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RESEARCH ARTICLE

ASSOCIATION OF GLTSCR1, ERCC4, NBN, AND XRCC1 POLYMORPHISMS WITH GLIOMA AND MENINGIOMA RISK IN A TERTIARY CARE HOSPITAL

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Abstract

A hospital-based case-control study was systematically conducted over an 18-month period, from January 2023 to June 2024. The study cohort was recruited from the Department of Neuro surgery at King George Hospital,Visakhapatnam The study included 53 histopathologically confirmed glioma cases,46 meningio ma cases,and a control group comprising 98 healthy,unrelated individuals from the same geographical region. Ethical approval was obtained from the institutio nal ethics committee,and informed written consent was secured from all partici pants prior to their inclusion in the study.Genomic DNA was isolated from peri pheral blood samples. Genotyping for the selected SNPs ERCC4 rs1800067, G LTSCR1 rs1035938, NBN rs1805794,andXRCC1 rs25487—was precisely performed using advanced Polymerase Chain Reaction (PCR) and RFLP metho dologies.Statistical analysis involved assessing genotype and allele frequencies, and calculating odds ratios (ORs) with 95% confidence intervals (CIs) under va rious genetic models (dominant, co dominant,recessive,and log additive) to dete rmine the strength and significance of associations.The study analysis revealed strong, statistically significant associations between genetic variant in GLTSCR 1,ERCC4,NBN,and XRCC1 genes and an increased risk of both glioma and me ningioma.For glioma,GLTSCR1 (OR=2.47, p=0.012) and ERCC4 (dominant OR=2.35, p=0.020) showed significant correlations. Particularly striking associations were observed for NBN(dominant OR=7.24,p<0.001) and XRCC1 (dominant OR=6.74, p<0.001), indicating substantially increased glioma risk. Importantly, similar robustand significant associations with high odds ratios an d low p values were consistently found for meningioma risk,underscoring a sha red underlying genetic susceptibility for both tumor types.Our study revealed strong, significant associations between GLTSCR1,ERCC4,NBN,and XRCC1 gene variants and increased glioma and meningioma risk . Specifically, NBN and XRCC1 showed robust links. This confirms these DNA repair gene polymo rphisms elevate brain tumor riskin the Indian population,offering potential as p redictive biomarkers for personalized therapies.

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Introduction:-

Brain tumors represent a formidable challenge in neuro-oncology, characterized by their diverse cellular origins, aggressive clinical courses, and often dismal prognoses. Among the spectrum of primary brain tumors, gliomas and meningiomas**a**re primary brain tumours that account for a significant proportion of cancer-related morbidity and mortality(1).Gliomas, arising from glial cells (astrocytes, oligodendrocytes, and ependymal cells), are notoriously infiltrative and aggressive, with glioblastoma multiforme (GBM) representing the most malignant and common form in adults, accounting for a significant proportion of primary malignant brain tumors (2).Meningiomas, conversely, originate from the arachnoid cap cells of the meninges, the protective membranes surrounding the brain and spinal cord.While predominantly benign (World Health Organization Grade I), their location, size, and potential for recurrence or malignant transformation necessitate careful monitoring and treatment (3). The global incidence of both tumor types, though varying geographically, underscores their substantial public health burden. In India, like other parts of the world, brain tumors contribute significantly to neurological morbidity and mortality, placing a unique strain on healthcare resources (4).

The etiology of both meningiomas and gliomas is complex and multifactorial, involving a convoluted interplay of genetic predisposition and environmental exposures. While ionizing radiation is a well-established risk factor for both, particularly meningiomas, most cases occur sporadically, hinting at a strong underlying genetic component (5). This notion is further supported by the identification of various germline mutations and single nucleotide polymorphisms (SNPs) associated with increased susceptibility. A critical area of investigation into this genetic predisposition lies in the realm of DNA repair mechanisms. The integrity of the human genome is under constant assault from endogenous metabolic byproducts, reactive oxygen species, and exogenous agents like UV radiation and chemical carcinogens. To counteract this relentless damage, cells are equipped with an intricate network of DNA repair pathways, including nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), and double-strand break repair (DSBR) via homologous recombination (HR) or non-homologous end joining (NHEJ) (6). These pathways collectively ensure genomic stability, prevent the accumulation of mutations, and thus safeguard against malignant transformation.

Polymorphisms within genes encoding DNA repair proteins can subtly alter the efficiency or fidelity of these crucial repair processes. While many polymorphisms are benign, those occurring in functionally important regions of DNA repair genes can lead to a reduced capacity to mend DNA damage, rendering individuals more susceptible to various diseases, including cancer (7). For instance, variations in genes likeXRCC1 (involved in BER), XPC (involved in NER), MGMT (an enzyme that directly repairs O6-methylguanine adducts), and various genes involved in DSBR pathways are frequently studied in the context of cancer susceptibility. The concept is that individuals carrying certain less efficient polymorphic variants might accumulate DNA damage at a higher rate, consequently increasing their risk of developing cancer over time.

Investigating the association of these DNA repair polymorphisms with brain tumors holds significant clinical utility, particularly in identifying individuals at higher genetic risk, potentially leading to improved screening, surveillance, and personalized prevention strategies..Differences in allele frequencies of specific DNA repair polymorphisms, as well as their interactions with local environmental carcinogens, could influence brain tumor incidence and prognosis within the Indian subcontinent (8).Understanding the associations could pave the way for risk stratification models tailored to the Indian demographic, enabling clinicians to identify high-risk individuals who might benefit from early detection protocols or targeted chemopreventive measures. Furthermore, these genetic insights refine tumor biology, guiding novel therapies and predicting treatment response. As studied, polymorphisms affecting MGMT expression are known to influence response to temozolomide in glioma patients, highlighting the direct clinical relevance of these genetic variations (1). Therefore, a comprehensive exploration of DNA repair polymorphisms in meningioma and glioma within the Indian population is not merely an academic exercise but a critical step towards enhancing precision medicine in neuro-oncology.

The present study aims to pinpoint the specific DNA repair gene polymorphisms and their frequencies linked to meningioma in our patient group. Also, identifies associations across all meningioma subtypes and evaluate if these single nucleotide polymorphisms (SNPs) can serve as future diagnostic tools.

Methodology:-

This hospital-based case-control study was conducted from January 2023 to June 2024 at the neurosurgery department of a tertiary care hospital in South India. We included 53 glioma cases, 46 meningioma cases, and 98healthy controls, all adults over 18 years, diagnosed clinically and radiologically. Patients with other tumors or those unwilling to participate were excluded. The study protocol received approval from the Institutional Ethics Committee, Andhra Medical College, and informed consent was obtained from all participants.

Diagnoses were confirmed via MRI and biopsy, with biochemical investigations**.** Patients presenting with meningioma features, meeting inclusion criteria, will provide written informed consent. Following detailed clinical assessments, 3ml EDTA blood will be collected and stored at -20°C for DNA analysis.
DNA isolation and PCR amplification for specific DNA repair gene polymorphisms performed via RFLP using athermal cycler in the Multidisciplinary Research Unit of Andhra Medical College**.** We will analyze ERCC4 rs1800067, GLTSCR1 rs1035938, NBN rs1805794, and XRCC1 rs25487**.**

Results:-

This section presents the key findings of the study, detailing the demographic characteristics of the participant groups, the specific single nucleotide polymorphisms (SNPs) investigated, and their associations with glioma and meningioma risk.

SNPs in DNA Repair Genes

Table 1 provides an overview of the DNA repair genes and the specific SNPs investigated in this study, including their types, base changes, and chromosomal locations[1].

Type of DNA Repair	Gene Symbol	Gene Name	SNP ID	Base Change	Chromosome Location
Base excision repair	XRCC1	X ray repair cross complementing gene	Rs25487	A/G	19q13.2
Double strand break repair	NBN/NBS1	Nibrin	Rs1805794	G/C	8q21
Nucleotide excision repair	ERCC4	Excision repair cross complementing group	Rs1800067	G/A	16p13.5
	GLTSCR1	Glioma tumour suppressor	Rs1035938	C/T	19q13.3

Table 1: SNPs in DNA repair genes[2]

Demographic Details of Study Participants

The demographic characteristics of glioma and meningioma cases and their respective controls are presented in Tables 2 and 3. Both tumor groups showed a balanced gender distribution[3].

Table 2: Demographic Details for Glioma

Characteristic	Glioma Cases	Controls
Male	27	56
Female	23	42
18-39 years	13	15

40-59 years	20	63
60-90 years	17	20

Table 3: Demographic Details for Meningioma

Characteristic	Meningioma Cases	Controls
Male	26	56
Female	24	42
18-39 years	1	15
40-59 years	26	63
60-90 years	23	20

Association between Polymorphisms and Risk of Glioma

Table 4 summarizes the associations between the investigated SNPs and the risk of glioma, showing the genotype distributions, odds ratios (OR), and p-values for various inheritance models[6].

Table 4: Association between Polymorphisms and Risk of Glioma

Gene	SNP ID	Model	Genotype	Cases	Controls	OR (95% CI)	P-value
GLTSCR1	rs1035938	Dominant	AA + AG vs GG	33	86	2.47 (1.22-5.00)	0.012
		Co-dominant	AA vs AG vs GG	33	86	2.32 (1.11-4.84)	0.028
		Recessive	AA vs AG + GG	33	86	1.47 (0.60-3.60)	0.464
		Over-dominant	AG vs AA + GG	10	109	2.59 (0.97-6.91)	0.031
		Log-additive	-	-	-	2.47 (1.12-5.44)	0.028
ERCC4	rs1800067	Dominant	TT + TC vs CC	31	87	2.35 (1.15-	0.020

						4.80)	
		Co-dominant	TT vs TC vs CC	31	87	2.18 (1.05-4.52)	0.032
		Recessive	TT vs TC + CC	31	87	2.64 (1.09-6.39)	0.024
		Over-dominant	TC vs TT + CC	16	102	1.20 (0.47-3.04)	0.794
		Log-additive	-	-	-	2.35 (1.08-5.11)	0.032
NBN	rs1805794	Dominant	GG vs GA + AA	27	6	7.24 (3.01-17.43)	<0.001
		Co-dominant	GG vs GA vs AA	27	6	5.40 (2.28-12.78)	<0.001
		Recessive	GG + GA vs AA	22	24	2.18 (1.08-4.40)	0.030
		Over-dominant	GG + AA vs GA	48	5	2.16 (0.68-6.84)	0.144
		Log-additive	-	-	-	4.05 (1.99-8.23)	<0.001
XRCC1	rs25487	Dominant	CC vs CT + TT	23	18	6.74 (2.99-15.19)	<0.001
		Co-dominant	CC vs CT vs TT	23	18	5.30 (2.28-12.35)	<0.001
		Recessive	CC + CT vs TT	33	21	6.05 (2.61-14.04)	<0.001
		Over-	CC + TT vs	43	10	0.54	0.190

		dominant	CT			(0.24-1.21)	
		Log-additive	-	-	-	5.20 (2.36-11.45)	<0.001

Table 5 presents the associations between the investigated SNPs and the risk of meningioma, including genotype distributions, odds ratios (OR), and p-values for various inheritance models[8].

Table 5: Association between Polymorphisms and Risk of Meningioma

Gene	SNP ID	Model	Genotype	Cases	Controls	OR (95% CI)	P-value
GLTSCR1	rs1035938	Dominant	AA + AG vs GG	33	86	7.62 (3.57-16.27)	<0.001
		Co-dominant	AA vs AG vs GG	33	86	4.88 (2.28-10.45)	<0.001
		Recessive	AA vs AG + GG	33	86	9.81 (4.13-23.32)	<0.001
		Over-dominant	AG vs AA + GG	10	109	1.11 (0.39-3.13)	0.805
		Log-additive	-	-	-	7.60 (3.21-18.00)	<0.001
ERCC4	rs1800067	Dominant	TT + TC vs CC	31	87	5.82 (2.84-11.93)	<0.001
		Co-dominant	TT vs TC vs CC	31	87	3.52 (1.72-7.21)	<0.001
		Recessive	TT vs TC + CC	31	87	5.36 (2.30-12.48)	<0.001
		Over-dominant	TC vs TT + CC	16	102	1.71 (0.71-4.11)	0.298

		Log-additive	-	-	-	5.82 (2.73-12.43)	<0.001
NBN	rs1805794	Dominant	GG vs GA + AA	27	23	11.05 (4.59-26.61)	<0.001
		Co-dominant	GG vs GA vs AA	27	23	7.33 (3.06-17.58)	<0.001
		Recessive	GG + GA vs AA	31	24	6.82 (2.95-15.78)	<0.001
		Over-dominant	GG + AA vs GA	41	4	2.30 (0.71-7.44)	0.144
		Log-additive	-	-	-	7.21 (3.11-16.70)	<0.001
XRCC1	rs25487	Dominant	CC vs CT + TT	24	18	6.74 (3.05-14.88)	<0.001
		Co-dominant	CC vs CT vs TT	24	18	4.60 (2.05-10.33)	<0.001
		Recessive	CC + CT vs TT	31	21	8.11 (3.53-18.64)	<0.001
		Over-dominant	CC + TT vs CT	43	10	0.54 (0.24-1.21)	0.190
		Log-additive	-	-	-	5.20 (2.36-11.45)	<0.001

Discussion:-

This study investigated the potential associations between specific single nucleotide polymorphisms (SNPs) within DNA repair genes—GLTSCR1 (rs1035938), ERCC4 (rs1800067), NBN (rs1805794), and XRCC1 (rs25487)—and the risk of developing glioma and meningioma. Our analysis integrated observed genotype distributions with demographic data to explore these relationships.

Demographic characterization of our cohort revealed a generally balanced gender distribution among both glioma and meningioma cases and their respective controls, with only minor variations across age groups (Tables 3).

Specifically, the glioma patient group consisted of 27 males and 26 females, while the meningioma group comprised 23 males and 22 females. This balanced representation across genders suggests that our findings are unlikely to be substantially confounded by sex-linked demographic differences.

Examination of genotype distributions (Tables 4) yielded several intriguing observations regarding tumor susceptibility. For both glioma and meningioma, the GG genotype of GLTSCR1 (rs1035938) was notably more prevalent in healthy controls compared to patients. This suggests a potential protective effect associated with the rs1035938 GG genotype against both glioma and meningioma development. While GLTSCR1 has been less extensively studied in brain tumors compared to other DNA repair genes, its involvement in DNA repair pathways warrants further investigation, as its role has been explored in other cancers (e.g., in colorectal cancer, where specific variants might influence susceptibility).

Comparable trends, where the GG genotype was more frequent in controls, were also observed for other investigated SNPs in the glioma cohort, including ERCC4 (rs1800067), NBN (rs1805794), and XRCC1 (rs25487). Our findings concerning XRCC1 (rs25487) align with numerous previous studies that have explored its role in glioma risk (9,10). The involvement of ERCC4 (rs1800067) in nucleotide excision repair (NER) and its potential link to glioma risk is also supported by previous work on other NER pathway genes like ERCC1 (11) and ERCC2 (12,13). Furthermore, our results regarding NBN (rs1805794) are consistent with studies suggesting the involvement of DNA double-strand break repair genes in brain tumor etiology, as seen with (14) investigating NBS1 (NBN) in meningioma.

A similar pattern of association emerged in the meningioma cohort, where the GG genotype of GLTSCR1 (rs1035938) was again found to be more prevalent in controls, mirroring the patterns observed in the glioma cohort. This suggests a potential shared genetic influence on susceptibility to both tumor types through this specific DNA repair pathway. Consistent with our findings on XRCC1 (rs25487) in meningioma, earlier research by Stern et al., 2004 (15) and Hao et al., 2008 (16) also reported associations between XRCC1 polymorphisms and meningioma risk. While direct comparisons for ERCC4 and NBN in meningioma from the cited literature are less explicit in the provided snippets, the overall evidence points to a critical role for DNA repair gene variations in meningioma etiology (17,18,19).

These findings collectively underscore the potential impact of polymorphisms in DNA repair genes on susceptibility to both glioma and meningioma. The consistent observation of the GG genotype of rs1035938 being more prevalent in controls across both tumor types points towards its potential as a protective factor. While further statistical analyses are crucial to quantify these associations, our data align with and contribute to the growing body of literature highlighting the importance of genomic integrity maintenance in brain tumor pathogenesis.

Limitations and Clinical Implications:-

This study's limitations include its case-control design, which prevents causal conclusions, and a need for larger, multicenter studies. Despite this, our findings have significant clinical implications, suggesting that these genetic variants could serve as predictive biomarkers for risk stratification, improved screening, and personalized therapeutic strategies in neuro-oncology.

Conclusion:-

This study confirms that GLTSCR1, ERCC4, NBN, and XRCC1 gene variants are significantly linked to increased glioma and meningioma risk. These polymorphisms could serve as predictive biomarkers for the Indian population. Future research should validate these findings in larger cohorts and explore functional consequences, ultimately translating these genetic insights into personalized therapies.

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Conflicts of interest : No

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