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EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) POLYMORPHIC VARIATIONS (-216G/T & –191 C/A) POSE A HIGH RISK TO PATIENTS WITH MALIGNANT GLIOMA

Background. Malignant gliomas are the most frequent and lethal brain tumors. Their molecular aspects remain intangible but current studies have pointed to certain genetic polymorphic loci that pose the risk. The polymorphic sequence variations of the epidermal growth factor receptor gene (*EGFR*) pathway play a vital role in the glioma risk, and the *EGFR* variants (216G>T and 191C>A) are identified to affect the risk for the development of different tumors including glioma. **Aim.** To examine genetic variations of *EGFR* T rs712829 (216G/T) and rs712830 (191C>A) with respect to glioma risk. **Materials and Methods.** 129 confirmed glioma cases were genotyped against 180 malignancy-free healthy controls by polymerase chain reaction-restriction fragment length polymorphism technique (RFLP). **Results.** The frequency of the TT homozygous variant of the *EGFR* -216 G/T genotype differed significantly between cases and controls (49.6% *vs.* 23.0%) ($p < 0.0001$). The *EGFR* -216 G>T allele 'T' was found significantly more frequently in cases (0.56 *vs.* 0.33 in controls; $p < 0.0001$). The *EGFR* -191C>A homozygous 'AA' genotype was implicated significantly more frequently in cases than in controls ($p < 0.0001$). The distribution of the 'A' variant allele was also more frequent in cases (41.9%) than in controls (14.0%) (0.55 *vs.* 0.30; $p < 0.0001$). TC and TA haplotypes showed varied frequency in cases and controls. **Conclusion.** *EGFR* -216 G>T and -191 C>A variants and haplotypes (TA and TC) of the *EGFR* gene are very strong risk factors in the development of glioma in the Kashmiri population.

Keywords: germline, genetic variants, epidermal growth factor receptor gene, haplotype, glioma, allele.

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Glioma is the most frequent brain tumor [1]. Although we have witnessed a marked advancement in its molecular biological study, it still remains mostly incurable. By the histological classification, most gliomas can be classified as oligodendroglial astrocytic, mixed oligo-astrocytic or ependymal tumors by the World Health Organization (WHO) criteria [2]. Glioblastoma (GBM), a type of astrocytic tumors, is the most frequent and malignant type of glioma. Even though ependymal tumors are often relatively restricted, the majority of astrocytic and oligodendroglial tumors frequently metastasize to the nearby brain tissue [3]. Among these, diffuse gliomas are the most lethal cancers owing to their aggressive mode of development and insensitivity to the curative therapies. The incidence of malignant gliomas is about 5 per 105 persons with GBM being the most common among all glioma subtypes. A 5-year survival varies significantly depending on the histological type of glioma and its grade with GBM having the poorest survival rate [4]. There are several noted factors, like occupations and environmental carcinogens that have been seen to be linked to a growing risk of glioma [4]. Besides, genetic factors such as polymorphic variations (SNPs) may contribute to a small but absolute cancer risk either individually or in combination and can be a reason for the disproportion of crucial metabolic activities implicated in cancer predisposition [5].

The epidermal growth factor receptor (EGFR) is involved in gliomagenesis and also confers the prognosis of these tumors by interacting with alkylating agents of chemotherapy. EGFR pathway plays a prominent part in regulating cell growth, apoptosis, and differentiation in cancer. Apart from the somatic genetic changes, polymorphic variations in the EGF/EGFR pathway have also been observed to be implicated in tumor risk, the response to chemotherapy, and patient's outcome [6—8]. There are two prominent SNPs located in the essential promoter region of the *EGFR* gene (216G>T and 191C>A), where T variant in the 216G>T is found to enhance the promoter activity in an Sp1-dependent manner, which causes higher gene expression [9].

Keeping in view the important role in cellular growth and development, the disruption of *EGFR* at genetic or protein level is proposed to be linked with tumorigenesis. The significance of EGFR sequence variations in defining glioma susceptibility was supported by the data published by Costa et al. [10], with potential application of personalized therapies in GBM patients, whose molecular stratification is evident. The predictive role of three *EGFR* polymorphisms (191C>A 216G>T and (CA)n) and the prognostic value of 191C>A genotype have been found in GBM patients. In particular, it has been summarized that the *EGFR* intron 1 homozygous (CA)n repeat short genotypes pose a strong risk of the glioma development and the heterozygous 191C>A genotype is a prognostic marker of poor survival in GBM patients [10]. Therefore, *EGFR* polymorphic sequence variations could add to the divergence between different populations or ethnic groups with respect to the risk of the disease and consequently may act as promising candidates for glioma treatment. Few studies have analyzed the role of the *EGFR* gene sequence variations in glioma development. We carried out a case-control study to analyze the distribution and/or association of *EGFR* gene variants (rs712829 and rs712830) with glioma cases in our population (Kashmir, North India).

Materials and Methods

Patients and samples. The study included 129 histologically confirmed glioma cases referred from the Departments of Medical Oncology and Neurosurgery at Sher-I-Kashmir Institute of Medical Sciences (SKIMS), J&K (India). A pre-informed consent was taken from all patients. The blood and corresponding tumor tissue samples were taken from all these patients. The surgically resected glioma tissue samples were divided into two parts: one part was placed into sterile vials containing phosphate buffered saline (pH = 7.2) for molecular investigations, and the other was sent for histopathological examination for the confirmation of the glioma type and stage/grade. The biopsy samples were reviewed by neuropathologists to substantiate the diagnosis of malignant glioma. Further, 180 blood samples were collected from healthy controls without history of malignancy from the same region and with the same ethnic background. The sample size of the study was determined as 80% using nMaster2.0 statistical software. The peripheral blood (5 ml) was taken from both cases and controls in EDTA containing vials and stored at –20 °C till processing for DNA extraction.

Extraction of genomic DNA. The blood samples from both cases and controls were subjected to DNA extraction by the phenol-chloroform method and/or by using DNA isolation kit (Zymo Research Corporation, USA).

Polymerase chain reaction for amplification of EGFR gene. The PCR amplification reaction was carried out in 25 μl reaction mixture containing 250 ng/ml of DNA, 1x PCR buffer mix (Biotools, Spain) with dNTPs (dATP, dCTP, dGTP, dTTP, 0.2 mM each), 10 pM primers (Sigma–Aldrich, USA) in sterile water, and 1 U/μl Taq DNA polymerase (Biotools, Spain). The set of the primers used for the amplification of the two SNPs were as follows: F: 5’-CTCCTCCTCCTCTGCTCCTC-3’, R: 5’-GGGGCTAGCTCGGGACTC-3′ encompassing 197 bp with both SNPs of the interest *EGFR*-216 G>T and 191C>A within this locus. The thermal conditions used for PCR were: initial denaturation at 95 °C for 5 min, 30 cycles of denaturation at 95 °C annealing at 63 °C and extension at 72 °C for 30 s with a final extension of 72 °C for 5 min.

Genotyping by restriction fragment length polymorphism (RFLP). A 10 μl of the PCR products were subjected to endonuclease restriction digestion with *BSER1* (*EGFR* 216 G/T) and *SacII* (*EGFR191*C>A) with 5 U at 37 °C for 16 h (Genie, USA). *EGFR* 216 G>T generated 171 bp and 26 bp for wild ‘TT’, 197 bp, 171 bp, 26 bp for heterozygote (GT) and 197 bp uncut for GG variant while as *EGFR*_191C>A generated 197 bp for homozygous variant ‘AA’ and 197 bp, 171 bp, 26 bp for heterozygotes (CA). Supplementary Fig. 1[1] depicts the genotyping of *EGFR* -216 G>T and -191 C>A. The PCR products were visualized on a 3% agarose gel containing 0.5 μg/ml ethidium bromide and photographed in gel documentation system (Protein Simple, Alpha Imager, UK). Distilled water as a negative control was used for quality control as an alternative of DNA template. About 20% randomly selected samples from both cases and controls were repeatedly analyzed by RFLP to ascertain the reproducibility of the results.

Statistical analysis. IBM Statistics SPSS software (Version-23) was employed for the statistical evaluation of the values. A goodness-of-fit chi-square test was conducted to determine if the polymorphisms between cases and controls were in the Hardy — Weinberg equilibrium. Estimates of the odds ratios (OR) were used for the relative risk, and 95% confidence intervals (CI) were evaluated to observe the association between certain genotypes or other related risk factors of glioma. p value < 0.05 was considered significant.

Results

This study included 129 glioma cases and 180 healthy controls without differences in gender and smoking habits between the groups ($p > 0.05$). Almost all types of malignant glioma were included in the study: GBM accounted

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[1] Supplementary materials are posted at https://figshare.com/articles/dataset/Supplementary_material_docx/23996640

for 65 (50.4%) cases, oligodendroglioma for 24 (16.3%) cases, and astrocytoma for 21 (16.3%) cases. The clinical details of other clinic-pathological characteristics are provided in Supplementary Table S1.

The genotypic and allelic frequencies of *EGFR* -216 G>T and *EGFR* -191 C>A in both the cases and controls are shown in Table 1. *EGFR* -216 G>T and EGFR -191 C>A SNPs in controls were in the Hardy — Weinberg equilibrium.

The distribution of the *EGFR* -216G/T genotypes GG, GT, and TT observed in glioma cases were 36.4%, 13.9%, and 49.6 as compared to 57.0%, 20.0%, and 23.0% in controls respectively ($p < 0.05$). The frequency of TT homozygous genotype in cases was 49.6% *vs.* 23.0% in controls with OR = 3.4 (1.9—5.5; $p < 0.0001$). *EGFR* -216G/T GT heterozygous genotype frequency was comparable between two groups ($p = 0.8$). Further, the frequency of the variant ‘T’ allele was found to differ significantly between two groups (cases 0.56 *vs.* controls 0.33) with OR = 2.7 (CI = 1.8—3.6; $p < 0.0001$). The combined variant genotype (GT + TT; dominant model) also was implicated significantly more frequently in cases (63.6%) than controls (43%), OR = 2.29 (1.4—3.6; $p = 0.0005$). Except age, no another characteristic feature of glioma cases showed an association with *EGFR* -216 G>T genotype variation (Table 2).

In the glioma cases, the combined genotype (GT + TT) was present more frequently in higher grade tumors (G IV). Likewise, the combined genotype GT+TT was present significantly more frequently in GBM (62.2%) than the wild type GG genotype (OR 9.4; $p < 0.0001$) (Table 2).

The frequencies of the *EGFR* -191C>A genotypes CC, CA, and AA in glioma cases were found as 31.8%, 26.4%, and 41.9% vs. controls (54%, 32%, and 14%, respectively, Table 1). The frequency of *EGFR* -191C>A homozygous AA genotype was significantly higher in the cases than in controls (41.9% *vs.* 14.0%, $p < 0.0001$) with OR = 4.9 (2.7—8.9). The distribution of the variant allele was significantly more frequent in the cases (0.55) than controls (0.30) with adjusted OR = 2.9 (2.1—3.8; $p < 0.0001$).

On the stratification of various parameters (Table 3), the *EGFR* -191C>A combined genotype (CA + AA) was found to be significantly more often in the cases than controls (68.2% vs. 46.1% and OR = 2.5 (CI=1.5—4.0; $p = 0.0001$)). Similarly, the combined genotypes were present more frequently in patients ≥ 40 years age in cases than in controls with frequencies 82.9%

Table 1. **The genotypic and allelic frequencies of *EGFR* -216 G/T and *EGFR* -191 C/A in both cases and controls**

SNP	Genotype	Cases n = 129 (%)	Controls n = 180 (%)	OR (95% CI)	*p*
EGFR -216G/T	GG	47 (36.4)	102 (57)	Reference	
	GT	18 (13.9)	36 (20)	1.1 (0.5—2.1)	0.8
	TT	64 (49.6)	42 (23)	3.4 (1.9—5.5)	<.0001
	G	112 (43.4)	240 (67)	Reference	
	T	146 (56.6)	120 (33)	2.7 (1.8—3.6)	<.0001
EGFR -191C/A	CC	41 (31.8)	97 (54)	Reference	0.2
	CA	34 (26.4)	57 (32)	1.4 (0.8—2.5)	<.0001
	AA	54 (41.9)	26 (14)	4.9 (2.7—8.9)	
	C	116 (44.9)	251 (70)	Reference	
	A	142 (55.0)	109 (30)	2.9 (2.1—3.8)	<.0001

Table 2. **Genotypic/allelic distribution of *EGFR* -216 G/T gene polymorphism in glioma cases and healthy controls dependent on clinical-pathological characteristics**

Parameter	CASES		CONTROLS		OR (95%CI)	*p*
	GG (%)	GT+TT (%)	GG (%)	GT+ TT (%)		
Overall genotype	47 (12.9)	82 (63.6)	102 (57)	78 (43)	2.29 (1.4—3.6)	0.0005
Age						
≥40	35 (74.5)	65 (79.3)	52 (51)	26 (33)	1.3 (0.6—3.1)	0.6
<40	12 (25.5)	17 (20.7)	50 (49)	52 (67)	0.5 (0.3 —0.9)	0.02
Sex						
Male	23 (48.9)	44 (53.7)	55 (54)	41 (53)	1.2 (0.6—2.4)	0.7
Female	24 (51.1)	38 (46.3)	47 (46)	37 (47)	0.9 (0.5—1.8)	0.8
Residence						
Urban	23 (48.9)	33 (40.2)	38 (37)	31 (40)	0.7 (0.3—1.4)	0.4
Rural	24 (51.1)	49 (59.7)	64 (63)	47 (60)	1.1 (0.6—2.0)	0.7
Tumor stage						
GBM	14 (29.8)	51 (62.2)	—	—	4.8 (2.3—9.8)	< 0.001
ASTRO	15 (31.9)	6 (7.3)			0.5 (0.2—1.4)	0.1
OLIGO	4 (8.5)	20 (24.4)			10.2 (3.1—33.2)	< 0.001
Histological type						
GI/GII	26 (55.3)	13 (15.9)	—	—	0.2 (0—1.4)	0.2
GIII	9 (19.1)	19 (23.2)			2.7 (1.1—6.7)	0.03
GIV	12 (25.5)	50 (60.9)			5.5 (2.6—11.6)	< 0.0001

Table 3. **Genotypic/allelic distribution of *EGFR* -191 C/A gene polymorphism in glioma cases and healthy controls dependent on clinical-pathological characteristics**

Parameter	CASES		CONTROLS		OR (95%CI)	*p*
	CC (%)	CA + AA (%)	CC (%)	CA + AA (%)		
Overall genotype	41 (31.8)	88 (68.2)	97 (53.9)	83 (46.1)	2.5 (1.5—4.0)	0.0001
Age						
≥40	27 (65.9)	73 (82.9)	42 (43)	36 (43)	3.1 (1.6—5.9)	0.0002
<40	14 (34.1)	15 (17.04)	55 (57)	47 (57)	1.2 (0.5—1.8)	0.3
Sex						
Male	27 (65.9)	40 (45.5)	57 (59)	39 (47)	2.1 (1.2—4.0)	0.01
Female	14 (34.1)	48 (54.5)	40 (41)	44 (53)	3.1 (1.5—6.4)	0.003
Residence						
Urban	18 (43.9)	38 (43.2)	37 (38)	32 (39)	0.9 (0.5—2.1)	1.0
Rural	23 (56.1)	50 (56.8)	60 (62)	51 (61)	1.0 (0.5—1.9)	1.0
Tumor stage						
GBM	20 (48.8)	45 (51.1)	—	—	0.9 (0.3—2.7)	1
ASTRO	6 (14.6)	15 (17.04)			0.8 (0.3—2.2)	0.6
OLIGO	6 (14.6)	18(20.5)			2.0 (0.8—5.7)	0.2
Histological type						
GI/GII	14 (34.1)	25 (28.4)	—	—	0.5 (0.2—1.5)	0.2
GIII	6 (14.6)	22 (25)			0.9 (0.4—2.1)	1
GIV	21 (51.2)	41 (46.6)				

vs. 43% respectively ($p = 0.0002$) with OR = 3.1 (CI 1.6—5.9).

A haplotypic assessment analysis was carried out to demonstrate the linkage disequilibrium for *EGFR* -216 G>T and *EGFR* -191 C>A for their mutual impact on the risk for glioma patients (Table 4). Interestingly, two haplotypes exhibited significant risk for patients with glioma. Haplotype TC showed a significantly varying frequency of 0.19 in cases as compared to 0.03 in controls and, similarly, TA haplotype was found with a frequency of 0.23 *vs.* 0.083 between two groups respectively. The estimated two marker haplotypes frequencies in cases and controls along with overall distribution of various haplotypes are depicted in Table 4.

Discussion

The current molecular research in glioma focuses on the germ-line genetic polymorphism to estimate the risk of glioma and the management of the disease. The studies have confirmed that the polymorphic variants implicated in the *EGFR* pathway pose an increased risk of cancer and affect the patient's outcome [7, 8, 10]. Accounting the plausible role of *EGFR* -216 G>T and -191 C>A we conducted this study where the variant genotype and the haplotype depicted a strong association with glioma.

In our study, the frequency of *EGFR* -216, TT homozygous variant showed 3.4 fold-increased risk for glioma cases ($p < 0.0001$) and similarly in *EGFR* -191C>A genotypes homozygous AA genotype showed a significant 4.9-fold risk for glioma cases ($p < 0.0001$). A strong association found in glioma patients with both homozygous variants of *EGFR* SNPs is possibly due to the involvement of EGFR pathway, which is frequently altered in malignant gliomas where mostly glioblastomas are known to have overamplified and overexpressed *EGFR*, causing abnormal activation of *EGFR* pathway [11—13]. In partial agreement to our study, Costa et al. [10] also observed *EGFR*-191C>A as a risk factor for glioma and found it as a prognostic indicator for GBM, while *EGFR* -216 G>T was observed to have no association with glioma risk. On contrary, the study by Carpentier et al. [14] is in agreement with our study depicting -216T allele to confer an increased risk for GBM. This incongruity of the findings may be partly delineated by the specific ethnic variations in the population under study. Moreover, the frequency of -216G>T allele in the healthy control population in our study is in agreement with several reports [9]. The earlier investigations have substantiated that *EGFR* rs712829 and rs712830 are related to the enhanced activity of the promoter of the gene and the subsequent protein expression [15]. The study found that homozygous variants of the two *EGFR* SNPs rs712829 and rs712830 are significantly associated with 2.7 and 2.9-fold risk for glioma. Torres-Jasso et al. [16] found the relation of both SNPs with gastric cancer. The importance of rs712830and rs712830 have been substantia-

Table 4. **Haplotype analysis of *EGFR* -216 G>T and *EGFR* -191 C>A for overall association with malignant glioma cases and healthy controls**

Haplotype *EGFR* -216 G>T *EGFR* -191 C>A		Cases (%)	Controls (%)	OR (95% CI)	*p*
G	C	0.13	0.45	Ref.	
G	A	0.17	NIL	—	—
T	C	0.19	0.03	10.5 (3.6—31.4)	< 0.005
T	A	0.23	0.083	9.1 (4.1—20.3)	< 0.0001

ted with *EGFR* overexpression [9] in various studies of GBM [14] and several other cancers [17]. The haplotypic analysis was carried out to observe a linkage disequilibrium for *EGFR* -216 G>T and -191 C>A for their collective effect on the risk to glioma patients. A haplotype-based association approach is increasingly accepted for genetic association studies [27]. Two haplotypes of TC and TA were seen to confer significant risk to patients with glioma. TA haplotype was also seen to be increased in gastric cancer by Torres-Jasso et al. [16] but not to a significant proportion where GA combination was observed to increase the risk. To summarize, *EGFR* gene alterations, both sporadic and germline, play an important role in glioma genesis.

Therefore, the current study further substantiates the evidence of the association of *EGFR* gene polymorphic variants -216 G>T -191 C>A and haplotypes (TA and TC) as a strong risk factor in glioma.

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Ethical compliance

This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for the experiments in humans. A pre-informed consent was sought from each patient as per the standards of Institutional Ethics Committee and ethical approval was obtained from Institutional Ethical Committee (SKIMS Study ref: Protocol 81/2013).

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ПОЛІМОРФНІ ВАРІАНТИ РЕЦЕПТОРА ЕПІДЕРМАЛЬНОГО ФАКТОРА РОСТУ (EGFR) (-216G>T& –191 C>A) ЯК ФАКТОР ВИСОКОГО РИЗИКУ РОЗВИТКУ ЗЛОЯКІСНИХ ГЛІОМ

Вступ. Злоякісні гліоми є найбільш поширеними і смертельними пухлинами головного мозку. Молекулярні аспекти їх виникнення залишаються мало з'ясованими, але поточні дослідження вказують на певні генетичні поліморфні локуси, які асоціюються з ризиком розвитку цих новоутворень. Поліморфні варіанти послідовності гена рецептора епідермального фактора росту (*EGFR*) асоційовані з ризиком розвитку гліоми, причому варіанти *EGFR* (216G>T і 191C>A) ідентифіковано як такі, що впливають на ризик розвитку різних пухлин, включаючи гліому. **Мета.** Дослідити зв'язок генетичних варіантів *EGFR* T rs712829 (216G/T) та rs712830 (191C>A) з ризиком розвитку гліом. **Матеріали та методи.** 129 підтверджених випадків гліоми були генотиповані та співставленні з аналогічними результатами дослідження 180 здорових осіб без злоякісних новоутворень контрольної групи з використанням полімеразної ланцюгової реакції — методу поліморфізму довжини рестрикційних фрагментів (RFLP). **Результати.** Частота TT-гомозиготного варіанта генотипу *EGFR* -216 G/T істотно відрізнялася у хворих з гліомами порівняно з контролем (49,6% проти 23,0%) ($p < 0,0001$). У пацієнтів з гліомами алель «Т» *EGFR* -216 G>T виявлявся значно частіше (0,56 проти 0,33 у контрольній групі; $p < 0,0001$). Зазначимо, що у хворих із гліомами також виявлено вищу частоту гомозиготного генотипу «АА» *EGFR* -191C> ($p < 0,0001$). Розподіл алелі варіанту «А» також був частішим у пацієнтів із гліомами (41,9%) порівняно із здоровими особами (14,0%) (0,55 проти 0,30; $p < 0,0001$). Гаплотипи TC і TA показали різну частоту в пацієнтів із гліомами в порівнянні з контрольною групою. **Висновок.** Варіанти *EGFR* -216 G>T і -191 C>A і гаплотипи (TA і TC) гена *EGFR* є значущими факторами ризику розвитку гліоми в Кашмірі.

Ключові слова: зародкова лінія, генетичні варіанти, ген епідермального фактора росту, гаплотип, гліома, алель.