SNP type	Sig.	Variant summary
	No. (%)	No. (%)						
G/T	16	2	349	31575806	1.26 (0.46–3.43)	Missense variant	0.03	NC_000006.12; 31575806G>T (rs1405990400)
	53.3%	10%						
G/G	12	16	349	31575806	1.53 (0.55–4.18)		0.04	NC_000006.12; 31575806G/G
	40%	80%						
T/T	2	2					0.56	
	6.7%	10%						
Totals	30	20						
Allele								
T	62	20			1.32 (0.72–2.41)		0.029	
G	38	80						

OR: odds ratio

Table 5: Genotyping of *KIR2DS2* gene (530 bp) comparison with the NCBI referring sequences (GenBank acc. no. NC_000019.10)

Zygosity status	Brain tumors	Control	Position in PCR fragment	Position in the reference genome	OR (95%)	SNP type	Sig.	Variant summary
	No. (%)	No. (%)						
A/T	17	3	225	54742106	3.85 (1.46–10.17)	Missense variant	0.02	NC_000019.10;54742106A>T (rs78713511)
	56.7%	15%						
A/A	12	15	225	54742106	2.45 (0.88–6.80)		0.047	NC_000019.10;54742106A>T
	40%	75%						
T/T	1	2					0.00	
	3.3%	10%						
Total	30	20						
Allele								
T	61	32			2.56 (1.44–4.54)		0.02	
A	39	68						

OR: odds ratio

Table 6: Genotyping of IL-1Ra gene (477 bp) comparison with the NCBI referring sequences (GenBank acc. no. NC_000019.10)

Zygosity status	Brain tumors	Control	Position in PCR fragment	Position in the reference genome	OR (95%)	SNP type	Sig.	Variant summary
	No. (%)	No. (%)						
rs2234679								
C/C	21	17	329	113118007	1.23 (0.32–0.85)	Intron variant	0.65	rs2234679
	70%	85%						
C/G	2	1	329	113118007	1.06 (0.26–0.73)	Intron variant	0.54	rs2234679
	6.7%	5%						
G/G	7	2	329	113118007	1.92 (0.15–0.65)	Intron variant	0.76	rs2234679
	23.3%	10%						
Total	30	20						
Allele								
C	80%							
G	20%							
rs16065								
C/C	25	16	376	113118054	1.33 (0.28–0.78)	Intron variant	0.58	rs16065
	83.3%	80%						
C/T	4	3	376	113118054	1.53 (0.21–0.68)	Intron variant	0.62	rs16065
	13.3%	15%						
T/T	1	1	376	113118054	1.18 (0.23–0.79)	Intron variant	0.63	rs16065
	3.4%	5%						
Total	30	20						
Allele								
T				55%				
C				45%				

OR: odds ratio

However, there was no significant correlation among types of brain tumors and SNPs of TNF-α, KIRs, and IL-1Ra in brain tumors ($r = 0.323$, $P = 0.5$; $r = 0.432$, $P = 0.5$; and $r = 0.439$, $P = 0.5$), respectively, as illustrated in Table 7.

Discussion

According to certain theories, cytokines are crucial in the biology of brain tumors, neurodegeneration, and impaired neuronal function. Brain tumors and cytokine gene polymorphisms indicated a relationship pattern that could affect disease management and family counseling.[18]

TNF-α polymorphism of clinical isolates in patients with brain tumors

The current results of TNF-α gene polymorphism according to G\G, G\T, and T\T was 40%, 53.3%, and 6.7%, respectively, in patients with brain tumors and 80%, 10%, and 10%, respectively, in the control group. The difference in the genotype distribution frequency of the polymorphism between patients and control groups was statistically significant. This implies that patients carrying allele T of this polymorphism have about a 1.3-time chance of developing cancer compared

Table 7: Spearman's rho statistical testing of age, types of brain tumors, *HTLV-1* and SNPs of TNF-α, KIRs, and IL-1Ra to evaluate the studied markers in patients with brain tumors

Spearman's rho	*HTLV-1*	TNF-α	KIRs	IL-1Ra
Age				
R	0.123	0.986**	0.678**	0.721**
P	0.5	0.007	0.03	0.03
Types of brain tumors				
R	0.788**	0.323	0.432	0.439
P	0.009	0.5	0.5	0.5
Gender				
R	0.279	0.763*	0.743*	0.674*
P	0.6	0.02	0.03	0.04
HTLV-1				
R		0.739*	0.834*	0.969**
P		0.04	0.03	0.02

with those carrying allele G, regardless of other characteristics.

Settin *et al*.[18] found that TNF-α-308 A/A was more prevalent in malignant and nonmalignant brain cases compared with controls. Results showed that both groups' TNF-α-308 G/A was found to be significantly lower between both groups than in controls. Significant frequency higher TNF-α-308 A/A.

Waters *et al*.'s[19] TNF-α-308 SNP revealed a statistically significant association, with 39% of allele 2 carriers having an unfavorable outcome compared with 31% of noncarriers (adjusted odds ratio, 1.67; confidence range, 1.19–2.35; $P = 0.003$).

By analogy, the current results indicated that subjects carrying the TNF-α-308 GA and AA genotypes and the A allele had a higher risk of ischemic stroke (IS) development. In line with the current findings, previous reports have shown that the TNF-α-308 A allele was associated with a risk of cerebral infarction in Korean populations[20] and that North Indian subjects carrying TNF-α-308 GA and AA genotypes had a higher risk of coronary artery disease.[21] By contrast, the TNF-α-308G/A polymorphism was not associated with IS risk in the Chinese population[22] but was associated with protection against IS in East Asians.[23,24]

The fact that tumorigenesis occurs despite the presence of many tumor-associated macrophages has led to the speculation that macrophages contribute to tumor development, presumably by secreting growth signals, angiogenic factors, matrix-degrading proteinases, and immune suppressors. Macrophages and some of their secreted products, especially TNF, act as a tumor promoter, and inhibiting these inflammatory components are currently regarded as potential therapeutic tools to block tumor progression. Infiltrating macrophages represented a significant as nonneoplastic cells within malignant gliomas, which were the exclusive producers of TNF. Macrophages alter brain tumor development through a TNF-dependent process that culminates in the formation of microcysts[25]; glial cell tumors are characterized by their rapid growth and ability to infiltrate diffusely in the parenchyma.

KIR polymorphism of clinical isolates in patients with brain tumors

An important HLA class I activity is its binding to killer immunoglobulin-like receptors (KIR) expressed on the surface of NK cells. The HLA-KIR interaction may promote the inhibition or the activation of NK cell functions.[26] Genes that code for KIR present a sizeable genetic variability, resulting in different types of receptors.[27]

The results of the present study showed that DNA polymorphism distribution were DNA polymorphism distributions according to A\T, A\A, and T\T were 40%, 56.7%, and 0.00%, respectively, in patients with brain tumors and 75%, 20%, and 5%, respectively, in the control group. Statistical comparison of this polymorphism revealed significant differences. This implies that patients carrying allele T of this polymorphism have about a 2.6-time chance of developing cancer compared with those carrying allele A, regardless of other characteristics.

Gras Navarro *et al*.[28] show that the KIR2DS2 gene may identify alloreactive NK cell subsets with higher potency against GBM, independently of the repertoire of inhibitory or other activating KIRs. KIR2DS4+ NK cells were more potent against GBM than KIR2DS2−/KIR2DS4− NK cells but were not significantly more potent than KIR2DS2+ NK cells.

The KIR2DL2 gene plays a dual role in *HTLV-1* infections, improving protection while also reducing HLA class I-mediated immunity. KIR2DL2 improves immunity against *HTLV-1* by activating two cell types, NK cells and CD8+ T lymphocytes, which may lead to more effective regulation of disease progression.[29]

Different types of KIR subtypes (KIR2DL1 + 2+, KIR2DL2+C1+, KIR2DL2+C2+, KIR2DL3+C1+, KIR2DL1− or KIR2DL1+C2−, KIR2DL3− or KIR2DL3+C) were found to improve HLA class I associations during *HTLV-1* infection when the protective impact of HLA-B × 57 was assessed. These results may be associated with CD8+ T cell survival being enhanced when functional KIRs are present.[30]

Despite the importance of HLA and KIR in the anti-viral immune response, studies comparing the effects of *HTLV-1* infection and related diseases in people of different ethnic backgrounds are rare. It seems crucial to expand the analysis of SNPs in the genes of pro and anti-inflammatory cytokines in the search to identify possible haplotypes associated with the regulatory and activating functions of the immune system, given the role of cytokines in the signaling and activation of mediators of the innate and adaptive immune response.

IL-1Ra polymorphism of clinical isolates in patients with brain tumors

Increased glial activation, pro-inflammatory cytokine concentration, blood–brain barrier permeability, and leukocyte invasion are frequent occurrences after brain injury and have been documented in neurodegenerative diseases. Additionally, IL-1 receptor signaling potently stimulates the production of secondary inflammatory cytokines and chemokines such as IL-6, TNF, Kupffer cell, and granulocyte-colony stimulating factor, which ultimately indicates the central role of IL-1 in sterile inflammation.[31]

The results of IL1Ra gene (rs2234679) showed that the genotype distribution according to C\C, C\G, and G\G was 70%, 6.7%, and 23.3%, respectively, in patients with brain tumors, while in the control group was 85%, 5%, and 10%, respectively. Also, the results of IL1Ra gene (rs16065) showed that the genotype distribution according to C\C, C\T, and T\T was 83.3%, 13.3%, and 3.4%, respectively, in patients with brain tumors, while in the control group was 80%, 15%, and 5%, respectively. The results of rs16065 show that DNA polymorphism distribution according to C\C, C\T, and T\T was 83.3%, 13.3%, and 3.4%, respectively, in patients with brain tumors and 80%, 15%, and 5%, respectively, in the control group. The difference in frequency of genotype distribution of the polymorphism between patients and control groups was statistically nonsignificant.

El-Din *et al*.[32] show that these cases have shown no significant difference regarding the distribution of IL-1Ra variable number of tandem repeat (VNTR) genotype and allele polymorphism compared with controls.

Other studies, including ours, have yet to find any difference. When we carefully examined the *P* value obtained as a result of statistical analysis, IL-1Ra allele 2 homozygous genotype and frequency were not statistically different between schizophrenia patients and controls,[33,34]. Additionally, Rafiei *et al*.[35] reported that bipolar disorder (BD) patients had a higher prevalence of the IL1RN × 1/2 genotype than controls.

In a recent published case–control study, genotyping of IL-1Ra (VNTR; rs2234663), IL-1α (rs1800587), IL-1β + 3954 (rs1143634), and IL-1β − 511 (rs16944) loci revealed that three haplotypes including two SNPs of C-T (rs1800587-rs16944), T-C (rs1143634-rs16944), T-A1 (rs16944-rs2234663), and one haplotype including three SNPs of C-C-T (rs1800587-rs1143634-rs16944) was related to the BD.[36]

One of the essential mediators of the inflammatory response is cytokines, and the pro-inflammatory cytokine IL-1 has been associated with several chronic neurological disorders. It serves as the single example of a naturally occurring antagonist molecule that competes with both IL-1α and IL-1β, thus decreasing inflammatory signaling and inhibiting them from further prompting the expression of other pro-inflammatory molecules.[37] The inhibitory impact of IL-1Ra on neuronal loss suggests its potential as a beneficial therapeutic agent for the treatment of neurodegenerative illnesses.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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