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LABORATORY INVESTIGATION - HUMAN/ANIMAL TISSUE

Association of matrix metalloproteinase-1 gene polymorphism with glioblastoma multiforme in a northern Indian population

Nitin Malik · Raj Kumar · Kashi N. Prasad · Priyanka Kawal · Arun Srivastava · Ashok K. Mahapatra

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Abstract Matrix metalloproteinase-1 (MMP-1) is known to be involved in the pathogenesis of glioma. It damages the extra-cellular matrix to produce invasiveness in cancer tissue, and hence has a direct effect in cancer invasion. The study aims to explore the association of single nucleotide polymorphism of -1607 MMP-1 gene with susceptibility to glioblastoma multiforme (GBM) in northern Indian subjects. One hundred and ten GBM patients and 150 healthy controls were included in this study. 1607 MMP-1 gene was studied by PCR–RFLP; different genotypes being combinations of 1G and 2G allele (1G/1G, 1G/2G and 2G/2G). 2G/2G genotype was significantly associated with GBM patients (OR, 2.24; $P = 0.016$; 95% CI, 1.16–4.30) as compared to controls. Prevalence of the 2G allele of -1607 MMP-1 polymorphism was significantly greater in GBM patients as compared to controls (62.3 vs 48.3%, OR, 1.76; $P = 0.002$; 95% CI, 1.23–2.52). This study suggests that the 2G/2G genotype and 2G allele of -1607 MMP-1 polymorphism are associated with an increased susceptibility for developing GBM.

Keywords Glioblastoma multiforme (GBM) · Glioma · Matrix metalloproteinase-1 · Polymorphism

N. Malik · R. Kumar (✉) · P. Kawal · A. Srivastava
Department of Neurosurgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, India
e-mail: rajkumar1959@gmail.com

K. N. Prasad
Department of Microbiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, India

A. K. Mahapatra
Department of Neurosurgery, All India Institute of Medical Sciences, New Delhi 110029, India

Introduction

Gliomas are neoplasm of neuroglial cells and account for 33% of all primary central nervous system tumours, glioblastoma multiforme (GBM) being the most malignant of them [1]. Gliomas as a whole account for about 2% of all the malignant tumours in adults in India [2]. GBM is the most common primary malignant brain tumour accounting for 17.6% of all primary brain and central nervous system tumours and 54.0% of all gliomas [1]. Despite significant advancements in the diagnosis and treatment of GBM, this tumour remains nearly incurable. Although surgery and radiotherapy substantially improve patient survival, 95% of patients have a mean survival of 2 years following diagnosis and treatment [3]. However, without treatment, the mean survival is only 4 months.

Several factors are involved in the development of a tumour. Interactions between neoplastic cells and the surrounding microenvironment are crucial to each step of tumourigenesis. The matrix metalloproteinases (MMPs) are a family of zinc-dependent metallopeptidases belonging to subfamily M10A [4], and these enzymes can degrade most of the macromolecules involved in the synthesis of the extracellular matrix, including collagens, laminin, fibronectin, vitronectin and proteoglycans [5]. MMPs are the key enzymes involved in invasion of tumour cells through stroma and endothelia during extravasations and colonisation of secondary sites. Multiple MMPs can be expressed by tumour and/or host stromal cells. These protein molecules play an important role in both physiological as well as pathological processes such as angiogenesis, invasion and metastasis, cell proliferation, apoptosis, remodelling and modulation of bioactivity of chemokines [6]. These are secreted as latent proenzymes (zymogens) which are activated by proteolytic cleavage of the N-terminal propeptide

domain by other proteinases [7] and are inhibited by the tissue inhibitors of metalloproteinases (TIMPs) [8]. Amongst all MMPs, MMP-1 is the most ubiquitously expressed interstitial collagenase degrading fibrillar collagens, and is also called collagenase-1 which specifically degrades type 1 collagen. Its over-expression has been demonstrated in tumour tissues and is suggested to be associated with tumour invasion and metastasis [9–11]. Increased expression of MMP-1 has been associated with poor prognosis in several malignancies including colorectal and oesophageal cancers [11–13], bladder cancer [14], oral carcinoma [15, 16], and nasopharyngeal carcinoma [17]. Polymorphisms in the MMP genes are responsible for remodelling of the extra-cellular matrix (ECM) in various diseases. A guanine insertion (2G) polymorphism at nucleotide-1607 in the promoter of the MMP-1 gene creates an Ets-1-binding site leading to a higher expression of MMP-1 which increases transcription activity. Over-expression of this gene is implicated in tumour invasion and metastasis. Patients with the 2G allele are predisposed to the development of several cancers and/or their rapid progression, such as bladder cancer [14], colorectal cancer [13, 18], oral cancer [16, 19] nasopharyngeal carcinoma [17], cervical cancer [20], ovarian cancer [21], lung cancer [22] and cerebral astrocytoma [23, 24].

MMP-1 has not been well characterised in human brain tumours compared to other MMPs such as MMP-2 and MMP-9 [25–30], probably due to preconceptions that a collagenase would not be expected to play a major role in gliomas due to absence of significant amount of collagen 1 in brain [23]. However, other studies have shown a significant association between expression of 2G allele of MMP-1 with increasing tumour grade and glioma invasiveness [23, 24, 31–36]. Worldwide, the precise role of MMP-1 polymorphism in glioblastoma cases is yet incompletely understood and remains controversial. A study on this subject among Indian population remains elusive. In the present study, therefore, we have looked for any association of -1607 MMP-1 gene polymorphism in patients with GBM.

Materials and methods

Study population

One hundred and ten patients with GBM (mean age ± SD, 37.01 ± 14.62 years; male:female, 81:29) enrolled in the department of Neurosurgery and 150 age- and gender-matched control subjects (mean age ± SD, 39.87 ± 11.85) were included in the study. GBM patients were selected on the basis of histopathological confirmation of the tumour tissue at the Department of Pathology of this Institute. In the patient population, we did not include any patient who was re-operated or with an evidence of malignant transformation from a lower grade to GBM or with a presenting history of longer duration than 4 months. The Institutional Ethics Committee (IEC, SGPGIMS) granted approval for the study, and consent was obtained from all the studied subjects.

DNA isolation

Genomic DNA was extracted from EDTA anti-coagulated peripheral blood by salting-out method [37] and stored at −20°C until use. DNA samples of 10 ng/μl concentration were used for the detection of single nucleotide polymorphism (SNP).

-1607 MMP-1 genotyping

We determined MMP-1 genotypes by a polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP)-based method, as previously described [38]. The primer sequences for MMP-1 were: forward 5′- TGACTTT TAAAACATAGTCTATGTTCA-3′ and reverse 5′- TCTT GGATTGATTTGAGATAAGTCATAGC-3′ (Sigma, USA). All PCR amplifications were performed in a 20 μl volume containing 10× assay buffer, 200 μM each dATP, dCTP, dGTP, dTTP, 0.1 μM each primer, 1.0 U Taq DNA polymerase (Bangalore Genei, India). PCR conditions were as follows: an initial denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 30 s, followed by final extension step at 72°C for 5 min and cooling to 4°C. Template-free water was used as a negative control. After amplification, the purified 4 μl PCR products were subjected to restriction digestion by *AluI* restriction endonuclease (Fermentas, Vilnius, Lithuania) for MMP-1 polymorphism with 1 μl 10× enzyme buffer (Fermentas) overnight at 37°C. The digested DNA fragments were then separated on 3% agarose gel electrophoresis. After digestion, fragment sizes for carriers of the polymorphic allele decreased from 269 bp (homozygous, 2G/2G) to 269 bp, 241 bp and 28 bp (heterozygous, 2G/1G) and to 241 bp and 28 bp (homozygous, 1G/1G). All the experiments were repeated twice for confirmation of the RFLP results. No discrepancy was found after sequencing the 10% randomly selected samples.

Statistical analysis

Power of the study was calculated using Quanto software version 1.0 (http://hydra.usc.edu/gxe). Hardy–Weinberg equilibrium was checked in controls by goodness of fit χ^2test. For comparisons between the groups of study

populations, χ^2 test was used. Independent Student's t test was performed to compare continuous data (age). Logistic regression analysis was applied to estimate association with GBM susceptibility after adjusting for age and gender. The SPSS 17.0 statistical package (Chicago, IL, USA) was used for data management and analysis.

Results

Characteristics of GBM patients and control subjects

In this study, GBM patients and control groups were comparable in age (39.87 ± 11.85 vs 37.01 ± 14.62 years, $P > 0.05$) and gender (male/female: 81/29 in patients and 99/51 in controls; $P > 0.05$ for both) (Table 1). The MMP-1 polymorphism was in agreement with Hardy–Weinberg equilibrium in control subjects.

MMP-1 (-1607) polymorphisms and GBM

To analyse the association of -1607 MMP-1 polymorphism with GBM susceptibility, the genotype frequency was compared between patients and controls. The genotypic distribution of -1607 MMP-1 polymorphism demonstrated increased risk of GBM in patients with 2G/2G genotype (OR, 2.24; $P = 0.016$; 95% CI, 1.16–4.30). Futhermore, patients with GBM showed a significantly higher prevalence of 2G allele of -1607 2G/1G polymorphism (62.3 vs. 48.3%, OR, 1.76; $P = 0.002$; 95% CI, 1.23–2.52) compared to controls (Table 2).

Discussion

In the present study, we investigated the association of -1607 MMP-1 polymorphism with the susceptibility of developing GBM in a northern Indian population. We have noted a significant association of MMP-1 -1607 2G/2G genotypes with the cases of GBM ($P = 0.016$). The variant allele 2G of this polymorphism was significantly associated with susceptibility to GBM ($P = 0.002$) compared to control subjects. Although the 2G/2G genotype has been shown to be significantly higher in other cancers, no such study has been done so far to look for an association in an Indian population.

Table 1 Demographics of study subjects

Characteristics	Patients (110)	Controls (150)	P value
Age in years (mean ± SD)	39.87 ± 11.85	37.01 ± 14.62	>0.05
Gender (male)	81 (66.0%)	99 (73.6%)	>0.05

The importance of MMP-1 polymorphism in GBM is as yet incompletely understood. The 2G variant allele frequency of -1607 MMP-1 polymorphism was significantly higher in GBM than in controls (62.3% vs 48.3%; P, 0.002), which suggests a risk of the development of the disease. Our results were in accordance with an earlier study by McCready et al. 2005 [23], in which the authors have shown the frequency of 2G allele to be significantly higher as compared to healthy population (62.9% vs 47.3%; $P = 0.002$), which was associated with increased expression of MMP-1 gene. It is located on chromosome 11q22 and expressed in a wide variety of normal cells such as stromal fibroblast cells, macrophages, endothelial and epithelial cells, and in various tumour cells [39]. It has been implicated in tumour invasion, metastasis and angiogenesis [40]. The level of MMP-1 expression can be influenced by different SNPs in the promoter region. Brinckerhoff et al. proposed a model suggesting that the 2G allele of this polymorphism contributes to the pathological process and is associated with increased expression of MMP-1 gene [23, 39]. An insertion/deletion of guanine at position -1607 has been identified in the promoter of the human MMP-1 gene and generates two different alleles: one having a single (1G) and the other with two guanines (2G) [41]. The two guanines together with an adjacent adenosine create a core-binding site (5′-GGA-3′) for the Ets family of transcription factors, leading to a higher expression of MMP-1. Promoter assays have also pointed it out as a functional polymorphism which may lead to a higher expression of MMP-1. There are several studies that have confirmed the association of this polymorphism with many cancers and other pathological conditions, such as colorectal cancer [13, 18], oral cancer [16, 19, 42], bladder cancer [14], nasopharyngeal carcinoma [17], cervical cancer [20], ovarian cancer [21, 43], lung cancer [22, 38], renal cell carcinoma [44], endometrial carcinoma [45], severe chronic periodontitis [46], peripheral arterial occlusive disease [47], degenerative disc disease [48], endobronchial tuberculosis [49], sclerosing cholangitis [50] and coronary artery disease [51].

Regarding the distribution of the two alleles, both were almost equally distributed in the normal population with a slight predominance of 1G allele (51.7%), whilst in GBM patients, 2G allele became more common (62.3%) in the present study. The difference in the distribution pattern of the wild-type allele 2G is statistically significant ($P = 0.002$).

In GBM patients, 2G/2G was the most frequent genotype, with a frequency of 47.3% in present study. This is in agreement with the results of Mc Cready et al. where its frequency was 42% as well as in the Lu et al. series (64.7%) [23, 24]. Our data also demonstrate that genotype distribution in the normal Indian population is consistent with the previously published frequency of various

Table 2 Influence of MMP-1 polymorphisms on Glioblastoma Multiforme (GBM) susceptibility

Gene polymorphism	Patients (%)	Controls (%)	*P* value	OR[a] (95% CI)
MMP1 (-1607) genotype				
1G/1G	25 (22.7)	44 (29.3)	–	Reference
1G/2G	33 (30.0)	67 (44.7)	0.574	0.83 (0.43–1.59)
2G/2G	52 (47.3)	39 (26.0)	0.016	2.24 (1.16–4.30)
Allele				
1G	83 (37.7)	155 (51.7)	–	Reference
2G	137 (62.3)	145 (48.3)	0.002	1.76 (1.23–2.52)

[a] Age- and gender-adjusted odds ratio (OR)

genotypes in a healthy population [38], which emphasises that 1G/2G (47.0%) is the most frequent genotype in a normal population. The 2G allele along with adenosine creates a core-binding site for transcription factors leading to higher expression of MMP-1 and increasing the susceptibility to disease progression [23]. However, in heterozygous conditions when 2G is present with the 1G allele, due to dosage effect of 1G allele, there is no functional change in the MMP1 gene expression and the 2G/1G genotype does not significantly influence the susceptibility to this tumour [24]. A recent study suggests that the 1G/1G genotype has a protective role in adult astrocytoma [24]. This may indicate that the allele is a common ancestor allele that reduces the risk of developing the disease. Significantly, our results contradict the series by Lu et al. [24], where, also in a normal population, 2G/2G remains the most frequent genotype (53.0%). This disagreement could be due to smaller sample sizes in the studies and racial or ethnic variations. Ju et al. [52] tried to determine if a true difference existed between the genotype distribution of the -1607 MMP-1 polymorphism in different races and in normal populations from Japan, Taiwan, US, UK, France, Italy, Poland and Brazil. The study showed that the allele frequencies of MMP-1 -1607 SNP in Asians showed no significant difference, but significant differences between allele frequencies were seen in white populations indicative of ethnic variations between Asians and Caucasians. However, the representatives of the world's two most populous nations, i.e. China and India, that may have different gene pools, were not included in their study. Hence, the study will not be considered complete without the genotype data of these populations. Therefore, in order to clarify the contribution of genetic polymorphisms to the development and progression of the disease, we have performed -1607 MMP-1 gene polymorphism in patients with GBM and in control subjects from a northern Indian population. A significant association of this genetic variation with susceptibility of developing GBM in our population was found in this pilot study. However, these results could also be a chance finding because the sample size in the present study was relatively small, and further studies on a larger study population may substantiate these findings in the future.

In conclusion, the present study suggests that the -1607 MMP-1 2G/2G genotype may be a risk factor for the development of GBM and that the 2G allele may be responsible for the increased susceptibility to this disease in a northern Indian population. However, more studies in different geographical ethnic groups is required in larger population to confirm the present results.

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Conflict of interest The authors declare that they have no conflict of interest.

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