Polymorphisms Associated with Asthma Are Inversely Related to Glioblastoma Multiforme

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Abstract

A reduced risk of primary malignant adult brain tumors is observed among people reporting asthma, hay fever, and other allergic conditions; however, findings may be attributed to prediagnostic effects of tumors or recall bias. To determine whether asthma and allergic condition polymorphisms are inversely related to glioblastoma multiforme (GBM) risk, we conducted a population-based case-control study of 111 GBM patients and 422 controls. We identified five single nucleotide polymorphisms on three genes previously associated with asthma [interleukin (IL)-4RA, IL-13, ADAM33] and one gene associated with inflammation (cyclooxygenase-2). Confirming previous literature, we found that self-reported asthma, eczema, and fever are inversely related to GBM [e.g., asthma odds ratio (OR), 0.64; 95% confidence interval (CI), 0.33-1.25]. In addition, IL-4RA Ser478Pro TC, CC, and IL-4RA Gln551Arg AG, AA are positively associated with GBM (OR, 1.64; 95% CI, 1.05-2.55; 1.61; 95% CI, 1.05-2.47), whereas IL-13 −1,112 CT, TT is negatively associated with GBM (0.56; 95% CI, 0.33-0.96). Each of these polymorphism-GBM associations is in the opposite direction of a corresponding polymorphism-asthma association, consistent with previous findings that self-reported asthmatics and people with allergic conditions are less likely to have GBM than are people who do not report these conditions. Because we used germ line polymorphisms as biomarkers of susceptibility to asthma and allergic conditions, our results cannot be attributed to recall bias or effects of GBM on the immune system. However, our findings are also consistent with associations between IL-4RA, IL-13, and GBM that are independent of their role in allergic conditions. (Cancer Res 2005; 65(14): 6459-65)

Introduction

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor accounting for 23.0% of all primary brain and central nervous system tumors and 51.9% of all gliomas. The median age at diagnosis is 65 years and the age-adjusted incidence rate is 3.24/100,000 although it increases to 13.74/100,000 for ages 65 to 74. The average 5-year relative survival rate from time of diagnosis for GBM is only 3.3% and is lower for people age >65 years at diagnosis (0.3%; ref. 1).

There is evidence for a role of the immune system in GBM growth and development (2). In particular, a consistent inverse association between self-reported allergic conditions and glioma has recently been reported in a cohort and several case-control studies (3–7). Although the cohort study had a rather small number of cases, case-control results can be subject to preclinical effects of the tumor on the immune system or to errors in recall among brain tumor patients who may have cognitive deficits (depending on tumor lateralization and type of therapy; ref. 8). Wiemels et al. take another approach to the question of whether allergic disease reduces brain tumor risk by comparing serum IgE levels of cases and controls (9). Although they find that glioma patients have lower serum IgE levels than do controls, the possibility that the tumor itself or its treatment may affect serum IgE levels cannot be excluded. In general, definitive evidence of associations between immunologic biomarkers and glioma risk must be based on measurements taken well before the time of tumor diagnosis. To avoid the influence of the brain tumor itself on an indicator of susceptibility to asthma or allergic conditions, we used germ line polymorphisms previously associated with asthma and other allergic conditions as biomarkers of susceptibility. Clearly, these genetic variants cannot be influenced by the presence of a brain tumor.

The rationale for using polymorphisms to test the validity of asthma and allergy self-reports is not their superior sensitivity or specificity to self-report because most individual polymorphisms are neither sensitive nor specific indicators of complex diseases (10). Furthermore, asthma, and to a lesser extent allergy, self-reports are relatively sensitive indicators of these conditions (11, 12). Rather, the advantage of using germ line polymorphisms as biomarkers of susceptibility is that, unlike asthma self-report or possibly IgE levels, they cannot be influenced by the presence of GBM and therefore case and control asthma and allergy measurements are subject to the same degree of error. Although this error may reduce the size of measures of association between asthma or allergic conditions and GBM, it will not cause the measure of association to change direction, as may happen when case and control allergic conditions are each measured with a different degree of error (13).

From the extensive literature on asthma and allergic condition polymorphisms, we selected genetic variants that are consistently associated with asthma or allergic conditions in at least two populations and whose functions relate to either glioma development or normal brain physiology. Two of the polymorphisms that meet these criteria are Ser478Pro and Gln551Arg on the interleukin (IL)-4 receptor α gene (IL-4RA; ref. 14). These IL-4RA polymorphisms are associated with asthma and allergies in 2 and 11 studies, respectively, each study based on different populations (15).

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Two additional polymorphisms consistently associated with asthma and other allergic conditions are Arg130Gln (16) and −1,112 C/T (17) on the IL-13 gene. Associations between these two IL-13 polymorphisms and asthma or allergic conditions have been identified in nine and four studies, respectively (15). IL-4 and IL-13 are cytokines that share immunoregulatory functions and a common IL-4RA chain on their receptors. They both play a central role in allergy by inducing IgE synthesis and both can inhibit inflammatory cytokines (18, 19). Importantly for the present research, IL-4 and IL-13 show strong antitumor activity in mice and inhibit proliferation of astrocytoma and low-grade glioma cell lines (20, 21).

We also looked at the T1 polymorphism of a newly identified asthma gene, ADAM33 (22), that was found to be associated with asthma in three different populations (22–24). This gene is a member of a family of matrix metalloproteases, extracellular proteases that participate in matrix degradation and glioblastoma invasion (25).

Finally, the last polymorphism that we evaluated is found on the cyclooxygenase-2 (COX-2) gene (−765 GC) and is associated with postsurgical C-reactive protein levels (ref. 26; C-reactive protein is produced in response to inflammatory cytokines during the acute phase response). Although IL-4 and IL-13 function as proinflammatory mediators in asthma, allergy, and helminth infection, these cytokines also have antiinflammatory properties resulting, in part, from their inhibition of both cell-mediated immune responses (27, 28) and COX-2 expression (29). In addition, our selection of the COX-2 gene was based on our previous findings of an inverse association between nonsteroidal antiinflammatory drug use and GBM (30).

Materials and Methods

Glioma and meningioma cases that occurred in Sweden between September 1, 2000 and August 31, 2002 were identified in collaboration with brain tumor treatment centers. Regional cancer registries were searched approximately every third month for additional case identification, to make sure that no cases had been missed. This system was effective in reducing the time between diagnosis and interview as indicated by the fact that proxy interviews were necessary for only 9% of glioma and 3% of meningioma cases (a low proportion of proxy interviews when compared with other brain tumor studies; ref. 7). We restricted our study to the most common type of adult glioma, GBM, to reduce genetic heterogeneity.

Controls were randomly selected within strata defined by glioma or meningioma patients' age, sex, and geographic region from a continuously updated population registry. Computer-assisted interviews were conducted by research nurses. Information collected on allergies included questions about whether the participant had been diagnosed with asthma, hay fever, or eczema and the length of time these conditions were present. In addition, data were collected on allergy medication including type of medication and frequency of use. Although information concerning type of glioma of individuals who refused to participate was not available to investigators (to protect nonrespondents' privacy), we know that of the 499 glioma patients,

Table 1. Demographic variables and age- and sex-adjusted self-reported physician-diagnosed asthma and allergic condition and inflammation variables from population-based Swedish case-control study of GBM (2000-2002)

Demographic variables	All study participants		
	Cases (n = 174)	Controls (n = 633)	
Median age (interquartile range)	56 (49-62)	53 (43-60)	
Sex (% male; 95% CI)	59.18 (51.89-66.49)	48.02 (44.14-51.90)	
Allergic and inflammatory variables	**Cases* (n)**	**Controls* (n)**	**ORs (95% CI)**
None	163	570	1.00
Asthma	11	63	0.64 (0.33-1.25)
None	147	532	1.00
Hay fever	27	101	0.98 (0.62-1.57)
None	141	490	1.00
Asthma or hay fever	33	143	0.82 (0.54-1.26)
None	144	485	1.00
Eczema	29	148	0.67 (0.43-1.05)
None	160	573	1.00
Contact allergy	12	46	1.02 (0.53-2.00)
None	161	583	1.00
Food allergy	11	37	1.23 (0.61-2.49)
None	151	523	1.00
Allergy medication	23	110	0.78 (0.48-1.27)
Fever never (last 10 years)	43	102	1.00
Fever once or less per year	83	410	0.54 (0.35-0.84)
Fever two or more times per year	24	92	0.78 (0.43-1.40)

*Differences in numbers of cases and controls among variables are attributable to missing responses.

73.9% agreed to be interviewed, and of the 956 potential controls identified, 66.2% agreed to be interviewed. However, once interviewed, slightly more controls (66.7%) than GBM cases (63.8%) consented to having their blood drawn.

Statistical analysis. We used unconditional logistic regression to compare case and control polymorphism prevalence adjusted for age and sex. The variable geographic region had no influence on our findings so we eliminated it from our regression models.

Genotyping. Dynamic allele-specific hybridization (DASH) was done as previously described (31–35). For this, two PCR primers and one DASH probe per target mutation/single nucleotide polymorphism (SNP) were designed by means of custom software (36) provided by DynaMetrix, Ltd. (United Kingdom). These oligonucleotides were provided and HPLC purified by Biomers GmbH (Germany). The DASH PCRs entailed amplifying 50 to 90 bp genomic fragments spanning the variant of interest, with one of the primers carrying a 5′-biotin label. Amplifications were done in 5 μL volume, containing 1 to 2 ng genomic DNA, 0.38 μmol/L biotinylated primer, 0.75 μmol/L nonbiotinylated primer, 0.03 units AmpliTaq Gold (PE Biosystems, Foster City, CA), 10% DMSO, 1× AmpliTaq Gold Buffer including 1.5 mmol/L of MgCl2 (Applied Biosystems, Foster City, CA) and 0.2 mmol/L each deoxynucleotide triphosphate. Thermal cycling was conducted on an MBS 384 device (Thermo-Hybaid, Ashford, United Kingdom) as follows; 1× (10 minutes at 94°C), 35× (15 seconds at 94°C, 30 seconds at annealing temperature). To verify successful amplification, 0.5 μL of several randomly chosen samples were examined on a 3.0% low-melt agarose gel.

DASH analysis of the PCR product was conducted on membrane macroarrays, using the DASH-2 protocol (34). Briefly, this entailed transferring samples to the membrane array by centrifugation or robotic gridding (37). Resulting individual arrays with up to 9,600 distinct samples/features were rinsed in 0.1 mol/L NaOH to denature the PCR products, and then exposed to 2 mL HE buffer [0.1 mol/L HEPES, 10 mmol/L EDTA (pH 7.9)] containing 4 nmol of suitable probe, itself end-labeled with ROX. After heating to 85°C and cooling to room temperature, the membrane was briefly rinsed in HE buffer. The array was then soaked in 40 mL HE-buffer containing SYBR Green I dye at 1:20,000 dilution for up to 3 hours. Using a DASH-2 device (DynaMetrix), the membrane was taken through a DASH heating ramp (heating at 3°C/min from room temperature to 85°C) as fluorescence from the ROX acceptor dye on the probe was monitored. Data were collected at intervals of 0.5°C. Fluorescence changes with temperature (DNA melting profiles) were used to distinguish different alleles, and this was done by means of the DASH-2 device software which uses negative derivatives of fluorescence against temperature to reveal peaks of denaturation rate (target-probe melting temperatures; Tm) and thereby automatically assign DNA samples into genotype groups. Finally, a random sample of 15% of all DNA samples was reassayed and the genotype assignment confirmed. An error rate of <1% was observed.

No samples were sequenced because DASH is an extensively validated method (31–35). Quality control data included in the preceding references confirms the error rate of the method across many different SNPs is <0.1%.

Results

In Table 1, the distributions of age, sex, and allergic condition variables are shown for interviewed cases and controls who did

Table 1. Demographic variables and age- and sex-adjusted self-reported physician-diagnosed asthma and allergic condition and inflammation variables from population-based Swedish case-control study of GBM (2000-2002) (Cont'd)

Interviewed only			Interviewed and collected blood sample		
Cases (*n* = 63)	Controls (*n* = 211)		Cases (*n* = 111)	Controls (*n* = 422)	
57 (53-63)	52 (41-58)		55 (46-61)	54 (44-61)	
58.73 (46.48-70.78)	53.08 (46.34-59.82)		59.46 (50.29-68.63)	45.50 (40.75-50.23)	
Cases* (*n*)	Controls* (*n*)	ORs (95% CI)	Cases* (*n*)	Controls* (*n*)	ORs (95% CI)
57	186	1.00	106	384	1.00
6	25	0.76 (0.29-2.00)	5	38	0.53 (0.20-1.38)
52	176	1.00	95	356	1.00
11	35	1.16 (0.54-2.50)	16	66	0.82 (0.47-1.60)
49	159	1.00	92	331	1.00
14	52	0.88 (0.44-1.77)	19	91	0.77 (0.45-1.34)
47	172	1.00	97	313	1.00
16	39	1.54 (0.97-3.08)	13	109	0.40 (0.21-0.74)
59	157	1.00	101	378	1.00
2	9	1.06 (0.20-5.57)	10	37	1.09 (0.52-2.29)
60	196	1.00	101	387	1.00
1	10	0.63 (0.07-5.31)	10	27	1.55 (0.72-3.30)
55	182	1.00	96	341	1.00
8	29	1.04 (0.43-2.50)	15	81	0.70 (0.38-1.28)
15	35	1.00	28	67	1.00
32	132	0.68 (0.37-1.45)	51	278	0.46 (0.27-0.79)
11	25	1.37 (0.51-3.68)	13	67	0.53 (0.25-1.14)

and did not consent to having their blood drawn. Overall, results are similar except when the sample size for a category is small, as is the case for the variable food allergy among people who did not have their blood drawn. For both groups, there are consistent inverse relationships between self-reported asthma, eczema, fever during the 10 years prior to the interview and GBM. The reason that cases and controls differ with respect to age (median age for all participants: cases, 56 years; controls, 53 years) and sex (for total participants: male cases, 59.18%; male controls, 48.02%) is that we include controls who were initially matched to age and sex of all glioma and meningioma cases (see Materials and Methods).

The second column of Table 2 shows previously reported associations between the first five polymorphisms and asthma (14, 16, 17, 22). Column 3 contains results from the present study for associations of these same polymorphisms with GBM. For each SNP, odds ratios for asthma that are greater than or less than the null value (OR, 1.0) correspond to odds ratios for GBM that are greater than or less than the null value. However, because reference categories that we use for the two diseases differ, our findings indicate that these asthma susceptibility polymorphisms have opposite relationships with asthma and GBM. For example, individuals with the TT polymorphism for the IL-4RA Ser478Pro SNP seem to be more susceptible to asthma and less susceptible to GBM than are individuals with the TC or CC variants. Also reported at the bottom of the second column are maximum levels of C-reactive protein after coronary bypass surgery stratified on alleles of the COX-2 −765 GC polymorphism (26). The odds ratio characterizing the association between the COX-2 polymorphism and GBM indicates that higher postsurgical levels of C-reactive protein, perhaps indicating a stronger acute phase inflammatory response, are associated with a greater risk of GBM.

Further details describing associations between each of the six polymorphisms and GBM are reported in columns 4 to 8 of Table 2. The genotype distribution of GBM cases and controls is shown together with the same distributions for asthma cases and controls from previous literature. For each of the first five polymorphisms, if GBM and asthma cases and controls are ranked by the percentage having the most common polymorphism, GBM and asthma cases are at the extremes and controls lie between them. For example, for the IL-13 −1,112 C/T polymorphism, 80% of GBM cases have the CC genotype, whereas only 58% of asthma cases are in this category. This pattern is reversed for IL-4RA Ser478Pro where a gradient from GBM (59% TT genotype) to asthma cases (77% TT genotype) can be seen. The order of these percentages does not change when people reporting asthma or other allergic conditions are excluded from the GBM case group (data not shown). GBM asthma and control genotype distributions are similar, except those for the ADAM33, T1 SNP (22). These control distributions remain similar when people with asthma or other allergic conditions are excluded from the GBM control group (data not shown).

In Fig. 1 the previously reported effect of the interaction between IL-4RA Ser478Pro and IL-13 −1,112 C/T on asthma risk is shown (14). Consistent with findings in Table 2, GBM odds ratios are inversely associated with previously reported asthma odds ratios. Although we find no similar interaction in the present study among GBM controls (the middle bar labeled 4 is not higher than the sum of middle bars labeled 2 and 3), asthma genotype odds ratios in our sample are similar to those previously reported. However, there is little additional evidence of associations between individual asthma susceptibility polymorphisms reported in Table 2 and self-reported asthma, hay fever, fever, or any of the allergic conditions shown in Table 1 among controls in our data (data not shown). Nor did our findings change when asthma or allergic condition variables were stratified on age at onset or duration of disease.

Discussion

Using previously identified polymorphisms as biomarkers of susceptibility to asthma, we found an association between three of these biomarkers (IL-4RA Ser478Pro TC, CC; IL-4RA Gln551Arg AG, AA; and IL-13 −1,112 CT, TT) and GBM. In addition, as predicted by both previous epidemiologic and asthma susceptibility polymorphism literature (3–7, 14, 16, 17, 22, 26, 38), odds ratios for GBM were the inverse of those for asthma. Ours is the first study to suggest the validity of the consistently observed inverse association between self-reported asthma and GBM because we used biomarkers that cannot be altered by the presence of GBM. By basing our selection of polymorphisms on strong a priori epidemiologic and genetic evidence (2), we reduce the risk of false-positive results which so often characterize the genetic polymorphism literature (39). However, because the individual polymorphisms that we identified are not related to self-reported asthma or allergic conditions among controls in our data, our results may reflect a relationship between IL-4RA, IL-13, and GBM that is independent of their role in asthma and other allergic conditions.

Asthma is an inflammatory disease of lung airways that may or may not have an allergic component. Here we define allergy as immune reactions to common environmental proteins characterized by elevated IgE levels and distinguished by allergic symptoms from atopy. Although asthma and other allergic conditions such as hay fever are clinically distinct, they are genetically linked. For example, the AG and AA genotypes of the IL-13 Arg130Gln polymorphism are associated with atopy, allergen-specific IgE, and asthma (16). A further manifestation of this genetic association among allergic conditions is that within the same family, individuals may have allergic diseases of different target organs such as asthma, hay fever, and eczema (40). Because of this genetic link, inferences from our findings can be extended from asthma to other allergic conditions.

Possible reasons for our failure to find expected associations between individual polymorphisms and allergic conditions among controls include both the relatively small numbers of controls reporting asthma or allergic conditions and misclassification of these conditions. In most case-control studies of asthma, all study participants (including controls) are actively screened for asthma by spirometry, reversibility to albuterol or bronchial responsiveness testing to albuterol (24). Whereas in the present study asthma and other allergic conditions are identified only by self-report of physician diagnosis. Errors in measurement of allergic conditions may also explain the reason for relatively weak associations between allergic conditions (Table 1, measured with error) and GBM as opposed to relatively strong associations between allergic disease susceptibility polymorphisms (Table 2, measured with little error) and GBM (41).

Additional evidence for an association between allergic conditions and GBM includes the findings of Weimels et al. (9) that glioma cases have lower serum IgE levels than do controls, however, their findings need to be validated with prospectively collected data. Perhaps related to the role of allergic disease in the etiology of GBM, are findings from a clinical trial of an IgE blocking drug for asthmatics (Omalizumab) that show a higher rate of solid tumors in

the treatment group compared with the control group (rate ratio for solid tumors excluding nonmelanoma skin cancer, 3.8; 95% CI, 0.9-34.3; ref. 42). However, because the number of tumors found is relatively small (Omalizumab group, $n = 16$; control group, $n = 2$), random allocation of study participants may not have equally distributed individuals with differing prior risks of cancer to the treatment and control groups.

It is also possible that IL-4RA and IL-13 play a role in GBM development that is independent of their roles in asthma and allergic conditions. The function of IL-4 and IL-13 in brain tumor growth has been the subject of several investigations. Barna et al. found that three normal astrocytic, two low-grade astrocytoma, and three out of four GBM cell lines that they evaluated express IL-4Rα receptors. However, IL-4 suppresses DNA synthesis and cell proliferation only in the normal astrocytic and low-grade astrocytoma cell lines but not in the GBM cell lines (21). Their results suggest that IL-4 may interfere with progression from lower to higher grade glioma but may have no role in *de novo* glioblastomas (43). Saleh et al. attribute the growth-inhibiting properties of mouse IL-4 on implanted C6 glioma cell lines to its

Table 2. Sex- and age-adjusted associations between asthma polymorphisms and GBM from population-based Swedish case-control study (2000-2002), and comparisons with previously published associations between polymorphisms and asthma or inflammatory conditions

Gene (SNP)	Previous asthma literature	GBM (present study)				Previous asthma literature	
	Asthma, OR (95% CI)	GBM, OR (95% CI)	GBM, OR (trend test)	GBM, cases*,† *n* (%)	GBM controls*,† *n* (%)	Asthma cases (%)	Asthma controls (%)
IL-4RA (rs1805015, Ser478Pro)	Asthma (14)					Asthma (14)	
TT	1.96 (1.13-3.44)	1.00	1.00	64 (59)	288 (70)	77	63
TC	1.00	1.64 (1.05-2.55)	1.73	40 (37)	107 (26)	20	33
CC			1.09	4 (4)	16 (4)	3	4
			$P = 0.07$ (trend)				
IL-4RA (rs1801275, Gln551Arg)	Asthma (14)					Asthma (14)	
AA	1.25 (0.72-2.01)	1.00	1.00	53 (49)	243 (60)	68	64
AG	1.00	1.61 (1.05-2.47)	1.52	45 (41)	236 (34)	26	32
GG			2.09	11 (10)	24 (6)	5	4
			$P = 0.02$ (trend)				
IL-13 (rs20541, Arg130Gln)	Asthma (16)					Asthma (16)	
GG	0.48 (0.30, 0.76)	1.00	1.00	74 (67)	254 (60)	36	54
AG	1.00	0.75 (0.48-1.17)	0.81	33 (30)	144 (33)	48	39
AA			0.41	3 (3)	24 (7)	16	7
			$P = 0.12$ (trend)				
IL-13 (rs1800925, −1,112 C/T)	Asthma (17)					Asthma (17)	
CC	0.51 (0.31-0.84)	1.00	1.00	84 (80)	277 (69)	58	73
CT	1.00	0.56 (0.33-0.96)	0.55	18 (17)	111 (28)	37	25
TT			0.64	3 (3)	15 (4)	5	2
			$P = 0.05$ (trend)				
ADAM33 (rs2280091, T1)	Asthma (22)					Asthma (22)	
TT	0.24 (0.15-0.39)	1.00	1.00	82 (77)	297 (71)	58	85
TC	1.00	0.82 (0.50-1.33)	0.85	24 (22)	106 (26)	37	14
CC			0.56	2 (1)	13 (3)	6	1
			$P = 0.35$ (trend)				
COX-2 −765 GC	C-reactive protein levels (26)*					C-reactive protein (26)‡	
GG	173.64	1.00	1.00	80 (74)	286 (72)		75
GC	149.57	0.84 (0.45-1.57)	0.90	27 (25)	105 (26)		24
CC			0.52	1 (1)	8 (2)		1
			$P = 0.53$ (trend)				

*Differences in numbers of cases and controls among polymorphisms reflect failure to identify genotype for some DNA samples.
†Numbers in parentheses are percentages of genotypes for GBM cases and controls excluding people reporting physician-diagnosed asthma or hayfever.
‡Papafili et al. (26) do not report C-reactive protein distribution of case group.

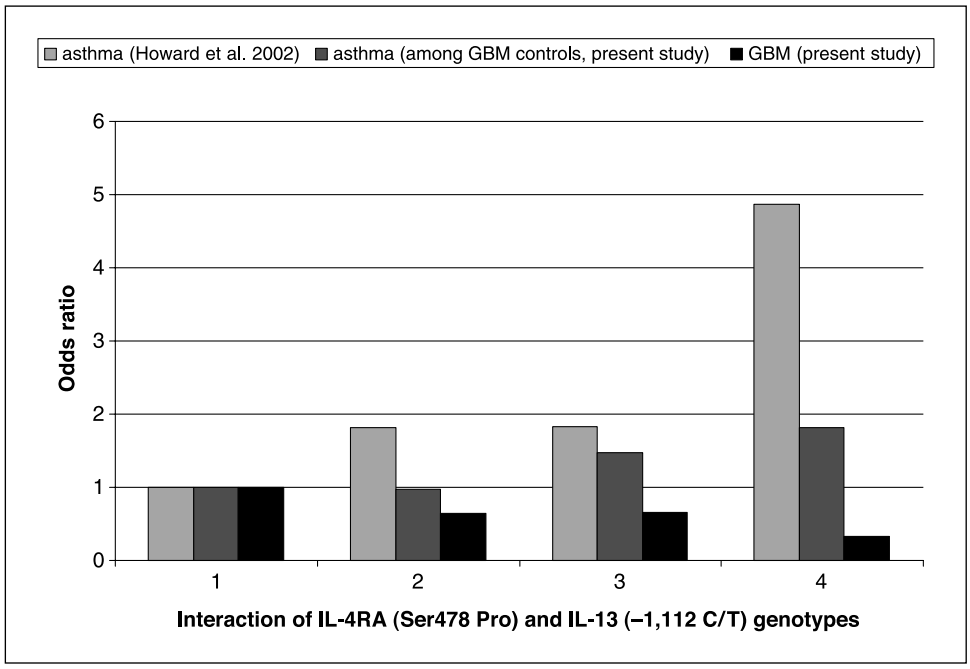

Figure 1. Interaction between IL-4RA ($Ser^{478}Pro$) and IL-13 (−1,112 C/T) genotypes in a Dutch population for asthma (14), a Swedish populaion for GBM, and asthma among GBM controls in a Swedish population. (1) IL-4RA (TC, CT) / IL-13 (CC); (2) IL-4RA (TT) / IL-13 (CC); (3) IL-4RA (TC, CC) / IL-13 (CT, TT); (4) IL-4RA (TT)/ IL-13 (CT, TT).

ability to promote eosinophil infiltration and to inhibit angiogenesis. Furthermore, Saleh et al. observe that implantation of C6 cell gliomas that produce IL-4 retrovirus are rapidly eradicated in rats (44, 45). Consistent with Saleh et al.'s results, Volpert et al. show that IL-4 blocks corneal neovascularization by fibroblast growth factor in mice as well as inhibiting the migration of cultured bovine and human microvascular cells (46). However, because IL-4 is species-specific, the above findings may not be directly applicable to human disease.

IL-13 shares the IL-4Rα signaling receptor chain with IL-4, and like IL-4, inhibits astrocyte and low-grade astrocytoma proliferation but does not inhibit GBM cell proliferation (20). In addition, Shin et al. found that IL-13 controls brain inflammation by inducing death of activated microglia (major inflammatory cells of the central nervous system; ref. 47). Further evidence for a role of IL-13 in GBM development or growth comes from the overexpression of IL-13Rα2 receptors in glioblastoma tissue (48, 49). The role of these receptors in GBM cells is to inhibit IL-13- and IL-4-dependent signal transduction (50).

Not only do IL-4 and IL-13 not inhibit cell growth in GBM (as they seem to do in lower grade gliomas) but also IL-4 or IL-13 stimulation of IL-4RA contributes to the pathogenesis of GBM cells (51). In addition, Madhankumar and Debinski found that IL-13 stimulates a signaling cascade that increases the oncogenic potential of GBM cells (52). There is also extensive evidence indicating that IL-13 down-regulates antitumor response by indirectly suppressing production of cytotoxic T cell production (ref. 53; although these effects have not been observed for brain tumors, they may be in the future). As a consequence, Berzofsky et al. have suggested a possible benefit of IL-13 withdrawal as a means of both increasing antitumor immunity and the efficiency of vaccines (54). There are also proposals that asthma and allergic conditions could be prevented or treated by inhibiting IL-13 production (55, 56).

Our findings of an inverse association between IL-4RA, IL-13 polymorphisms, and GBM suggest that IL-13 withdrawal therapies to treat allergic conditions may interfere with possible tumor-inhibiting effects of this cytokine in the brain. However, if these tumor-inhibiting effects occur early in GBM development then perhaps reducing endogenous IL-13 production after GBM development may still be beneficial.

Further research should include investigation of additional allergy susceptibility polymorphisms, use of biomarkers of allergic conditions measured before GBM diagnosis, and validation of asthma and allergic condition self-reports. Overall, one of the goals of subsequent research should be to determine whether allergic conditions per se or their related cytokines affect GBM risk.

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