Polymorphisms in the *Interleukin-4 Receptor* Gene are Associated with Better Survival in Patients with Glioblastoma

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Abstract

Purpose: Previous literature provides some evidence that atopic diseases, IgE levels, and inflammatory gene polymorphisms may be associated with risk of glioblastoma. The purpose of this study was to investigate the effects of certain inflammatory gene single nucleotide polymorphisms (SNP) on patient survival. Malignant gliomas are the most common type of primary brain tumor in adults, however, few prognostic factors have been identified.

Experimental Design: Using 694 incident adult glioma cases identified between 2001 and 2006 in Harris County, TX, we examined seven SNPs in the interleukin (IL)-4, IL-13, and IL-4 receptor (*IL4R*) genes. Cox proportional hazards regression was used to examine the association between the SNPs and overall and long-term survival, controlling for age at diagnosis, time between diagnosis and registration, extent of surgical resection, radiation therapy, and chemotherapy.

Results: We found that among high-grade glioma cases, *IL4R* rs1805016 (TT versus GT/GG) was significantly protective against mortality over time [hazard ratios (HR), 0.59; 95% confidence intervals (CI), 0.40-0.88]. The *IL4R* rs1805016 and rs1805015 TT genotypes were both found to be significantly associated with survival beyond 1 year among patients with high-grade glioma (HR, 0.44; 95% CI, 0.27-0.73 and HR, 0.63; 95% CI, 0.44-0.91, respectively). Furthermore, the *IL4R* haplotype analysis showed that SNPs in the *IL4R* gene may be interacting to affect long-term survival among high-grade glioma cases.

Conclusions: These findings indicate that polymorphisms in inflammation pathway genes may play an important role in glioma survival. Further research on the effects of these polymorphisms on glioma prognosis is warranted.

Although malignant gliomas are the most common type of primary brain tumor in adults, there is a lack of definitive information regarding their etiology, and identification of the prognostic factors that influence patient survival remains incomplete. Median survival time for patients with glioblastoma, the most fatal form of brain tumor, is ~1 year, and 90% die within 3 years after diagnosis.[6] Therefore, it is important to determine the factors that influence survival for this rapidly fatal disease, and by doing so, perhaps contribute to the understanding of the complex biological interactions that regulate glioma development and control.

To date, the primary differentiating factor for glioma survival is tumor histology; patients with glioblastoma experience the worst survival regardless of treatment. However, recent reports suggest that glioma survival can also be modified by germ line polymorphisms in several genes, including *HLA-A*, *HLA-B*, *GLTSCR1*, *ERCC2*, *GSTP1*, and *GSTM1* (1, 2). In addition, a polymorphism in the ataxin 2-binding protein gene (*A2BP1* rs8057643) was associated with a significant reduction in time to death in a population of 112 patients with newly diagnosed glioblastoma (2). Wrensch et al. also reported that the *ERCC1* C8092A (rs3212986) and *GSTT1* deletion polymorphisms were significantly associated with glioma survival (1). These studies lend support to the hypothesis that genetic factors may be important in glioma prognosis.

Variants in inflammatory genes contribute to individual susceptibility in risk for atopic disorders, which have been linked to protection against various malignancies, including gliomas (3, 4). It is therefore relevant to examine such polymorphisms in relation to not only glioma risk but also survival. Interleukin-4 (IL-4) is important, in conjunction with IL-13, in

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[6] American Cancer Society. Cancer facts and figures 2007 [accessed 07-01-2007]: http://www.cancer.org/downloads/STT/caff2007PWSecured.pdf.

the regulation of allergic inflammation. These two cytokines interact with heterodimers of IL-4 and IL-13 receptors to directly affect inflammation and allergy through activation of the Janus-activated kinase and signal transducer and activator of transcription pathways. The interactions of several non-synonymous coding single nucleotide polymorphisms (SNP) in *IL4*, *IL13*, and *IL4R* have been associated with asthma (5–8), infection-related inflammation (9, 10), and glioma risk (11).

Although some studies have examined the effects of SNPs in inflammation genes on the risk of developing glioma, few have focused on their effects on glioma survival. Previous etiologic studies provide evidence that polymorphisms in the *IL4R* gene may play important roles in the pathways that regulate glioma development and control, whether by influencing IgE levels and thus affecting the effectiveness of treatment or through a more direct pathway that is currently unknown. Thus, the purpose of the current study was to examine the association between seven common polymorphisms in the *IL4*, *IL13*, and *IL4R* genes, and overall, as well as long-term, patient survival.

Materials and Methods

Subjects. Cases were adults (18 years or older) with newly diagnosed glioma (ICD-O-3 codes 9380-9481) identified by hospital physicians in Harris County, TX between January 2001 and January 2006. Glioma diagnosis was confirmed by the study neuropathologist (K.D. Aldape). Blood samples were collected from the cases before initiation of chemotherapy or radiation therapy, but in most cases, this was after initial surgical resection. The original study population (n = 761) was restricted to non-Hispanic whites (n = 694) for the genetic analyses presented here. The male to female ratio was 1.4:1 with 92% of patients being non-Hispanic white. Other detailed information on the study population has been previously reported (12). The study was approved by the institutional review boards of all participating institutions, and written informed consent was obtained from each participant.

Determination of vital status. Treatment and survival (overall and disease-free) data were collected from medical record review for all cases. This was done in a systematic way to determine the medical treatment course, dates of treatment, and survival information. For patients not followed at the M. D. Anderson Cancer Center, the patient or next-of-kin was contacted as allowed by institutional review board approval to request release of medical records for abstraction, and to update treatment and survival information.

Table 1. Study population characteristics and genotypes by tumor histology

	All cases (n = 694)	By histology		
		High grade (n = 343)	Medium/low grade (n = 351)	*P*
Sex				
Male	419 (60)	210 (61)	209 (60)	
Female	275 (40)	133 (39)	142 (40)	0.65
Chemotherapy				
Yes	473 (70)	233 (72)	240 (69)	
No	201 (30)	92 (28)	109 (31)	0.41
Radiation therapy				
Yes	573 (83)	306 (89)	267 (76)	
No	121 (17)	37 (11)	84 (24)	<0.0001
Surgery extent				
Gross total	305 (44)	158 (52)	147 (48)	
Subtotal	388 (56)	185 (48)	203 (52)	0.28
Age at diagnosis				
Median (range)	45.50 (18.00-72.80)	52.29 (20.10-72.80)	38.32 (18.00-65.00)	
Mean (SD)	44.62 (11.78)	50.38 (9.85)	38.99 (10.76)	<0.0001
IL4 rs243250				
CT/TT	194 (30)	94 (29)	100 (31)	
CC	449 (70)	227 (71)	222 (69)	0.62
IL13 rs1800925				
CT/TT	240 (37)	116 (36)	124 (39)	
CC	403 (63)	205 (64)	198 (61)	0.53
IL4R rs1805011				
AC/CC	133 (21)	68 (21)	65 (20)	
AA	511 (79)	253 (79)	258 (80)	0.73
IL4R rs1805012				
CT/CC	126 (20)	65 (20)	61 (19)	
TT	517 (80)	257 (80)	260 (81)	0.71
IL4R rs1805015				
CT/CC	188 (29)	99 (31)	89 (28)	
TT	454 (71)	220 (69)	234 (72)	0.33
IL4R rs1801275				
AG/GG	232 (36)	121 (38)	111 (34)	
AA	412 (64)	200 (62)	212 (66)	0.38
IL4R rs1805016				
GT/GG	71 (11)	37 (12)	34 (11)	
TT	573 (89)	284 (88)	289 (89)	0.69

NOTE: Values in table expressed as n (%).

SNP selection and genotyping. SNPs in the *IL4*, *IL13*, and *IL4* genes were selected for this pathway-based analysis from a panel of proinflammatory and anti-inflammatory genes. Nonsynonymous coding SNPs and SNPs previously reported to be associated with atopic disorders or glioma were selected for genotyping using the Sequenom MassARRAY iPLEX platform. This multiplexed assay provides call rates of >95%. Quality control analysis included genotyping internal positive control samples, no template controls, and replicates for 10% of the samples. Positive, negative, and DNA controls were organized in specific patterns on the genotyping plates to ensure correct plate orientations during processing and to assist in the quality control process and data review.

Statistical analyses. The distribution of population characteristics was examined, overall and by tumor histology, using the χ^2 test for categorical variables and Student's *t* test for continuous variables. Analyses were stratified by histology because of dramatic differences in survival for high-grade (grade 4) versus intermediate-grade/low-grade (grades 3/2) tumors. Survival time was calculated beginning at the date of hospital registration.

Total survival probability over time and survival probability beyond 12 months were visualized, overall and stratified by genotype, using Kaplan-Meier survival curves created with SAS PROC LIFETEST. Log-rank tests were used to determine significant differences ($\alpha = 0.05$) in survival curves stratified by genotype. Furthermore, yearly survival probabilities conditional upon surviving the previous year in two *IL4R* SNPs (IL4R805015 and IL4R805016) and the *IL4R* haplotype were calculated among high-grade glioma patients using the Kaplan-Meier life table method.

Cox proportional hazards regression, using SAS PROC TPHREG, was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for each SNP, adjusting for age at diagnosis, chemotherapy, radiation therapy, extent of surgery, and time between hospital registration and diagnosis among the entire cohort and among those surviving beyond 1 year. Probable haplotypes for the five *IL4R* SNPs were calculated using SAS PROC HAPLOTYPE using an expectation-maximization algorithm to calculate the maximum-likelihood estimate of the haplotype frequencies.[7] The SNPs were ordered according to numerical position in the gene: rs1805011, rs1805012, rs1805015, rs1801275, and rs1805016. HRs and 95% CI were computed for the most probable haplotype, compared with all others, and with Cox proportional hazards regression. The proportional hazards assumption for each model was tested using log-log plots; there was no evidence that the proportional hazards assumption was violated for any of the models. All statistical analyses were conducted in SAS, version 9.1.

Results

Of the 694 non-Hispanic white cases included in this analysis, 343 (49.4%) had high-grade (grade 4) glioma and 351 (50.6%) had low-grade (grade 2) or intermediate-grade (grade 3) glioma. Included in the high-grade group were 340 glioblastomas and 3 gliosarcomas. In the intermediate-grade group, there were 138 anaplastic astrocytomas, 87 anaplastic oligodendrogliomas, 23 anaplastic oligoastrocytomas, 3 anaplastic ependymomas, and 1 anaplastic glioma not otherwise specified. In the low-grade group, there were 46 oligodendrogliomas, 18 oligoastrocytomas, 17 astrocytomas, 5 juvenile pilocytic astrocytomas, 5 gliomas not otherwise specified, 4 gangliogliomas, 2 ependymomas, and 2 pleomorphic xanthoastrocytomas. Table 1 presents the distribution of demographic characteristics and SNP genotypes by histologic group. High-grade glioma cases were older at diagnosis, on average, and were more likely to have received radiation therapy.

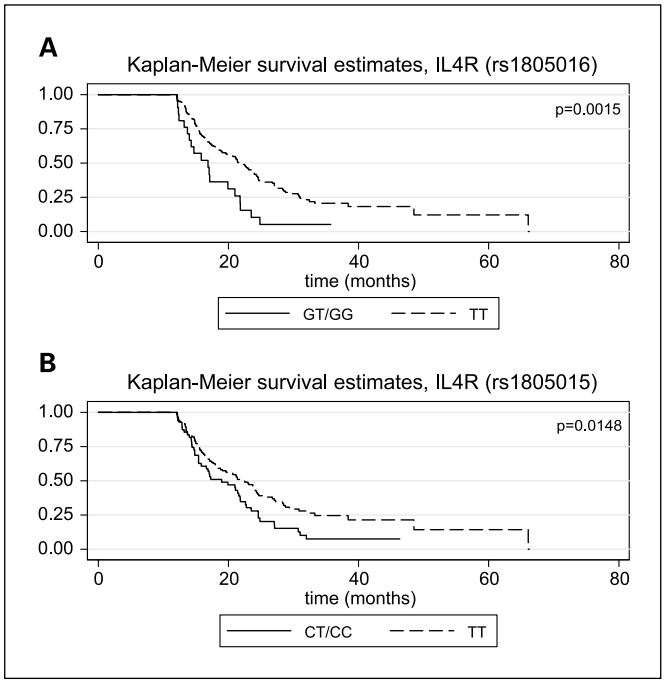

Fig. 1. Kaplan-Meier survival curves beyond 12 mo by genotype for IL4R SNPs among high-grade gliomas. *A,* patients with the TT genotype for IL4R rs1805016 SNP experienced a median survival 4 mo longer than those with the GT/GG genotypes. *B,* patients with the TT genotype for IL4R rs1805015 SNP experienced a median survival 5 mo longer than those with the CT/CC genotypes. The benefit of the TT genotypes seemed to increase as the patients lived longer.

Using Cox regression, we found that the *IL4R* rs1805016 T allele is significantly protective against mortality over time among high-grade glioma cases (HR, 0.59; 95% CI, 0.40-0.87); although not among the low-grade and intermediate-grade cases. Furthermore, when we restricted the survival curves to only those high-grade patients who survived beyond 12 months, we saw a significant increase in survival for those carrying the TT genotype of rs1805016 or rs1805015, both in the *IL4R* gene (Fig. 1). None of the other polymorphisms examined were significantly associated with overall or long-term glioma survival for either histologic group (Table 2).

When examining combinations of SNPs for the *IL4R* gene, the most probable haplotype (A-T-T-A-T) had an estimated frequency of 79%. Compared with all other haplotypes, it was associated with a 20% decrease in mortality hazard of borderline statistical significance (HR, 0.80; 95% CI, 0.61-1.04) among those with high-grade gliomas, but not medium/low-grade tumors (Table 2). This *IL4R* haplotype was also significantly associated with long-term survival among patients with high-grade glioma (HR, 0.68; 95% CI, 0.48-0.96).

Yearly survival estimates conditional on surviving the previous year were calculated for two of the *IL4R* SNPs and for the *IL4R* haplotype that showed significant effects in the Cox models among high-grade gliomas. The results shown in Fig. 2 are consistent with those seen in Fig. 1. High-grade patients with the IL4R805015 CT/CC genotype had poorer year-to-year survival, the longest surviving just past 3 years, compared with those patients with the TT genotype. A very similar trend is seen with the IL4R805016 SNP. Among

[7] SAS Genetics Software Brochure [accessed 07-01-2007]: http://www.sas.com/industry/pharma/genetics/brochure.pdf.

high-grade patients, those with the TT genotype had ~41.7% survival between year 1 and year 2 of follow-up, whereas those with the GT/GG genotype only had 10.4% survival between those years. Finally, the effect of having the *IL4R* haplotype on year-to-year survival was favorable comparable to not having the haplotype and showed a moderate protective effect.

Discussion

Age and tumor grade are key prognostic factors in glioma survival (13). Although some germ line genetic factors have been suspected of playing an important role in prognosis, none have been firmly established. Previous investigations into SNPs in inflammatory genes have mostly focused on their effects on glioma risk, not disease prognosis. However, the current study found that two nonsynonymous SNPs in the *IL4R* gene, rs1805015 and rs1805016, are significantly associated with long-term survival among patients with high-grade glioma. In addition, the most common haplotype of the *IL4R* SNPs (A-T-T-A-T) showed a moderate protective effect overall and a statistically significant long-term protective effect, among cases with high-grade glioma.

Table 2. Associations between *IL4, IL13*, and *IL4R* SNPs and high and medium/low grade glioma

SNP rs no.	High grade			Medium/low grade		
	n	Died	HR (95% CI)*	*n*	Died	HR (95% CI)*
Overall survival						
IL4 rs243250						
CT/TT	94	68	ref.	100	33	ref.
CC	227	170	1.03 (0.76-1.39)	222	78	1.10 (0.73-1.66)
IL13 rs1800925						
CT/TT	116	83	ref.	124	41	ref.
CC	205	155	1.14 (0.87-1.51)	198	70	1.33 (0.90-1.97)
IL4R rs1805011						
AC/CC	68	52	ref.	65	28	ref.
AA	253	186	0.97 (0.70-1.34)	258	83	0.71 (0.46-1.11)
IL4R rs1805012						
CT/CC	65	49	ref.	61	26	ref.
TT	257	190	0.99 (0.71-1.37)	260	83	0.66 (0.42-1.04)
IL4R rs1805015						
CT/CC	99	78	ref.	89	35	ref.
TT	220	158	0.80 (0.60-1.06)	234	76	0.79 (0.53-1.19)
IL4R rs1801275						
AG/GG	121	91	ref.	111	43	ref.
AA	200	147	0.90 (0.68-1.18)	212	68	0.83 (0.57-1.22)
IL4R rs1805016						
GT/GG	37	32	ref.	34	10	ref.
TT	284	206	0.59 (0.40-0.87)	289	101	1.42 (0.73-2.75)
IL4R haplotype						
A-T-T-A-T†	220	158	0.80 (0.61-1.04)	270	90	0.87 (0.62-1.21)
Survival beyond 1 year						
IL4 rs243250						
CT/TT	59	43	ref.	81	19	ref.
CC	128	90	0.82 (0.56-1.19)	180	54	1.30 (0.77-2.20)
IL13 rs1800925						
CT/TT	72	51	ref.	105	29	ref.
CC	115	82	1.00 (0.69-1.43)	156	44	1.29 (0.79-2.08)
IL4R rs1805011						
AC/CC	41	32	ref.	51	18	ref.
AA	146	101	0.75 (0.49-1.13)	211	55	0.70 (0.40-1.23)
IL4R rs1805012						
CT/CC	40	31	ref.	47	16	ref.
TT	147	102	0.75 (0.50-1.14)	214	56	0.69 (0.39-1.24)
IL4R rs1805015						
CT/CC	57	46	ref.	69	20	ref.
TT	129	86	0.63 (0.44-0.91)	193	53	0.93 (0.55-1.57)
IL4R rs1801275						
AG/GG	67	50	ref.	88	25	ref.
AA	120	83	0.83 (0.58-1.19)	174	48	0.97 (0.60-1.59)
IL4R rs1805016						
GT/GG	21	19	ref.	28	5	ref.
TT	166	114	0.44 (0.27-0.73)	234	68	1.93 (0.77-4.84)
IL4R haplotype						
A-T-T-A-T†	129	86	0.68 (0.48-0.96)	226	64	0.91 (0.61-1.37)

*Adjusted for age at diagnosis, time between diagnosis and registration, chemotherapy, extent of surgery, and radiation therapy.
†SNPs are ordered rs1805011, rs1805012, rs1805015, rs1801275, and rs1805016. Referent group includes individuals without haplotype genotype.

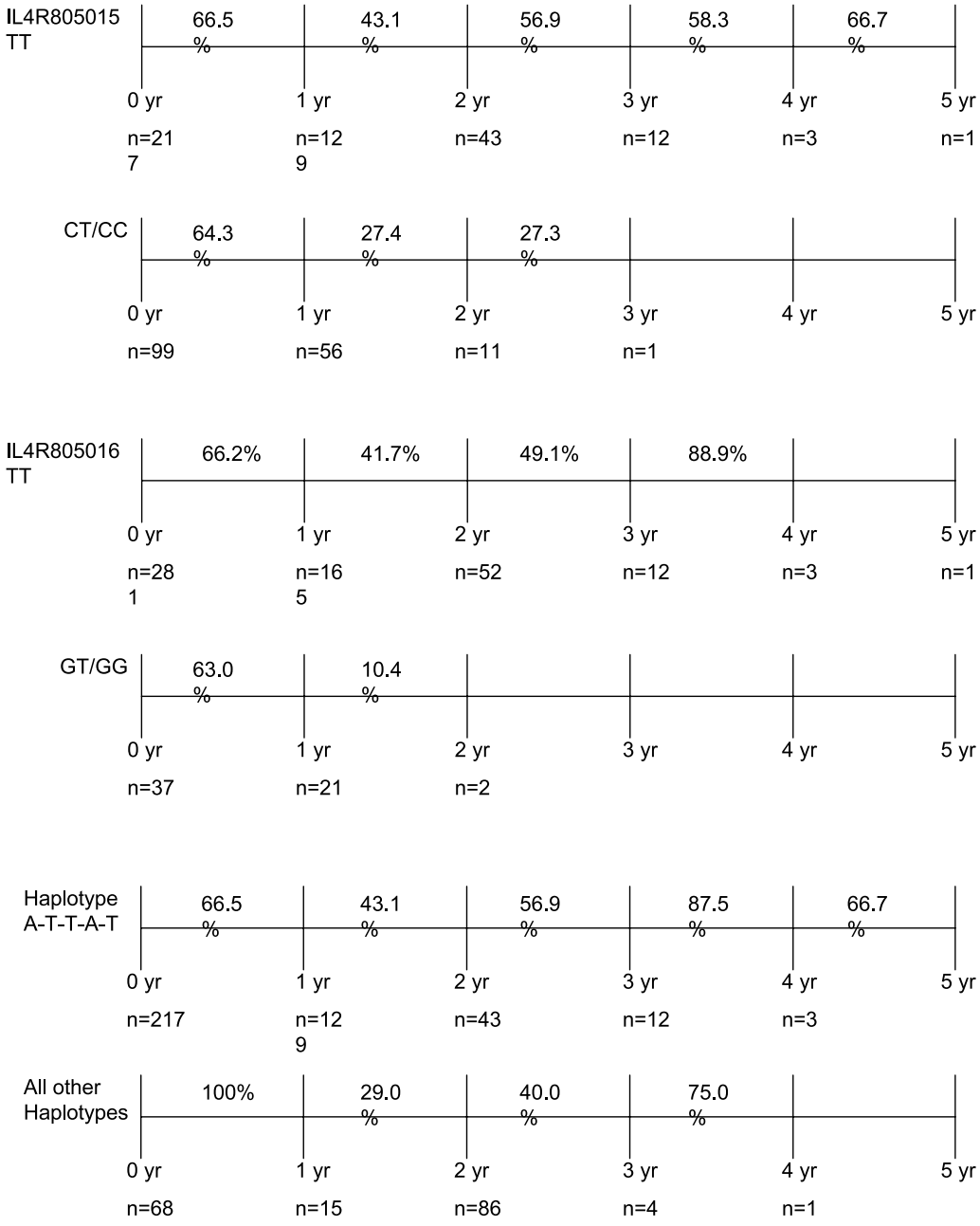

Fig. 2. Conditional yearly survival estimates for IL4R SNPs and haplotype among high-grade gliomas. Patients with the TT genotype for either SNP or with the A-T-T-A-T haplotype experienced better survival beyond 1 y when compared with other genotypes or haplotypes. This is consistent with and supports both the Cox regression models and the Kaplan-Meier curves for these SNPs and the haplotype. These genotypic differences were not experienced by patients with low-grade or anaplastic tumors.

Median survival time for patients with glioblastoma is usually considered to be ~1 year; however, for patients seen at tertiary care centers, the median survival has been increasing in recent years. Indeed, in our study group, overall median survival was 14.8 months for patients with high-grade glioma compared with just over 6 years for those in the low-grade/intermediate-grade group. However, among high-grade patients surviving past the median survival time, the effects of SNPs in the inflammatory genes seem to be more pronounced. It is clear that the range of survival times for those without the TT genotype at the IL4R805015 and IL4R805016 SNPs was much shorter among these high-grade glioma patients. The TT genotype for IL4R SNP rs1805016 was significantly associated with both overall and long-term survival, and the TT genotype of the *IL4R* SNPs rs1805015 was also significantly associated with survival past 12 months among patients with high-grade glioma. It is possible that during the first year after diagnosis, the effects of the disease and treatment mask the modulatory effects of these SNPs on survival. Our findings also lend support to this hypothesis by showing that during the first year of follow-up, the survival probabilities between the patients with different genotypes of the IL4R805015 and IL4R805016

SNPs were very similar. However, the 1- to 2-year survival probabilities between the genotypes diverge, indicating that the TT genotype for both SNPs may confer a protective effect after the first year of follow-up, and thus the effects of the inflammatory SNPs themselves would only be detectable among long-term survivors.

A few studies have reported on the effects of inflammatory pathways on glioma etiology, and several inflammatory gene SNPs have been shown to be important in glioma risk. For example, Schwartzbaum et al. examined SNPs in *IL4R*, *IL13*, and *ADAM33* in a population-based case-control study of 111 glioblastoma cases from Swedish regional cancer registries and 422 randomly selected controls (11). The *IL4R* SNPs T478C (C allele; rs1805015) and A551G (A allele; rs1801275) were significantly associated with increased glioma risk (odds ratio, 1.64; 95% CI, 1.05-2.55 and odds ratio, 1.61; 95% CI, 1.05-2.47, respectively). Another recent report by Wiemels et al. examined SNPs in the *IL4*, *IL4R*, and *IL13* genes among 456 glioma cases and 541 controls (14). They found that the *IL13* Arg110Gln (rs20541) and C-1112T (rs1800925) SNPs were significantly associated with higher IgE levels in the controls ($P < 0.05$ for both). Furthermore, the T allele of the *IL13* C-1112T polymorphism was protective against being a case ($P = 0.05$). Although they did not find a significant association between single polymorphisms in the *IL4* and *IL4R* genes, they did find an *IL4R* haplotype, different from our current findings, that was associated with an increase in glioma risk, although of borderline statistical significance (odds ratio, 1.5; 95% CI, 1.0-2.3). They also found that another rare *IL4* haplotype was inversely associated with glioma risk (odds ratio, 0.23; 95% CI, 0.07-0.83). These etiologic studies provide some clues about how polymorphisms in the *IL4R* gene are involved in the pathways that regulate glioma development and, in conjunction with our current findings, about glioma control and prognosis.

Although most published studies focus on glioma etiology, Wrensch et al. used population-based glioma patients from the San Francisco Bay Area Adult Glioma Study to conduct a study of prognostic factors, examining the association between survival and SNPs in various genes, including *IL4R* (1). They found that two *IL4R* SNPs (rs1805011 and rs1805012) were significantly associated with survival from "all gliomas", but not with glioblastoma survival, at an α level of 0.05. They also found that the number of *IL4R* variants was associated with slightly better survival (HR, 0.94; 95% CI, 0.90-0.99; $P = 0.03$). However, the two *IL4R* SNPs implicated in the current study (rs1805015 and rs1805016) did not prove to be significantly associated with glioblastoma survival in their study population (HR, 0.82; 95% CI, 0.64-1.07 and HR, 0.95; 95% CI, 0.63-1.43, respectively). Unlike the current study, Wrensch and colleagues included both white and non-white subjects, although they did adjust for race in their model. We restricted our current analysis to a non-Hispanic white population due to the differences in incidence and survival times between non-Hispanic whites and African Americans and the vast differences in minor allele frequencies of inflammation-related genes between whites and non-whites. Although our findings indicated that *IL4R* rs1805015 was important for survival beyond 1 year, our estimate for the effect of this SNP on overall survival was remarkably similar to that of Wrensch et al. (HR, 0.80; 95% CI, 0.60-1.06). Regardless, it is clear that additional studies are needed to clarify the association between these SNPs and the prognosis among different study populations, and that these studies should account for possible population stratification due to race and ethnicity.

Having a history of immune hyperactivity, such as allergies, asthma, other atopic diseases, is associated with decreased glioma risk (3, 11, 14). Cytokine-responsive genes include those that code for IgE, as well as the α component of the IL-4 receptor. The IL-4 receptor is expressed in several tissues, including the brain, which reflects the fact that this receptor has a wide range of functions. Although the specific mechanisms by which the *IL4R* polymorphisms examined here may affect patient survival are unknown, there are several end points of the pathway, potentially affected by these genetic variants, which are relevant to the carcinogenic process. For example, activation of the IL-4 pathway may lead to increased cell proliferation, cell growth, or apoptosis depending on which signal transduction pathway becomes initiated. Furthermore, certain *IL4R* SNPs, such as rs1805010, have already been shown to have a functional effect on IgE level by up-regulating the receptor's response to IL-4, which in turn, results in the activation of the Stat6 pathway (15). Although the functional effects of many of the SNPs examined here are largely unknown, if they lead to an overexpression or underexpression of IgE, the resulting change in the inflammatory response could have an effect on treatment efficacy, therefore potentially affecting survival. Therefore, future studies of the functionality of these SNPs are warranted to fully understand their effects on brain tumor control.

This study adds to the small, yet growing, body of literature examining the role of genetic prognostic factors for malignant gliomas. The number of glioma patients included in this analysis allowed us to examine genetic effects by histologic subtype. Given the dramatic differences in prognosis and treatment by histologic type, this is important when examining survival for these patients. In the future, we hope to examine the effects of these SNPs on treatment outcome, including adverse events, as well as survival. This study was limited to non-Hispanic white patients, a consequence of limited access to minority patients, due partly to the fact that glioma incidence among these populations is lower than the incidence among non-Hispanic whites. Although we found significant genetic effects on survival for two SNPs in the *IL4R* gene, further studies in other populations are needed to validate and support our findings.

Disclosure of Potential Conflicts of Interest

M. Gilbert is a member of the speakers' bureaus of Schering-Plough and Genentech.

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