



## Original Contribution

# Associations of High-Grade Glioma With Glioma Risk Alleles and Histories of Allergy and Smoking

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Glioma risk has consistently been inversely associated with allergy history but not with smoking history despite putative biologic plausibility. Data from 855 high-grade glioma cases and 1,160 controls from 4 geographic regions of the United States during 1997–2008 were analyzed for interactions between allergy and smoking histories and inherited variants in 5 established glioma risk regions: 5p15.3 (*TERT*), 8q24.21 (*CCDC26/MLZE*), 9p21.3 (*CDKN2B*), 11q23.3 (*PHLDB1/DDX6*), and 20q13.3 (*RTEL1*). The inverse relation between allergy and glioma was stronger among those who did not (odds ratio<sub>allergy-glioma</sub> = 0.40, 95% confidence interval: 0.28, 0.58) versus those who did (odds ratio<sub>allergy-glioma</sub> = 0.76, 95% confidence interval: 0.59, 0.97;  $P_{\text{interaction}} = 0.02$ ) carry the 9p21.3 risk allele. However, the inverse association with allergy was stronger among those who carried (odds ratio<sub>allergy-glioma</sub> = 0.44, 95% confidence interval: 0.29, 0.68) versus those who did not carry (odds ratio<sub>allergy-glioma</sub> = 0.68, 95% confidence interval: 0.54, 0.86) the 20q13.3 glioma risk allele, but this interaction was not statistically significant ( $P = 0.14$ ). No relation was observed between glioma risk and smoking (odds ratio = 0.92, 95% confidence interval: 0.77, 1.10;  $P = 0.37$ ), and there were no interactions for glioma risk of smoking history with any of the risk alleles. The authors' observations are consistent with a recent report that the inherited glioma risk variants in chromosome regions 9p21.3 and 20q13.3 may modify the inverse association of allergy and glioma.

allergy and immunology; glioma; hypersensitivity; polymorphism, single nucleotide

Abbreviations: Duke-UIC, Duke University Medical Center-University of Illinois, Chicago; SNP, single nucleotide polymorphism; UCSF, University of California, San Francisco.

Infiltrating glioma is the most common class of primary brain tumor, but little is known about the factors that lead to its development. Exposure to ionizing radiation (1, 2) and history of a familial cancer such as Li-Fraumeni or Turcot syndrome are well-recognized risk factors, but they explain only a very small proportion of glioma cases. Allergy has been consistently shown to be inversely related to glioma risk (3). Although it has been long supposed that smoking could increase risk of glioma through exposure of the brain to the numerous carcinogens in tobacco smoke, a large majority of studies of this topic have shown no association (4–7). The

recent genome-wide association studies of our group and another group identified inherited variants in 5 chromosomal regions associated with adult glioma risk, specifically: 5p15.3 (*TERT*), 8q24.21 (*CCDC26/MLZE*), 9p21.3 (*CDKN2B*), 11q23.3 (*PHLDB1/DDX6*), and 20q13.3 (*RTEL1*) (8, 9). Identification of interactions between inherited glioma risk variants and clinically apparent immune system activation, such as allergy or environmental exposures including smoking, could help to identify mechanisms of gliomagenesis. Schoemaker et al. (10) recently reported that the inverse association of allergy with glioma risk was significantly modified

by glioma risk alleles on 9p21.3 (rs4977756), and 20q13.3 (rs6010620). Here, we report the main effects on high-grade glioma risk for histories of medically diagnosed allergy and smoking and assess whether known glioma risk loci modify the effects of these risk factors using data from 3 US adult glioma case-control studies.

## MATERIALS AND METHODS

### Patient populations, questionnaire instruments, and data examined

Data were collected from 3 case-control studies conducted at 4 institutions—Mayo Clinic, Rochester, Minnesota; University of California, San Francisco (UCSF); Duke University Medical Center, Raleigh, North Carolina; and University of Illinois, Chicago (Duke-UIC). Two of these studies (Mayo Clinic and UCSF) were the basis for the genome-wide association study reported by Wrensch et al. (8). All participants for these analyses were white adults over the age of 20 years, and all cases were diagnosed with pathologically confirmed high-grade glioma (anaplastic astrocytoma or glioblastoma multiforme). These studies were approved by the Mayo Clinic Office for Human Research Protection, the University of California, San Francisco, Committee on Human Research, and the Duke University Health System Institutional Review Board. Informed consent was obtained from all study participants.

At the Mayo Clinic, cases were identified from a referral-based practice from 2005 to 2008. At UCSF, cases diagnosed from 1997 to 2004 were identified through the Northern California Rapid Case Ascertainment Program and the UCSF Neurooncology Clinic. At Duke-UIC, cases were recruited between August 2003 and April 2008 from Duke University Medical Center and the North Shore University Medical Center in Illinois.

Controls from the Mayo Clinic were identified from general internal medicine practices and were matched to the Mayo Clinic cases on age, gender, ethnicity, and residence. UCSF controls were identified by using random digit dialing and were frequency matched to UCSF cases on age, gender, ethnicity, and residence. At Duke-UIC, clinic-based controls were recruited from the Duke University Medical Center orthopedic and North Shore University Medical Center neurology clinics and were frequency matched to cases by age, gender, and ethnicity; additional details of this study are described elsewhere (11, 12).

Participation rates varied by study and by case status. At the Mayo Clinic, participation rates were 90% for controls and 86% for cases. At UCSF, out of 872 eligible white controls identified by random digit dialing and 526 eligible white cases with a high-grade astrocytoma, 602 (69%) controls and 319 (61%) cases gave blood, completed a questionnaire, and were included in this analysis. At Duke-UIC, 53% of eligible controls and 37% of eligible cases were participants in this study.

Medically significant allergy and smoking histories were obtained by interviewer-administered questionnaires at UCSF and Duke-UIC and by interviewer-assisted, self-administered questionnaires at the Mayo Clinic. The Mayo Clinic questionnaires

asked, “Have you ever been told by a doctor that you have allergy?” and “Did you ever smoke 100 cigarettes or more during your lifetime?” The UCSF questionnaires asked participants, “Were you ever told by a doctor that you have any allergies?” and “Have you ever smoked more than 100 tobacco cigarettes (5 packs) or cigars or pipe bowls in your life?” The Duke-UIC questionnaires asked, “Has any health care worker ever told you before 2 years ago that you had allergy?” and “Did you ever smoke 100 cigarettes or more during your lifetime?”

### Genotyping

*Mayo Clinic/UCSF.* Genotyping was performed on all Mayo Clinic cases and controls by using the Illumina 610 platform (Illumina, San Diego, California). We have previously described single nucleotide polymorphism (SNP) genotyping and quality control measures for UCSF cases and controls by use of the Illumina 370 duo array panel (8).

*DUKE-UIC.* Allelic discrimination was done by using the TaqMan assay on the Applied Biosystems Prism 7700 system (Life Technologies Corporation, Carlsbad, California). Center for Human Genetics genotyping quality control measures were divided into pregenotyping (DNA handling and set up) and postgenotyping (assessment of genotype data quality). DNA samples from cases and controls were intercalated within a microtiter plate, when genotyping in a plate format (96 well or 384 well) by real-time polymerase chain reaction (TaqMan). A number of asymmetrically arranged quality control DNAs were routinely included to highlight experimental errors (either in DNA aliquoting or chemistry of the reaction) if the duplicate DNA samples did not segregate in the same genotyping clusters.

Ten glioma risk SNPs from 5 regions were analyzed: rs2736100 in region 5p15.3 of the *TERT* gene; rs4295627 in region 8p24.21 of the *CCDC26* gene; rs1063192, rs1412829, rs2157719, and rs4977756 in region 9p21.3 of the *CDKN2A/B* gene; rs498872 in region 11q23.3 of the *PHLDB1* gene; and rs6089953, rs4809324, and rs6010620 in region 20q13.3 of the *RTEL1* gene.

### Statistical analysis

The frequency distribution at each SNP locus was tested against the Hardy-Weinberg equilibrium under the Mendelian biallelic expectation by using the chi-square test. SNPs with Hardy-Weinberg equilibrium  $P < 0.001$  for control subjects were excluded from the analysis. An additive logistic regression model for 0, 1, or 2 copies of the minor allele for each candidate SNP was used to investigate the association of glioma risk. Logistic regression was also used to investigate the association of smoking history or medically diagnosed allergy with glioma risk. To assess for differences across study site for the risk exposures, we fit logistic regression models with exposure, study site, and exposure  $\times$  study site interaction as the independent variables. For each SNP and exposure of interest, 2-way interactions between the SNP and exposure were investigated. When appropriate, stratified logistic regression models by the exposure or allele of interest were fit. For all models, case/control status was the dependent

**Table 1.** Demographic Characteristics and Odds Ratios of High-Grade Glioma (Anaplastic Astrocytoma and Glioblastoma) for Medically Significant Allergy and Smoking Histories, Stratified by Medical Center—Mayo Clinic, University of California, San Francisco, and Duke University Medical Center—University of Illinois, Chicago, 1997–2008

	Total No. <sup>a</sup>	Median Age, years	Male Gender		History of Allergies					Ever Smoked a Cigarette				
			No.	%	No.	%	OR	95% CI	P Value <sup>b</sup>	No.	%	OR	95% CI	P Value <sup>b</sup>
Mayo Clinic														
Cases	176	54	109	61.9	75	43.1	1.15	0.75, 1.77	0.53	77	44	1.02	0.67, 1.57	0.92
Controls	174	54.5	110	63.2	68	39.5				76	43.7			
UCSF														
Cases	319	57	198	62.1	74	34.3 <sup>c</sup>	0.53	0.37, 0.75	0.0004	182	57.4	1.05	0.79, 1.38	0.75
Controls	602	57	317	52.7	179	50 <sup>d</sup>				336	55.8			
Duke-UIC														
Cases	360	53	233	64.7	112	31.1	0.53	0.38, 0.72	<0.0001	167	46.4	0.74	0.55, 1.00	0.05
Controls	384	58	178	46.4	186	48.4				209	54.4			
Pooled							0.62	0.51, 0.76	<0.0001			0.92	0.77, 1.10	0.37

Abbreviations: CI, confidence interval; Duke-UIC, Duke University Medical Center—University of Illinois, Chicago; OR, odds ratio; UCSF, University of California, San Francisco.

<sup>a</sup> The Mayo Clinic cases include 62 anaplastic astrocytomas and 114 glioblastomas; the UCSF cases include 50 anaplastic astrocytomas and 269 glioblastomas; the Duke-UIC cases include 84 anaplastic astrocytomas and 276 glioblastomas.

<sup>b</sup> To assess for main effect (ever smoked cigarettes, history of allergies) differences, a model was fit with case/control as the dependent variable and main effect, medical center, and the main effect × medical center interaction as independent variables. Age and gender were also included as covariates. The  $P_{\text{interaction}}$  with medical center for each main effect was 0.004 for allergies and 0.12 for ever smoked cigarettes. This indicates significant main effect differences for the association of glioma with allergies across medical centers.

<sup>c</sup> Data were available for 216 subjects.

<sup>d</sup> Data were available for 358 subjects.

variable, and age and gender were included as covariates. Pooled analyses across all 3 study sites were performed by using logistic regression. Study site was included as a covariate in these analyses. Although the main effects for all 10 glioma risk SNPs are presented in Web Table 1, the first of 4 Web tables posted on the *Journal's* Web site (<http://aje.oupjournals.org/>), we present results for interactions only for the SNPs, with the strongest associations in regions with more than 1 risk locus (i.e., the 8p24.21, 9p21.3, and 20q13.3 regions).

## RESULTS

This analysis of data from 3 case-control studies and 4 institutions included 350 participants from the Mayo Clinic; 921 from the University of California, San Francisco; and 744 from Duke-UIC (Table 1). Separate analysis of data from these 3 study sites suggests some variation in associations of allergy with glioma by study site (Table 1), with no association observed at the Mayo Clinic and significant inverse associations observed at UCSF and Duke-UIC. No association of glioma with smoking history was observed at Mayo or UCSF, but a significant inverse association of ever smoking with glioma was seen at Duke-UIC (Table 1). As noted in footnote b to Table 1, the  $P_{\text{interaction}}$  with medical center for each main effect was 0.12 for ever smoked cigarettes and 0.004 for allergies, indicating main effect differences for allergies across medical centers. The pooled results (Table 1) strongly confirm an inverse relation between glioma and

medically diagnosed allergy with an odds ratio of 0.62 (95% confidence interval: 0.51, 0.76;  $P < 0.0001$ ). The pooled results indicate no relation between ever smoking greater than 100 cigarettes and glioma risk (odds ratio = 0.92, 95% confidence interval: 0.77, 1.10;  $P = 0.37$ ) (Table 1). SNP association analysis results from the 3 data sets presented separately and pooled (Web Table 1) show a consistent association for multiple SNPs on chromosome regions 9p21.3 and 20q13.3 with high-grade glioma, further corroborating our previous 2-center findings (8).

With respect to stratified analyses by allergy and smoking history, consistent associations were observed for linked loci in regions with multiple risk loci (data not shown), but, as noted above, for simplicity we present only the results for 1 locus per region. We observed a significant interaction on glioma risk between allergy history and risk alleles on 9p21.3 and a notable, but nonsignificant interaction with allergy history and risk alleles on 20q13.3 (Tables 2 and 3). The inverse association of allergy history with glioma was stronger in people who did not carry the 9p21.3 risk allele than in those who did ( $P_{\text{interaction}} = 0.02$ ). For the 20q13.3 region, however, the inverse allergy-glioma association was more marked in those who carried the risk allele; the interaction, however, was not statistically significant ( $P = 0.14$ ). As with the main effects, there were some differences among study sites for these interactions (refer to Web Table 2). There was no interaction of allergy history with glioma risk SNPs on 8q24.21 in the pooled data; however, interactions were observed with data from the Mayo

**Table 2.** Odds Ratios of High-Grade Glioma With History of Medically Significant Allergy Stratified by 0 Versus 1 or 2 Risk Alleles in 3 SNPs—Mayo Clinic, University of California, San Francisco, and Duke University Medical Center—University of Illinois, Chicago, 1997–2008

Risk Alleles and No. of Risk Alleles	For Allergy		P Value	SNP-Allergy <sup>a</sup> P <sub>Interaction</sub>
	OR	95% CI		
rs4295627 (8q24.21, allele C)				
0	0.61	0.48, 0.79	<0.001	0.47
1 or 2	0.64	0.45, 0.90	0.01	
rs4977756 (9p21.3, allele G)				
0	0.40	0.28, 0.58	<0.001	0.016
1 or 2	0.76	0.59, 0.97	0.03	
rs4809324 (20q13.3, allele G)				
0	0.68	0.54, 0.86	0.001	0.14
1 or 2	0.44	0.29, 0.68	<0.001	

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.

<sup>a</sup> Adjusted for age, gender, and medical center.

Clinic study (Web Table 2). No interactions with allergy history for risk SNPs in chromosome region 5p15.33 or 11q23.3 were observed in pooled or study site-specific data (data not shown).

There were no significant interactions between any risk alleles and smoking history on glioma risk (Web Tables 3 and 4); data are not shown for 5p15.3, 11q23.3, or separate study sites.

**Table 3.** Odds Ratios of High-Grade Glioma With 3 SNPs Stratified by History of Medically Significant Allergy—Mayo Clinic, University of California, San Francisco, and Duke University Medical Center—University of Illinois, Chicago, 1997–2008

Risk Alleles and Allergies	For 1 or 2 Versus 0 Risk Alleles		P Value	SNP-Allergy <sup>a</sup> P <sub>Interaction</sub>
	OR	95% CI		
rs4295627 (8q24.21, allele C)				
Yes	1.40	1.06, 1.86	0.02	0.47
No	1.22	0.97, 1.52	0.09	
rs4977756 (9p21.3, allele G)				
Yes	1.59	1.27, 2.00	<0.001	0.016
No	1.13	0.95, 1.34	0.18	
rs4809324 (20q13.3, allele G)				
Yes	1.25	0.89, 1.76	0.2	0.14
No	1.80	1.35, 2.38	<0.001	

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.

<sup>a</sup> Adjusted for age, gender, and medical center.

## DISCUSSION

In this study of high-grade glioma, we pooled data from 3 case-control studies (Mayo Clinic, UCSF, and Duke-UIC) from 4 geographic regions of the United States. Allergy history has been shown to be a protective risk factor. Smoking is a biologically plausible but unproven environmental risk factor. We examined potential interactions between these factors and inherited glioma risk alleles. The main findings of this study are that glioma risk alleles may modify the strength of the inverse relation between glioma risk and a history of medically diagnosed allergy. In particular, the association is significantly stronger among those who do not carry the glioma risk allele in the 9p21.3 region and is suggestively stronger among those who do carry the glioma risk allele in the 20q13.3 region. These pooled findings are consistent with the observations of Schoemaker et al. (10) who reported significant interactions in the same direction as above for “any allergy” and these glioma risk loci. This consistency emerges despite the variability we observed for findings at the individual sites. Variations in main effects and interactions of glioma risk with allergies and the glioma risk loci could be due to different selection criteria for controls, variation in prevalence of allergies due to regional or other unknown characteristics, or smaller sample size in individual versus pooled results that can increase rates of both false positive and false negative findings.

The inverse association between atopy and adult glioma has been observed in several previous studies (3). This finding of an inverse correlation with atopy has also been noted for childhood nervous system tumors, especially between asthma and eczema and primitive neuroectodermal tumors. These conditions have also appeared protective in other cancers (13, 14), particularly adult and childhood leukemia (15), non-Hodgkin’s lymphoma (16–18), and pancreatic cancer (19). Melanoma risk appears reduced for patients with a history of atopic dermatitis (20). There have been no consistent associations between atopy and breast, lung, and colorectal cancers, while the risk of prostate cancer appears consistently increased (21, 22). The consistency of the observed inverse association between atopy and cancer across many studies and types of malignancies, including some relating to childhood tumors, minimizes the possibility that this finding is due to recall bias, other biases, or other limitations of retrospective studies.

These observations raise a number of provocative questions about the complex interrelations between the molecular genetics and the cellular machinery of immune system function and unchecked cell growth in certain tissues. Some studies have implicated systemic immune suppression caused by the malignancy or its treatment in the decreased prevalence of allergy and lower immunoglobulin E levels in some cancer patients (23, 24), particularly glioma. However, in most cases, allergy history long predates the onset of cancer. Although one might hypothesize that upregulation of immune system components in atopy and asthma may be related to immunosurveillance and elimination of occult tumors, the current understanding of cancer immunity, especially immunoediting as discussed by Koebel et al. (25) and Teng et al. (26), suggests that other important immunologic components are antitumorogenic.

Our results and those of others suggest that the biologic basis for atopy, from germline variation to specific states of immune system activation, is related to the development of some malignancies. Atopy and asthma are complex polygenic disorders (27, 28). Multiple gene association studies have identified susceptibility traits in 4 major groups of genes: innate immunity and immunoregulation, Th2 differentiation and effector functions, epithelial biology and mucosal immunity, and lung function. These conditions are also associated with higher levels of total immunoglobulin E, a trait which is tightly genetically regulated and for which gene association studies have also identified relevant loci (29). Those patients with glioma who do have allergy and who also have the highest levels of immunoglobulin E may have significantly longer survival (24), implying a potential role for immune system activation.

We and others have examined glioma risk in relation to various components of immunoregulatory pathways, such as genetic polymorphisms in pertinent genes or RNA expression profiles for immunologic proteins or cytokines (30–33). Findings suggest that glioma risk may, in part, be related to genetic or gene expression variation involved in the expression of atopy and asthma. However, our study and the work of Schoemaker et al. (10) assess the interaction between polymorphisms specifically linked to glioma risk and the presence or absence of medically diagnosed allergy. Glioma germline risk variation may influence the expression of allergy and atopy. Conversely, the expression of allergy and atopy may influence 1 or more pathways of gliomagenesis, including the functional effects of germline variants. One might hypothesize that proteins encoded in these chromosome regions may influence immune function. For example, the 9p21.3 polymorphisms are in a region coding for *CDKN2B* (cyclin-dependent kinase inhibitor 2B) (p15) and adjacent to *CDKN2A* (p16). This region is commonly mutated or deleted in many tumors (34–36). The expression of p15 protein is strongly induced by transforming growth factor- $\beta$  (37), a family of cytokines also known to have numerous and diverse roles in immune system regulation. The SNPs on 9p21.3 are also weakly linked to a family of alpha interferon genes, potentially encoding numerous functions in the regulation of adaptive immunity, notably through regulation of T-cell and dendritic cell homeostasis (38). The SNPs on 20q13.3 are in the same region as *RTEL1* (regulator of telomere elongation helicase 1), a gene that regulates telomere length and maintains genomic stability by suppressing homologous recombination (39). They are also close to *LIME 1*, one of a family of transmembrane adaptor molecules found on normal and neoplastic lymphoid cells (40, 41). The exact role for this novel class of proteins has not been well worked out.

Further analysis of our genome-wide association study data shows that germline glioma risk polymorphisms can be stratified by morphologic subtype (42). Chromosome 8q24.21 SNPs are highly associated with oligodendroglioma, mixed oligoastrocytoma, and probably, lower grade astrocytoma, but not with glioblastoma. Chromosome 20q13.3 SNPs are strongly associated with glioblastoma but not with oligodendroglioma or oligoastrocytoma. The 9p21.3 SNPs are associated with astrocytomas of all grades, most strongly for

glioblastoma, and not at all for low-grade oligodendroglioma. Therefore, it is of some interest that neither our study nor that of Schoemaker et al. (10) found interaction between 8p24 glioma risk loci and allergy history, while both studies found significant or suggestive interactions with allergy history and risk loci in 9p21.3 and 20q13.3. This raises several questions, not the least of which is whether the inverse association between glioma risk and allergy holds equally for all morphologic subtypes, especially oligodendroglioma, which was not included in this present analysis.

Another way to consider this is that 9p21.3 risk loci confer glioma risk only among those reporting allergy history, while the 20q13.3 risk loci only confer glioma risk among those without allergy history. This latter observation for 20q13.3, a SNP that is most strongly associated with glioblastoma (42), has some parallel with findings of a recent report from Amirian et al. (30). They identified SNPs in 1 proinflammatory gene (*COX2/PTGS2*) and 2 antiinflammatory genes (*IL10* and *IL13*) that were significantly associated with glioma risk. This risk increased with the number of SNPs present. However, this risk association was found only in the absence of an asthma history. Taken together, these findings may suggest that different pathways to gliomagenesis may be influenced by the status of components of immune system pathways associated with atopy and/or asthma. The normal state may somehow be permissive for gliomagenesis in 1 pathway while protective in another.

Although smoking has been proposed as a risk factor for glioma (4, 6), the majority of studies have revealed no association (4–7). We examined smoking in this study, because the previous lack of main effects could be due to a lack of consideration of interaction with appropriate genetic factors (43). However, our present results strongly suggest that there is no significant risk for glioma due to smoking (Table 1), and the effect of glioma risk polymorphisms does not vary by smoking status (Web Tables 3 and 4). This, of course, does not rule out the possibility that other as yet unknown factors might influence glioma risk in conjunction with smoking history.

The main strength of this study is the large sample size obtained from pooling data from 4 different areas of the United States. The pooling of data ensured adequate statistical power for detecting interactions. Despite some differences in study designs and some variation in site-specific findings, the findings presented here are robust, biologically plausible, and consistent with previous observations regarding glioma risk and allergy in general, and they clearly confirm those presented by Schoemaker et al. (10). In summary, smoking definitely does not appear to influence high-grade glioma risk irrespective of the presence or absence of any of the established glioma risk alleles. However, the inverse relation between glioma and allergy was stronger among people who do not carry a glioma risk allele on 9p21.3 and among people who do carry a glioma risk allele on 20q13.3. These observations that germline alterations modify the inverse association of allergies and glioma risk add further evidence that this frequently observed association is biologically plausible. Further investigations of the biologic mechanisms behind this association are clearly warranted.

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