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Joint effects between five identified risk variants, allergy, and autoimmune conditions on glioma risk

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Abstract

Common variants in two of the five genetic regions recently identified from genome-wide association studies (GWAS) of risk of glioma were reported to interact with a history of allergic symptoms. In a pooled analysis of five epidemiologic studies, we evaluated the association between the five GWAS implicated gene variants and allergies and autoimmune conditions (AIC) on glioma risk (851 adult glioma cases and 3,977 controls). We further evaluated the joint effects between allergies and AIC and these gene variants on glioma risk. Risk estimates were calculated as odds ratios (OR) and 95 % confidence intervals (95 % CI), adjusted for age, gender, and study. Joint effects were evaluated by conducting stratified analyses whereby the risk associations (OR and 95 % CI) with the allergy or autoimmune conditions for glioma were evaluated by the presence or absence of the ‘at-risk’ variant, and estimated p interaction by fitting models with the main effects of allergy or autoimmune conditions and genotype and an interaction (product) term

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Conflict of interest

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

between them. Four of the five SNPs previously reported by others were statistically significantly associated with increased risk of glioma in our study (rs2736100, rs4295627, rs4977756, and rs6010620); rs498872 was not associated with glioma in our study. Reporting any allergies or AIC was associated with reduced risks of glioma (allergy: adjusted OR = 0.71, 95 % CI 0.55–0.91; AIC: adjusted OR = 0.65, 95 % CI 0.47–0.90). We did not observe differential association between allergic or autoimmune conditions and glioma by genotype, and there were no statistically significant p interactions. Stratified analysis by glioma grade (low and high grade) did not suggest risk differences by disease grade. Our results do not provide evidence that allergies or AIC modulate the association between the four GWAS-identified SNPs examined and risk of glioma.

Keywords

Single-nucleotide polymorphisms; Glioma; Allergies; Autoimmune conditions; Gene–environment interaction

BACKGROUND

Although glioma is a rare cancer, it accounts for over 80 % of malignant brain tumors in adults [1], with the only conclusively identified environmental/exogenous risk factor being exposed to ionizing radiation [2]. There is strong evidence for heritability of developing glioma as demonstrated by familial aggregation of cases and candidate gene studies [3–6]. Two recent genome-wide association studies (GWAS) independently identified five single-nucleotide polymorphisms (SNPs) associated with glioma (TERT, rs2736100; CDKN2A-CDKN2B, rs4977756; PHLDB1, rs489972; CCDC26, rs4295627; and RTEL, rs6010620) [7, 8]. Allergic symptoms and autoimmune conditions resulting from an overactive immune response to either environmental allergens or self-allergens have been consistently associated with reduced risk of glioma [9–12]. Two recent reports [13, 14] have suggested the existence of gene–environment interaction for glioma development between allergic symptoms and the recently reported GWAS SNPs, such that those with self-reported asthma and the minor allele variant of PHLDB1 rs498872 [13], and any allergic conditions and at least one risk allele of CDKN2A-CDKN2B rs4977756, RTEL rs6010620 [13, 14], had a significantly reduced risk of glioma compared to those with only the SNP variant or allergic symptom.

Here, we follow up on these reports by evaluating potential gene–environment interaction between the effects of allergy and five GWAS-identified SNPs on glioma risk. We further evaluate the role for a joint effect between autoimmune conditions and these same SNPs on glioma risk. Our analysis includes 851 adult glioma cases and 3,977 controls from three cohort studies and two case–control studies of adult brain tumors with rapid case ascertainment.

MATERIALS AND METHODS

Study population

Glioma cases and controls were selected from two case–control studies of adult brain tumors conducted by the National Cancer Institute (NCI) [15] and the National Institute for Occupational Safety and Health (NIOSH) [16] and three prospective cohort studies—the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial [17], the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study [18], and the Agricultural Health Study (AHS) [19]. These studies have been described in detail elsewhere [15–19] and are summarized in Supplemental Tables 1, 2a, and 2b. In all, 851 glioma cases (ICD-O-3 code 9380-9480) and 3,977 controls were included in the present analysis. Glioblastoma and malignant glioma accounted for the majority of the histopathologic subtypes (Supplemental Table 3). Briefly, the NCI case–control study is a hospital-based study of adult (age ≥ 18 years) brain tumors (including glioma, meningioma, and acoustic neuroma), conducted between 1994 and 1998 at Brigham and Women's Hospital in Boston, MA; St Joseph's Hospital and Medical Center in Phoenix, AZ; and Western Pennsylvania Hospital in Pittsburgh, PA. Cases (n = 351) were patients with histologically confirmed incident glioma. Controls were patients admitted to the same hospital for a variety of non-malignant conditions, frequency-matched to the cases (2:1) by hospital, age (10 year strata), sex, race/ethnicity, and distance of residence to the hospital. Eligible cases (n = 305) from the NIOSH case–control study were patients aged over 18 years with incident, histologically confirmed glioma diagnosed between January 1995 and January 1997. Cases were identified from participating medical facilities and neurosurgical offices in four Midwestern states (Iowa, Michigan, Minnesota, and Wisconsin). Population controls were glioma-free individuals randomly selected from 10-year age- and sex-specific strata of state driver license or non-driver identification records (for those between 18 and 64 years) or from Health Care Financing Administration Medicare records (for those between 65 and 80 years). Controls were frequency-matched to cases (1.5:1) by state of residence, sex, and age. The US Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (cohort) recruited 155,000 men and women between the ages of 55 and 74 from 1993 to 2001, at 10 US screening sites. Eligible participants were free of the cancers under study at enrollment and had provided blood or buccal cells. Cases (n = 140) were defined as incident primary gliomas (n = 26 self-reported cases are pending confirmation). Controls comprised 857 participants free of glioma for whom genome-wide scans were previously completed (Supplemental Table 1).

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study is a cohort based on a randomized intervention trial of 29,133 men (50–69 years old) who smoked at least five cigarettes per day at study entry and resided in southwestern Finland. Eligible participants were enrolled from 1985 to 1988. Cases (n = 37) were defined as incident primary gliomas. Controls comprised 1,270 participants free of glioma for whom genome-wide scans were previously completed.

The US Agricultural Health Study (AHS) is a prospective cohort study of 57,310 licensed pesticide applicators (primarily farmers) from Iowa and North Carolina and 32, 346 spouses of the farmers. Eligible participants were enrolled from 1993 to 1997. Cases (n = 18) were

defined as persons with incident (n = 14) or prevalent (n = 4) primary gliomas and were identified by linkage to the state cancer registries. Controls (n = 35) were selected in a 2:1 ratio and were frequency-matched to cases based on calendar year of birth (+/− 5 years), gender, and broad categories of race and ethnicity. Controls were alive and free of glioma on the calendar date their matched case was diagnosed (Supplemental Table 1).

Basic demographic characteristics (age, sex, and race/ethnicity), family history of cancer, and other exposure measures for study participants were obtained from study-specific questionnaires. In addition, personal history of asthma, hay fever, eczema, allergic skin condition, and other allergies were also extracted from questionnaires. Specific autoimmune conditions queried in the questionnaires included diabetes, rheumatoid arthritis, ulcerative colitis, Crohn's disease, lupus erythematosus, psoriasis, multiple sclerosis, pernicious anemia, scleroderma, Grave's disease, vitiligo, myasthenia gravis, and Sjogren's syndrome. Information on allergy and autoimmune conditions was harmonized across the five studies. 'Any allergy' was classified as a positive response to at least one of the aforementioned allergic conditions compared to none. Similarly, 'any autoimmune disease' was classified as reporting at least one of the above-listed autoimmune conditions compared to none. In addition to these aggregate variables, we also evaluated conditions with the prevalence of over 3 % (asthma, hay fever, eczema, rheumatoid arthritis, and diabetes) among the entire study population separately. Not all conditions were asked about in all studies (Supplemental Table 5). Supplemental Tables 6 and 7 provide details of the questions asked in each study.

Laboratory methods

DNA was extracted from blood or buccal samples and genotyped using the IlluminaHap660 Human BeadChip for the NCI and NIOSH case–control studies, as well as cases and controls from AHS, and for the cases from PLCO and ATBC studies. For PLCO and ATBC controls, existing data were available from previous genotyping on the Illumina HumanHap550 and HumanHap610 arrays, respectively [20, 21]. Where necessary, SNP data were imputed for previously genotyped control samples using the method described by Marchini et al. [22]. None of the five GWAS SNPs examined for this analysis were imputed. Three percent of the total number of samples genotyped for this study (approximately n = 60) were included in duplicate as quality control (QC) samples. For all SNP assays, greater than 99.96 % concordance was obtained. Based on the chi-square test, none of the SNPs showed departure from Hardy–Weinberg equilibrium (HWE) at $p < 0.05$.

Statistical analysis

We restricted the analytic sample to individuals of European ancestry (98 %). We first evaluated the independent association between the five GWAS SNPs (rs2736100, rs4977756, rs489972, rs4295627, and rs6010620) and glioma risk. Supplemental Table 4 presents the allele frequencies of the risk alleles among cases and controls for each study. Next, we evaluated the association between history of allergies and autoimmune conditions and glioma risk by estimating odds ratios (OR) and 95 % confidence intervals (CI) using unconditional logistic regression. To test for independence of SNPs from allergy and autoimmune conditions, we evaluated the association between each genotype and each

allergy or immune condition among the controls. We further evaluated the joint effects of gene variants and allergic/autoimmune conditions by conducting stratified analyses whereby the risk associations (OR and 95 % CI) with the allergy or autoimmune conditions for glioma were evaluated by the presence or absence of the 'at-risk' variant. Finally, we tested for heterogeneity (interaction on multiplicative scale) between these stratified risks; to calculate the p interaction, we fitted models with the main effects of allergy or autoimmune conditions and genotype (modeled as both three- and two-level risk alleles) and an interaction (product) term between them. Only results of the two-level dominant models are presented, as they were similar to the three-level models. We also performed separate analyses for low- and high-grade glioma according to the WHO grading of central nervous system tumors [23]. All models were adjusted for study, gender, and age at diagnosis. Two-sided statistical tests were performed at $\alpha = 0.05$ level. SAS version 9.1.3 was used for analysis.

RESULTS

We first compared demographic characteristics of cases and controls included in this study. Briefly, the majority of cases originated from the case–control studies, and controls were older than cases (median age of controls 73 vs. median age of cases 57; Supplementary Tables 2a and 2b).

Table 1 shows the main effects of the five SNPs examined with risk of glioma. Overall, four of the five SNPs previously reported were statistically significantly associated with increased risk of glioma (rs2736100, rs4295627, rs4977756, and rs6010620). However, rs498872 was not associated with glioma in our study. Supplemental Figure 1 is a forest plot of the odds ratios and 95 % CI for the association between the four alleles and glioma, overall and for each study separately.

We observed an association between both allergies and autoimmune conditions and glioma risk (Table 2). Specifically, after adjusting for age, study, and gender, reporting any allergies or any autoimmune conditions was associated with reduced risks of glioma (allergy: OR = 0.71, 95 % CI 0.55–0.91; autoimmune disease: OR = 0.65, 95 % CI 0.47–0.90). Supplemental Figure 2 is a forest plot of the odds ratios and 95 % CI of 'any allergies' and 'any autoimmune condition' with glioma, overall and for each study separately.

We evaluated the relationship between the minor allele variants of the five SNPs and allergies or autoimmune conditions among controls. Of the five SNPs, only rs4977756 in CDKN2A-CDKN2B region was statistically significantly associated with decreased risk of any autoimmune condition (unadjusted OR = 0.72, 95 % CI 0.54–0.96). This association was largely driven by an association with rheumatoid arthritis (data not shown). No other SNPs were associated with either allergy or autoimmune conditions.

Finally, we evaluated the association between allergy or autoimmune conditions and risk of glioma, stratified by genotypes for the four significant SNPs. We did not observe any differential association between allergic or autoimmune conditions and glioma by genotype, and there were no statistically significant p interactions (Table 3). For comparability to the

previously published study [13], we restricted the analytic sample to the two case–control studies, but, again, did not observe any differences in association between allergic or autoimmune conditions and risk of glioma by genotype (data not shown). To facilitate comparison of our results to those by Schoemaker et al. [13], we also present results of risk of glioma in relation to any allergy and asthma with 0, 1, 2 risk alleles per SNP (Supplemental Table 8).

Finally, we further evaluated the interactions for glioma risk stratified by disease grade. We did not observe any interactions between SNPs examined and allergic or autoimmune conditions in the risk of either high- or low-grade glioma (data not shown).

DISCUSSION

We independently replicated the association of four out of the five SNPs identified in two GWAS reports with risk of glioma [7, 8]. In addition, we observed inverse associations between allergic or autoimmune conditions and risk of glioma, consistent with the previously published reports [9–12]. We found no evidence of joint effects between the four SNPs examined and allergic or autoimmune conditions and risk of glioma overall, or in analyses stratified by high- or low-grade glioma. While some of our estimates were in the same direction, this is in contrast to two recent reports which showed evidence for modification of the effect of glioma and asthma by PHLDB1 rs498872 [13] and glioma and any allergy by CDKN2A/B rs4977756 [13, 14] or RTEL1 rs6010620 [13] or RTEL1 4809324 [14]. One potential reason for this discrepancy is that these two reports were based on case–control studies, whereas the population in our study included cases and controls identified from three cohort studies in addition to one population-based case–control study and one hospital-based case–control study. However, analyses excluding cases and controls identified from the three cohort studies (thus restricted to the two case–control studies) also did not reveal any interactions between the SNPs and allergies or autoimmune conditions. The prevalence of asthma and any allergies was higher in the other studies (asthma = 11 %; any allergies = 43 %, among the controls) [13] than in ours (asthma = 8 % and any allergies = 18 %, among the controls), which could partially explain the differences. Our replication of the results for the main effect of allergy/autoimmune diseases, as well as the top SNPs, argue against exposure misclassification as an explanation for the discrepancy. Because our study was powered to detect large interaction, we could have missed subtle interactions even though our study was of similar sample size as the other studies. In summary, our study is complementary to the previous reports and adds to the growing number of glioma cases and controls for which interactions can be further interrogated in future collaborative efforts.

Strengths of our study include the quality and completeness of the genotyping data, availability of prediagnostic information on allergy and autoimmune diseases in the three cohort studies, and the evaluation of autoimmune conditions in relation to the GWAS-identified SNPs which is reported here for the first time. There are several limitations to be considered. Allergic and autoimmune conditions were assessed by self-report and are thus subject to recall bias. In addition, while self-report of some allergy/autoimmune conditions is valid [24], others, such as rheumatoid arthritis, are less valid [25] and could have led to non-differential misclassification of the exposures and thus underestimation of an

association. We also lacked details of some exposures, such as the inability to differentiate between type 1 and type 2 diabetes; however, given the age range of our study participants at baseline, we expect that the prevalence of type 1 diabetes in this population would be 5 % [26]. We were also unable to differentiate between atopic and non-atopic asthma; a recent report estimates that 56 % of asthma cases can be attributed to atopy [27]. For increased power, we combined the allergy and autoimmune variables into ever/never; however, these definitions varied by study based on what was collected in their questionnaires. Therefore, future studies with more accurate definitions of these conditions are needed to further evaluate the relationships by specific conditions. Additionally, SNPs were chosen as tagging markers of genetic regions, rather than presumed functional significance for evaluating the joint effects under study. None of the SNPs examined in this investigation were associated with the allergic/autoimmune conditions.

In summary, our results do not provide evidence that allergies or autoimmune conditions modulate the association between the five GWAS-identified SNPs examined and risk of glioma. Larger studies with detailed exposure assessment of allergic and autoimmune conditions coupled with high-quality genetic data are needed to further evaluate the joint effects between allergic or autoimmune conditions and glioma risk by genotype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Main effects of five SNPs previously associated with glioma, among Caucasians from five US studies (adjusted for age at diagnosis, study, and gender)

SNP	Chromosome	Gene	Genotype	Controls	Glioma	OR (95 % CI)	*p* value
rs2736100	5	*TERT*	TT	789 (25.62)	164 (20.25)	1 (ref)	.
			GT	1511 (49.06)	402 (49.63)	1.28 (1.00–1.56)	0.0502
			GG	780 (25.32)	244 (30.12)	1.40 (1.10–1.80)	0.0059
			GT + GG	2291 (74.38)	646 (79.75)	1.30 (1.06–1.61)	0.0126
						p trend	0.0064
rs4295627	8	*CCDC26*	TT	2025 (65.68)	483 (59.63)	1 (ref)	.
			GT	935 (30.33)	284 (35.06)	1.32 (1.10–1.59)	0.003
			GG	123 (4.00)	43 (5.31)	1.76 (1.16–2.68)	0.008
			GT + GG	1058 (34.32)	327 (40.37)	1.37 (1.15–1.64)	0.0005
						p trend	0.0002
rs4977756	9	*CDKN2A/B*	AA	1112 (36.09)	248 (30.62)	1 (ref)	.
			AG	1460 (47.39)	383 (47.28)	1.18 (0.97–1.44)	0.09
			GG	509 (16.52)	179 (22.10)	1.62 (1.27–2.07)	0.0001
			AG + GG	1969 (63.91)	562 (69.38)	1.29 (1.08–1.56)	0.006
						p trend	0.0002
rs498872	11	*PHLDB1*	CC	1427 (46.30)	363 (44.93)	1 (ref)	.
			CT	1341 (43.51)	359 (44.43)	1.07 (0.89–1.28)	0.476
			TT	314 (10.18)	86 (10.64)	1.09 (0.81–1.46)	0.585
			CT + TT	1655 (53.70)	445 (55.07)	1.07 (0.90–1.27)	0.433
						p trend	0.45
rs6010620	20	*RTEL1*	AA	148 (4.80)	26 (3.21)	1 (ref)	.
			AG	1014 (32.89)	245 (30.25)	1.48 (0.92–2.37)	0.107
			GG	1921 (62.31)	539 (66.54)	1.88 (1.18–2.98)	0.007
			AG + AA	2935 (95.20)	784 (96.79)	1.73 (1.09–2.74)	0.019
						p trend	0.0006

Table 2

Main effects of overall allergy and autoimmune variables on risk of glioma among Caucasians from five US studies (adjusted for age at diagnosis, study, and gender)

		Controls *n* (%)	Glioma *n* (%)	OR	(95 % CI)
Allergy					
Any allergy	No	2231 (81.60)	574 (81.07)	1	Ref
	Yes	503 (18.40)	134 (18.93)	0.71	(0.55–0.91)
Asthma	No	2521 (92.14)	652 (91.96)	1	Ref
	Yes	215 (7.86)	57 (8.04)	0.58	(0.42–0.81)
Eczema	No	2033 (91.70)	615 (92.34)	1	Ref
	Yes	184 (8.30)	51 (7.66)	0.83	(0.58–1.19)
Hay fever	No	1971 (89.63)	590 (88.86)	1	Ref
	Yes	228 (10.37)	74 (11.14)	0.88	(0.65–1.21)
Autoimmune					
Rheumatoid arthritis	No	2208 (95.87)	433 (95.80)	1	Ref
	Yes	95 (4.13)	19 (4.20)	0.65	(0.38–1.14)
Diabetes	No	2891 (94.66)	773 (96.63)	1	Ref
	Yes	163 (5.34)	27 (3.38)	0.51	(0.33–0.79)
Any autoimmune	No	2564 (89.21)	698 (92.33)	1	Ref
	Yes	310 (10.79)	58 (7.67)	0.65	(0.47–0.90)

Models run separately for each of the allergy and autoimmune conditions

Table 3

Stratified analysis of allergy and autoimmune factors by SNP for glioma risk among Caucasians in five US studies, adjusted for age, gender, and study

	rs2736100 *(TERT)*		**rs4295627 *(CCDC26)***		**rs4977756 *(CDKN2A-CDKN2B)***		**rs6010620 *(RTEL1)***		**rs498872 *(PHLDB1)***	
	TT OR (95 % CI)	**GT/GG OR (95 % CI)**	**TT OR (95 % CI)**	**GT/GG OR (95 % CI)**	**AA OR (95 % CI)**	**AG/GG OR (95 % CI)**	**AA OR (95 % CI)**	**AG/GG OR (95 % CI)**	**CC OR (95 % CI)**	**CT/TT OR (95 % CI)**
Allergy										
Asthma										
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.51 (0.25–1.05)	0.60 (0.41–0.87)	0.67 (0.45–1.01)	0.48 (0.26–0.88)	0.61 (0.33–1.11)	0.56 (0.37–0.83)	0.26 (0.04–1.68)	0.59 (0.42–0.83)	0.63 (0.39–1.01)	0.54 (0.34–0.87)
	p interaction = 0.71		*p* interaction = 0.51		*p* interaction = 0.68		*p* interaction = 0.61		*p* interaction = 0.92	
Any allergy										
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.66 (0.39–1.12)	0.72 (0.55–0.96)	0.80 (0.59–1.09)	0.60 (0.39–0.91)	0.79 (0.51–1.21)	0.66 (0.49–0.90)	0.36 (0.08–1.72)	0.73 (0.57–0.94)	0.64 (0.44–0.93)	0.78 (0.56–1.09)
	p interaction = 0.86		*p* interaction = 0.61		*p* interaction = 0.42		*p* interaction = 0.31		*p* interaction = 0.24	
Autoimmune										
Diabetes										
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.33 (0.11–1.01)	0.56 (0.34–1.01)	0.46 (0.26–0.82)	0.53 (0.27–1.07)	0.43 (0.18–1.00)	0.55 (0.33–0.93)	0 –	0.52 (0.33–0.81)	0.34 (0.18–0.67)	0.72 (0.40–1.31)
	p interaction = 0.42		*p* interaction = 0.68		*p* interaction = 0.60		*p* interaction = 0.97		*p* interaction = 0.16	
Any Autoimmune										
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.62 (0.31–1.25)	0.66 (0.46–0.96)	0.72 (0.48–1.06)	0.52 (0.29–0.91)	0.42 (0.22–0.81)	0.77 (0.53–1.11)	0.15 (0.01–1.67)	0.68 (0.49–0.95)	0.69 (0.44–1.11)	0.59 (0.37–0.92)
	p interaction = 0.86		*p* interaction = 0.44		*p* interaction = 0.14		*p* interaction = 0.24		*p* interaction = 0.50	