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Immunoglobulin genes implicated in glioma risk

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Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; FcγR, Fcγ receptor; GM, γ marker; GWAS, genome-wide association studies; HCMV, human cytomegalovirus; HER1, human epidermal growth factor receptor 1; HER2, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; HR, hazard ratio; IGHG, immunoglobulin heavy chain γ; *IRL*, internal repeat long; OR, odds ratio; *TRL*, terminal repeat long

Both genetic and environmental factors are thought to be causal in gliomagenesis. Several genes have been implicated in glioma development, but the putative role of a major immunity-related gene complex member, immunoglobulin heavy chain γ (*IGHG*) has not been evaluated. Prior observations that *IGHG*-encoded γ marker (GM) allotypes exhibit differential sensitivity to an immunoevasion strategy of cytomegalovirus, a pathogen implicated as a promoter of gliomagenesis, has lead us to hypothesize that these determinants are risk factors for glioma. To test this hypothesis, we genotyped the *IGHG* locus comprising the GM alleles, specifically GM alleles 3 and 17, of 120 glioma patients and 133 controls via TaqMan® genotyping assay. To assess the associations between GM genotypes and the risk of glioma, we applied an unconditional multivariate logistic regression analysis adjusted for potential confounding variables. In comparison to subjects who were homozygous for the GM 17 allele, the GM 3 homozygotes were over twice as likely, and the GM 3/17 heterozygotes were over three times as likely, to develop glioma. Similar results were achieved when analyzed by combining the data corresponding to alleles GM 3 and GM 3/17 in a dominant model. The GM 3/17 genotype and the combination of GM 3 and GM 3/17 were found to be further associated with over 3 times increased risk for high-grade astrocytoma (grades III-IV). Allele frequency analyses also showed an increased risk for gliomas and high-grade astrocytoma in association with GM 3. Our findings support the premise that the GM 3 allele may present risk for the development of glioma, possibly by modulating immunity to cytomegalovirus.

Introduction

Malignant glioma, the most common primary brain cancer, is divisible into histologic subgroups based on the specific types of glial cells involved. Despite recent advances in therapy, the prognosis for the majority of glioma patients remains grim. The most aggressive form of the disease *glioblastoma multiforme* is commonly lethal, with afflicted patients typically dying approximately 2 y, or less, following diagnosis. Therefore, there is an urgent need of novel routes of investigation in glioma research that might lead to more efficacious therapies to treat this malignancy.

Like other complex diseases, glioma is thought to result from both genetic and environmental factors. Several genes, including some belonging to the immune system, have been implicated in glioma pathogenesis.[1-10] But the putative role of γ marker (GM) allotypes, encoded by three highly polymorphic *IGHG* loci[11] on chromosome 14, has not been evaluated. There is a strong immunogenetic rationale for investigating the role of GM allotypes in the etiopathogenesis of glioma considering that these determinants modulate an immunoevasion strategy of human cytomegalovirus (HCMV), a common herpes virus that is thought to be an active promoter or oncological modulator of gliomagenesis.[12-16] In a previous study, we showed that an HCMV-encoded Fcγ receptor (FcγR), employed by the virus to evade the effector consequences of anti-HCMV antibody binding, has differential affinity for IgG1 proteins expressing distinct GM alleles. Specifically, the HCMV FcγR encoded by the viral *TRL11/IRL11* gene has significantly higher affinity for IgG1 proteins expressing the GM 3+,1-,2- allotypes than for those expressing the allelic GM 17+,1+,2+ allotypes.[17] These observations led us to hypothesize that these GM alleles might represent risk or protective factors, respectively, for the development of HCMV-induced glioma.[18] In the present work,

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we applied a case-control design to test the hypothesis that subjects expressing the GM 3 allele would be at higher risk of developing glioma.

Results

The demographics of our study population, including patient clinicopathologic features, are described in **Table 1**. Results of multivariate regression analysis to assess associations between GM genotypes or allele frequencies and glioma risk among the various histologic subgroups are presented in **Table 2**. In comparison to subjects who were homozygous for the GM 17 allele, the GM 3 homozygotes were over twice as likely (OR = 2.82, CI 1.05–7.59), and the GM 3/17 heterozygotes were over three times as likely (OR = 3.13, CI 1.15–8.52), to develop glioma, irrespective of disease subtype (all grades). Similarly, in comparison to GM 17/17 homozygotes, GM 3/17 heterozygotes were over three times as likely to develop high-grade astrocytoma (OR = 3.37, CI 1.05–10.87). Likewise, when comparing the combined GM 3/3+3/17 (i.e. GM 3-carriers) genotypes to the GM 17/17 genotypes, the presence of the GM 3 allele conferred a significantly increased risk for glioma (OR = 2.95, CI 1.13–7.73) and high-grade astrocytoma (OR = 3.11, CI 1.01–9.62). Similar results were obtained when assessing the allele frequencies. It was shown that the GM 3 allele was a risk factor for glioma (OR = 1.52, CI 1.10–2.11) and high-grade astrocytoma (OR = 1.49, CI 1.03–2.15), when compared with the reference GM 17 variant. No significant associations were found between GM genotypes or GM alleles and the risk of oligodendroglioma.

We also applied a multivariate Cox proportional hazard model (adjusted for patient age and sex) to investigate the association between GM polymorphism and overall survival. Glioblastoma patients for which follow up information was available who carried the GM 17/17 genotype (n = 4, 2 deaths) had a longer median overall survival than patients carrying the GM 3/17 (n = 18, 14 deaths) or GM 3/3 (n = 23, 17 deaths) genotypes with a median survival of 35 mo (range, 2–38) versus 16 mo (range, 3–52), respectively. However, the difference was not statistically significant (HR = 2.78; 95% CI, 0.61–12.65, $P = 0.19$), probably due to limited sample size in analysis (**Fig. 1**). (The survival curves for the three genotypes separately are presented in **Figure S1**.)

Table 1. Clinicopathologic features of gliomas and controls

Groups (WHO grade)	N	Age years (mean ± SD)	Male/female ratio
Controls	133	36–85 (54.80± 9.39)	1.6
Glioma (all grades)	120	20–83 (56.38 ± 12.55)	1.6
Astrocytoma (all grades)	97	22–83 (57.55 ± 12.21)	1.9
Oligodendroglioma (all grades)	23	20–78 (51.48 ± 13.08)	0.8
Astrocytoma (grades II-IV)	95	22–83 (57.67 ± 12.04)	1.9
Astrocytoma (grades III-IV)	90	22–83 (58.21 ± 11.80)	2.0

Table 2. Multivariate logistic regression analysis of associations between GM variants and risk of glioma

	Control	Glioma (All Grades)	OR (95% CI)[1]	Astrocytoma (Grades III-IV)	OR (95% CI)[1]	Oligodendroglioma (All Grades)	OR (95% CI)[1]
Genotypes* GM 17/17	18	6	-	4	-	2	
GM 3/3	64	61	2.82 (1.05–7.59) $P = 0.041$	46	2.91 (0.91–9.28) $P = 0.071$	10	1.67 (0.32–8.53) $P = 0.55$
GM 3/17	51	53	3.13 (1.15–8.52) $P = 0.026$	40	3.37 (1.05–10.87) $P = 0.042$	11	2.09 (0.41–10.61) $P = 0.37$
GM 3/3+3/17	115	114	2.95 (1.13–7.73) $P = 0.027$	86	3.11 (1.01–9.62) $P = 0.049$	21	1.86 (0.39–8.88) $P = 0.43$
	133	120		90		23	
Alleles**							
17	0.327	0.271	-	0.267	-	0.326	
3	0.673	0.729	1.52 (1.10–2.11) $P = 0.012$	0.733	1.49 (1.03–2.15) $P = 0.033$	0.674	1.15 (0.65–2.05) $P = 0.637$

Significance of associations between GM genotypes or alleles and risk of glioma in various histologic subgroups. *Reference genotype GM 17/17; **Reference allele 17; regression models included age and sex as covariates.1OR (95% CI)—Odds ratio with 95% confidence intervals.

Discussion

Results presented here show that carriers of the GM 3 allele of IgG1 have 3-fold higher risk of high-grade glioma than non-carriers. Potential underlying mechanisms could involve a direct contribution of GM alleles to immunity to self and non-self antigens relevant to gliomagenesis. Alternatively, it is possible that there may be another locus affecting glioma susceptibility that is distinct from GM on chromosome 14 and whose alleles are in significant linkage disequilibrium with those of the GM loci. This putative linkage disequilibrium could give rise to the associations observed. The most relevant among the self-antigens, immunity to which is influenced by GM alleles, are human epidermal growth factor receptor 1 (HER1/EGFR) and HER2. These tumor-associated antigens are aberrantly expressed in gliomas[19,20] and we have previously shown that GM alleles epistatically interact with FcγRIIIa alleles expressed on natural killer cells and mediate antibody-dependent cellular cytotoxicity of EGFR- and HER2-overexpressing cancer cells.[21] Though not yet investigated in glioma, antibody responses to HER2 are significantly associated with GM alleles in patients with breast cancer.[22,23] This may hold for patients with glioma as well.

The most relevant among the non-self factors, immunity to which is influenced by GM alleles, is HCMV. As mentioned before, the current consensus in the glioma field is that HCMV is an active promoter or oncogenic modulator of gliomagenesis, not merely a bystander.[16] GM alleles could influence HCMV-glioma association by influencing antibody responsiveness to viral epitopes and further by modulating the viral immunoevasion strategies. In the inflammatory autoimmune disease scleroderma (systemic sclerosis), HCMV appears to accelerate the development of disparate disease pathologies[24-26] and, of particular importance, we have found a highly significant association between anti-HCMV IgG antibody responses and the GM 3 and GM 17 alleles expressed on IgG1 in these patients.[27] Similar studies evaluating correlations between the presence of particular GM allelic variants and HCMV antibodies should be conducted for glioma patients.

GM allotypes are expressed in the constant region of γ chains. How could these constant-region determinants influence immune responsiveness thought to be exclusively associated with the variable-region genes? Recent investigations have challenged this central tenet of immunology. Several studies have shown that structural variation in the constant region affects the expression of certain idiotypes and causes variation in the specificity of variable-region-identical immunoglobulin molecules.[28] It is especially noteworthy that amino acid sequence polymorphism in the CH1 domain of the γ1 chain—where the allelic determinants GM 3 and GM 17 are located—has been shown to modulate the kinetic competence of antigen binding sites.[29] Thus, amino acid substitutions associated with GM allotypes cause structural changes in the constant region, which could translate to structural constraints (conformation) imposed on the variable region, resulting in variation in antibody specificity and affinity.

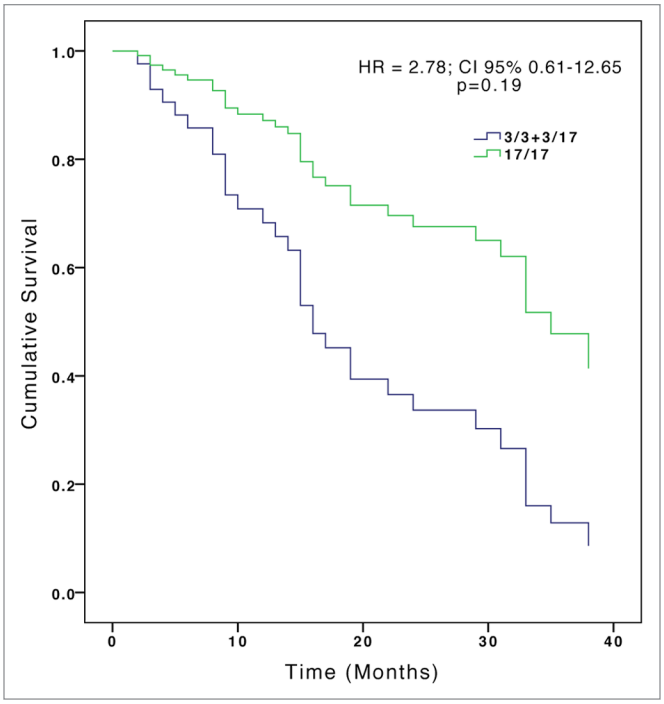

Figure 1. Correlation analysis of overall survival of glioblastoma patients with GM allotypes. Multivariate Cox proportional hazard model regression with respect to γ marker (GM) genotypes in the sub-groups of GM 17/17 (n = 4) and GM 3/3 + GM 3/17 (n = 38) and glioblastoma patient survival. Hazard ratio (HR) = 2.78; 95% confidence interval (CI) 0.61–12.65, $P = 0.19$.

As mentioned above, GM alleles modulate one of HCMV's immunoevasion strategies. The HCMV *TRL11/IRL11*-encoded FcγR—which enables the virus to evade the effector consequences of antibody binding, such as antibody-dependent cellular cytotoxicity, complement-dependent neutralization, and phagocytosis—discriminates between IgG1 proteins expressing GM 3 and GM 17 alleles. The HCMV-encoded FcγR has significantly higher affinity for IgG1 proteins expressing the GM 3+,1-,2- allotypes than for those expressing the allelic GM 17+,1+,2+ allotypes.[17] It naturally follows that individuals expressing the relatively higher affinity GM 3+,1-,2- alleles would be more likely to have their Fc domains scavenged, thereby reducing their immunological competence to eliminate the virus through Fc-mediated effector mechanisms. Therefore, one would anticipate that decreased immunity against HCMV would be conducive to glioma development, such that the frequency of GM 3+,1-,2- alleles would be expected to be higher in glioma patients than in healthy controls. In fact, our findings are fully consistent with this prediction.

If GM genes are risk factors for glioma, as shown here, why have they not been detected by the genome-wide association studies (GWAS) of this malignancy?[30] A likely reason underlying this deficiency may be the absence of these genes in many commonly used genotyping platforms. The *IGHG* gene segments harboring GM alleles are highly homologous (> 95%) and apparently not amenable to the high throughput genotyping technology used

in GWAS. Furthermore, because these genes were not typed in either the HapMap or 1000 Genomes projects, they cannot be imputed or tagged via linkage disequilibrium by single nucleotide polymorphisms (SNPs) included in the genotyping platforms. This underscores the necessity for the candidate gene approach to prospectively investigate the causal role for the *IGHG* gene complex, particularly the GM alleles, in the immunopathology of glioma.

Future studies involving GM allotypes and disease risk may also shed light on the reasons behind the racial differences in the prevalence of glioma. Age-adjusted glioma rates are considerably higher in Caucasians than in people of African descent.[2] In these regards, it is potentially highly relevant that the GM 3 allele, implicated in the risk of glioma in our study here, is either absent, or extremely rare, in people with unmixed African ancestry.[11]

Future studies should also consider examining the interactive effects of particular candidate genes in gliomagenesis. Genes do not act in isolation and there is preponderant evidence that epistasis—modification of the action of one gene by the action of one, or more, other genes—plays a significant role in human disease processes.[31-33] With this in mind, *IGHG* (GM allotypes) and *HLA* are excellent candidate genes for epistatic investigations in glioma, as both are targets of HCMV immunoevasion strategies[17,34] and have been shown to contribute to glioma risk, GM alleles in the present investigation and HLA alleles in previous studies.[1,2]

To our knowledge, this is the first report implicating GM genes in susceptibility to glioma, a devastating and often lethal malignancy. Replication, using a larger, independent cohort, is needed to validate the results presented here.

Material and Methods

Glioma patients and controls

The study population has been described in detail elsewhere.[6] All samples with available DNA isolated from peripheral blood lymphocytes were included in this work. Briefly, 120 glioma patients were recruited at Hospital de Braga, Braga and Hospital S. João, Porto, Portugal. Controls consisted of 133 cancer-free random blood donors. Both patients and controls were Caucasians. The study protocol was approved by the Institutional Ethical Committees. Peripheral blood samples from patients and normal controls were collected after informed consent, according to the Helsinki Declaration.

Quantitative PCR-based GM genotyping

At position 214 of the γ1 chain, an arginine residue characterizes the GM 3 allele and a lysine characterizes the GM 17 allele. This corresponds to a G to A nucleotide substitution in the γ1 gene. We used a pre-designed TaqMan® genotyping assay targeting these variants from Applied Biosystems Inc., according to manufacturer's instructions and employing the following primers and probes: forward primer (5` CCCAGACCTA CATCTGCAAC GTGA-3`); reverse primer (5` CTGCCCTGGA CTGGGACTGC AT-3`); reporter 1 (GM 17-specific) (VIC-CTCTCACCAA CTTTCTTGT-NFQ); reporter 2 (GM 3-specific) (FAM-CTCTCACCAA CTCTCTTGT-NFQ)

Statistical analyses to evaluate associations between glioma and GM genotype

Genotype frequencies were in Hardy–Weinberg equilibrium in both groups. To evaluate the effect of an IgG1 GM variant on the risk of glioma, odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by unconditional multivariate logistic regression analysis adjusted for potential confounding variables (i.e., patient age and sex). We estimated ORs of glioma risk associated with the GM 3/3 or GM 3/17 genotype relative to that of GM 17/17 used as reference. We also analyzed a model in which the combined GM 3/3+3/17 was compared with the genotype GM 17/17 (reference). Additionally, the allelic frequency of 3 and 17 alleles was estimated, as well as the ORs associated with risk of glioma. Associations between GM variants and patient survival were assessed using a multivariate Cox regression model adjusted for patient age, and sex. In this analysis, the genotypes and patient survival for GM 3/17+GM 3/3 were compared with those of GM 17/17 patients, again used as a reference standard. Our rationale for choosing the less frequent (GM 17) allele as reference is that our hypothesis is based on the fact that people expressing the GM 3 variant have a reduced immunological competence to eliminate HCMV and, as such, have an increased risk to develop glioma. Patients were followed until death or loss to follow-up. Statistical significance was defined as $P < 0.05$. All reported P values are 2-sided. Data analysis was performed using SPSS 20.0 software (SPSS, Inc.).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Supplemental Materials

Supplemental materials may be found here:
www.landesbioscience.com/journals/oncoimmunology/article/28609

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