Carcinogenesis vol.28 no.12 pp.2543–2547, 2007
doi:10.1093/carcin/bgm210
Advance Access publication October 4, 2007

Single-nucleotide polymorphisms in selected cytokine genes and risk of adult glioma

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A role of immunological factors in glioma etiology is suggested by reports of an inverse relationship with history of allergy or autoimmune disease. To test whether single-nucleotide polymorphisms (SNPs) in cytokine genes were related to risk of adult glioma, we genotyped 11 SNPs in seven cytokine genes within a hospital-based study conducted by the National Cancer Institute and an independent, population-based study by the National Institute for Occupational Safety and Health (overall 756 cases and 1190 controls with blood samples). The *IL4* (rs2243248, −1098T>G) and *IL6* (rs1800795, −174G>C) polymorphisms were significantly associated with risk of glioma in the pooled analysis (*P* trend = 0.006 and 0.04, respectively), although these became attenuated after controlling for the false discovery rate (*P* trend = 0.07 and 0.22, respectively). Our results underscore the importance of pooled analyses in genetic association studies and suggest that SNPs in cytokine genes may influence susceptibility to glioma.

Introduction

Although brain tumor etiology remains largely unknown (1–3), there are consistent reports of inverse associations between risk of adult glioma and personal history of allergy (4–10) and, to a lesser extent, autoimmune disease (4,6,7). It is unlikely that all reported associations are subject to similar bias or due to chance; however, it remains unclear whether changes in cellular/humoral immunity and cytokine pattern accompanying allergy or autoimmune disease are protective for glioma directly or through another unidentified factor. Interestingly, polymorphisms in *IL4RA* and *IL13* genes previously associated with decreased and increased risk of asthma, respectively, were found to have opposite associations with glioma in one study (11). In another study, however, polymorphisms in *IL4*, *IL4R* and *IL13* genes were unassociated with risk of glioma individually, yet certain *IL4R* and *IL13* haplotypes demonstrated suggestive associations (12). Our objective was to evaluate and extend the evidence that single-nucleotide polymorphisms (SNPs) in cytokine genes are related to risk of adult glioma using data from two large, independent case–control studies. Here, we report associations with 11 SNPs in seven cytokine genes.

Materials and methods

Study population and setting

Details of the studies conducted by the National Cancer Institute (NCI) and the National Institute for Occupational Safety and Health (NIOSH) were described previously (13,14) and are summarized in Table I. Briefly, the NCI study was conducted between June 1994 and August 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. Eligible cases were patients newly diagnosed with histologically confirmed intracranial glioma or neuroepitheliomatous tumors ($N = 489$; International Classification of Diseases for Oncology, second edition codes 9380–9473 and 9490–9506). Cases had to be at least 18 years old and reside within 50 miles of the hospital at the time of diagnosis (or within Arizona for the Phoenix hospital) and understand English or Spanish. Of the potentially eligible cases invited to participate in the study, 90% ($N = 489$) agreed. Controls were patients admitted to same hospitals for a variety of non-malignant conditions. The most common reasons for hospital admission among controls were injuries and poisoning [$N = 197$; ICD-9 (International Classification of Diseases, Ninth Revision) 800–999, V01–V82, E800–E999] and diseases of the circulatory ($N = 179$; ICD-9 390–459), musculoskeletal ($N = 172$; ICD-9 710–739), digestive ($N = 92$, ICD-9 520–579) and nervous systems ($N = 58$; ICD-9 320–389). Controls were frequency matched (1:1) to a total case series (glioma, meningioma and acoustic neuroma) by hospital, age (in 10-year strata), sex, race or ethnicity, and distance of residence from hospital. Of the potentially eligible controls contacted, 86% ($N = 799$) participated.

The NIOSH eligible cases were patients, 18–80 years old, diagnosed between January 1995 and January 1997 with new, histologically confirmed intracranial gliomas (International Classification of Diseases for Oncology, second edition codes 9380–9473) in the participating medical facilities and neurosurgeon offices in four upper Midwestern states (in counties where the largest population center had $< 250\,000$ residents) (14). Of the potentially eligible cases invited to participate in the study, 92% ($N = 798$) agreed. Population controls were individuals without glioma randomly selected from 10-year age–sex specific strata of the state driver's license or non-driver identification records (for those between 18 and 64 years of age) or from the 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. Of the potentially eligible controls contacted, 70% ($N = 1175$) participated.

Both studies were reviewed and approved by the respective institutional review boards, and all participants signed an informed consent upon enrollment.

Laboratory methods

Blood sample collection and DNA extraction In the NCI study, 431 cases (88%) and 611 controls (76%) provided blood samples, whereas in the NIOSH study 325 cases (41% of all participating cases or 71% of 458 alive at the time of interview) and 579 controls (73% of 793 asked) did so.

DNA was extracted from peripheral white blood cells of blood samples collected in the NCI study using a phenol–chloroform method described previously (15). DNA was extracted from whole-blood samples in the NIOSH study using a sodium perchlorate–chloroform method (16).

Genotyping Genotyping for both studies was performed by the NCI Core Genotyping Facility (Advanced Technology Corporation, Gaithersburg, MD) using optimized singleplex assays (17). The selection of a portion of common genetic variants was coordinated between the two studies to increase statistical power, provide protection against false-positive findings and reduce the probability of false-negative findings. The genes were chosen based on the most consistent evidence from association studies with allergy, autoimmune disease, cancer or neurologic diseases at the time of selection, with those SNPs known to have functional consequences in polymorphism or having assays available at Core Genotyping Facility given preference (Table II). Here, we report only on SNPs that were genotyped in both studies.

We observed no significant deviation from Hardy–Weinberg equilibrium for any SNP, and concordance rates for the quality control replicate and duplicate samples were at least 93 and 98%, respectively.

Statistical analysis

Data from each study were first analyzed separately. We used unconditional multivariate logistic regression models [PROC LOGISTIC, SAS 8.2 (18)] to estimate odds ratios associated with each SNP (using the homozygous wild-type genotype as referent) and to compute 95% confidence intervals adjusting for study-specific matching factors. For each SNP, we conducted a score test of linear trend using a three-level ordinal variable. As there was no evidence of heterogeneity in linear trends between the two studies, we combined data and estimated pooled odds ratios using fixed effects models (19). All analyses were restricted to non-Hispanic whites.

We assessed robustness of findings using the Benjamini–Hochberg approach to control for false discovery rate (FDR) (20), defined as the expected ratio of

Abrreviations: SNP, single-nucleotide polymorphism; NCI, National Cancer Institute; NIOSH, National Institute for Occupational Safety and Health.

Table I. Description of hospital-based case–control study of adult glioma conducted by the NCI and of population-based case–control study of adult glioma conducted by the NIOSH

Characteristic	NCI		NIOSH	
Study design	Hospital based[a]		Population based	
Hospital location	Boston, MA; Phoenix, AZ; Pittsburgh, PA		IA, MI, MN, WI	
Case ascertainment	June 1994–August 1998		January 1995–January 1997	
Matching criteria	Hospital, age, sex, race/ethnicity and distance of residence from hospital		State of residence, age and sex	
	Cases, *N* (%)	Controls, *N* (%)	Cases, *N* (%)	Controls, *N* (%)
Study participation	489 (90)[b]	799 (86)	798 (92)	1175 (70)
Blood samples collected	431 (88)[c]	611 (76)	325 (41)	579 (73)[d]
Mean age, years	51[e]	49	47	59
Females, %	45[e]	54	42	44
Non-Hispanic whites, %	91[e]	89	98	99

[a]The most common reasons for hospital admission among controls were injuries and poisoning ($N = 197$; ICD-9 800–999, V01–V82, E800–E999) and diseases of the circulatory ($N = 179$; ICD-9 390–459), musculoskeletal ($N = 172$; ICD-9 710–739), digestive ($N = 92$, ICD-9 520–579) and nervous systems ($N = 58$; ICD-9 320–389).
[b]In both studies, out of those cases/controls eligible to participate.
[c]Out of study participants.
[d]Out of inquired participants.
[e]In both studies, among cases/controls with genotyping results.

Table II. SNPs in cytokine genes: hospital-based case–control study of adult glioma conducted by the NCI and population-based case–control study of adult glioma conducted by the NIOSH

Gene	Name	Chromosomal location	dbSNP's reference number	SNP region (alias)	Amino acid change	Basis for selection[a]	Supplementary references[b]
IL4	Interleukin 4	5q31.1	rs2243250	−588C>T (−524, −590)		Asthma, atopy	1–8
			rs2243248	−1098G>T		Juvenile idiopathic arthritis	9
			rs2070874	Ex1−168C>T, 5′UTR[c]		RA[d]	10
						Asthma	6
IL4R	Interleukin 4 receptor (CD124)	16p11.2–12.1	rs1801275	Ex12+828A>G	Q576R	Asthma, atopy	1,5,11–16
IL5	Interleukin 5	5q31.1	rs2069812	−745C>T		Asthma, eosinophilia	17,18
IL6	Interleukin 6 (interferon, beta 2)	7p21	rs1800795	−236C>G (−174)		Stroke	19
						Ovarian cancer	20
						Type 1 diabetes	21,22
IL10	Interleukin 10	1q31–q32	rs1800871	−853C>T (−819)		Alters transcription	23
						MS[e]	24
						AD[f]	25
			rs1800872	−626A>C (−592)		Alters transcription	23
						SLE[g]	26
						MS	24
						AD	25
			rs1800896	−1116A>G (−1082)		Asthma	27
						Melanoma	28
						Lymphoma	29
						SLE	30
						MS	31
IL12A	Interleukin 12, alpha	3p12–q13.2	rs568408	Ex7+277G>A, 3′UTR, (8685G>A)		Decreased lymphocyte count	32
IL13	Interleukin 13	5q31	rs20541	Ex4+98A>G	Q144R	Asthma, atopy	33–43

[a]Epidemiological associations with other diseases and/or potential functional changes.
[b]Supplementary material are available at *Carcinogenesis* Online.
[c]UTR, untranslated region.
[d]RA, rheumatoid arthritis.
[e]MS, multiple sclerosis.
[f]AD, alzheimer's disease.
[g]SLE, systemic lupus erythematosus.

erroneous rejections of the null hypothesis to the total number of rejected hypotheses. We applied the FDR method to a set of 11 tests for trend (as this allows for the fewest number of comparisons) at the $\alpha = 0.05$ level.

To decrease phenotypic heterogeneity of the glioma case series and to compare our findings with those of Schwartzbaum *et al.* (11), all analyses were repeated limited to glioblastoma cases.

Results

The *IL4* (rs2243248, −1098T>G) polymorphism in the NCI study was significantly associated with overall risk of glioma. The associations with *IL4* (rs2243248, −1098T>G) and *IL6* (rs1800795, −174G>C) polymorphisms were compatible between the two studies (Table III), and the pooled odds ratios with GT and GG genotypes were 1.44 and 3.90 (P trend = 0.006), and with CG and CC genotypes were 0.98 and 0.70 (P trend = 0.04), respectively. These associations were attenuated after controlling for the FDR at the conservative level of 0.05 [P trend with *IL4* (rs2243248, −1098T>G) = 0.07 and P trend with *IL6* (rs1800795, −174G>C) = 0.22]. When limited to glioblastoma, the associations with *IL4* (rs2243248, −1098T>G) and *IL6* (rs1800795, −174G>C) polymorphisms were largely similar to the overall findings. The complete results for all SNPs for both studies are provided online (supplementary Table 1 for NCI results and supplementary Table 2 for NIOSH results are available at *Carcinogenesis* Online).

Discussion

Previous studies, including our own, have reported a consistent inverse relationship between adult glioma and history of allergy (4–10) and, to a lesser extent, autoimmune disease (4,6,7). Using six SNPs as biomarkers of susceptibility to asthma, a study with 111 cases and 422 controls reported significant associations with *IL4RA* (rs1801275) and *IL13* (rs1800925) polymorphisms and glioblastoma (11). In a recent study (12), association with *IL4RA* (rs1801275) was not confirmed, but association with *IL13* (rs1800925) appeared to be consistent with that by Schwartzbaum *et al.* (11), although it did not reach statistical significance. Similarly, we did not confirm the *IL4RA* (rs1801275) association, and the associations with *IL4* (rs2243250, rs2070874) polymorphisms were null. We found that common *IL6* (rs1800795, −174G>C) and rare *IL4* (rs2243248, −1098T>G) polymorphisms, previously not evaluated in relation to risk of adult glioma, were associated with it in our pooled analyses. While attenuated after controlling for FDR, these associations are noteworthy and warrant replication in larger, more powerful studies and pooled efforts.

Although the *IL4* promoter variant (rs224350, −588C>T), in strong linkage disequilibrium (D' = 1.0) with *IL4* (rs2243248, −1098T>G) in our population, was previously found to be associated with increased transcriptional activity of *IL4 in vitro* (21) and elevated risk of asthma (22,23), we do not yet know the functional relevance of the single-base substitution in the promoter of *IL4* (rs2243248, −1098T>G) (17) or its relationship with allergy or asthma. In at least one study, the G allele of the *IL4* (rs2243248, −1098T>G) polymorphism was associated with decreased risk of juvenile idiopathic ar-

Table III. Associations between *IL4* (rs2243248, −1098T>G) and *IL6* (rs1800795, −174G>C) polymorphisms and risk of adult glioma in non-Hispanic whites: pooled analysis of hospital-based case–control study conducted by the NCI and population-based case–control study conducted by the NIOSH

Study	Genotype	Controls		All glioma				Glioblastoma			
		N[a]	%	N	%	OR[b]	95% CI[c]	N	%	OR	95% CI
	IL4 (rs2243248, −1098T>G)										
NCI	TT	434	91.4	298	86.4	1.00[d]	Referent	150	86.7	1.00	Referent
	GT	40	8.4	43	12.5	1.50	0.95–2.40	22	12.7	1.45	0.79–2.61
	GG	1	0.2	4	1.2	5.34	0.77–105.67	1	0.6	1.94	0.08–50.44
	P trend					0.02				0.20	
	GT/GG	41	8.6	47	13.6	1.60	1.02–2.52	23	13.3	1.46	0.80–2.62
NIOSH	TT	488	88.2	257	83.2	1.00[e]	Referent	117	83.6	1.00	Referent
	GT	64	11.6	50	16.2	1.39	0.90–2.14	21	15.0	1.36	0.77–2.32
	GG	1	0.2	2	0.6	2.59	0.23–59.23	2	1.4	9.67	0.84–226.65
	P trend					0.10				0.08	
	GT/GG	65	11.8	52	16.8	1.41	0.92–2.17	23	16.4	1.47	0.85–2.47
Pooled	TT	922	89.7	555	84.9	1.00[f]	Referent	267	85.3	1.00	Referent
	GT	104	10.1	93	14.2	1.44	1.05–1.97	43	13.7	1.40	0.94–2.09
	GG	2	0.2	6	0.9	3.90	0.77–19.83	3	1.0	4.57	0.74–28.35
	P trend					0.006				0.03	
	GT/GG	106	10.3	99	15.1	1.49	1.10–2.03	46	14.7	1.47	1.00–2.17
	IL6 (rs1800795, −174G>C)										
NCI	GG	162	33.2	129	37.2	1.00[d]	Referent	63	36.8	1.00	Referent
	CG	238	48.8	168	48.4	0.91	0.67–1.24	85	49.7	1.05	0.70–1.59
	CC	88	18.0	50	14.4	0.75	0.49–1.14	23	13.4	0.74	0.41–1.30
	P trend					0.19				0.42	
	CG/CC	326	66.8	218	63.8	0.87	0.65–1.16	108	63.2	0.96	0.65–1.42
NIOSH	GG	157	28.8	93	30.3	1.00[e]	Referent	41	29.5	1.00	Referent
	CG	265	48.8	164	53.4	1.06	0.75–1.51	73	52.5	1.05	0.68–1.64
	CC	123	22.6	50	16.3	0.66	0.42–1.04	25	18.0	0.75	0.42–1.30
	P trend					0.12				0.37	
	CG/CC	388	71.2	214	69.7	0.93	0.67–1.30	98	70.5	0.95	0.63–1.46
Pooled	GG	319	30.9	222	33.9	1.00[f]	Referent	104	33.6	1.00	Referent
	CG	503	48.7	332	50.8	0.98	0.78–1.24	158	51.0	1.04	0.77–1.40
	CC	211	20.4	100	15.3	0.70	0.51–0.95	48	15.5	0.72	0.48–1.08
	P trend					0.04				0.18	
	CG/CC	714	69.1	432	66.1	0.90	0.72–1.12	206	66.4	0.94	0.71–1.25

[a]In both studies, column numbers do not add up to the total number of cases/controls with blood samples as we limited the analysis to non-Hispanic whites and not all may have had an adequate amount of blood or extracted DNA or been successfully genotyped.
[b]OR, odds ratio.
[c]CI, confidence interval.
[d]ORs adjusted for sex, age, study hospital and distance of residence from hospital.
[e]ORs adjusted for sex, age and state of residence.
[f]ORs adjusted for study and sex, age and residence within each study.

thritis (24) and, thus, an opposite association with *IL4* (rs2243248, −1098T>G) for glioma observed in our study appears to be consistent with the expectation based on epidemiologic studies (4,6,7). The *IL6* (rs1800795, −174G>C) polymorphism in the promoter region has been associated with decreased *IL6* expression and lower plasma levels of circulating IL-6 (25,26) as well as type-1 diabetes mellitus (27,28); however, the latter associations went in different directions in the two studies. Although it is conceivable that *IL4* and *IL6* promoter polymorphisms may be related to the altered expression of the respective cytokines, these variants could alternatively be in linkage disequilibrium with other variants not yet evaluated. Mirroring our findings for glioma, *IL4* (rs2243248, −1098T>G) and *IL6* (rs1800795, −174G>C) polymorphisms recently have been associated with increased (29,30) and decreased (29,31) risk of several lymphoma subtypes, respectively. Therefore, these polymorphisms may influence susceptibility to several types of cancer, strengthening the possibility that the observed associations in our study are not due to chance.

The complex relationship between glioma and allergy/autoimmune disease and cytokine gene polymorphisms remains unclear. However, it has been suggested that the effects of the *IL13* polymorphisms and IgE on glioma risk may be statistically independent (12). Such an independent effect of cytokines or their polymorphisms would be consistent with the emerging role of cytokines as important regulators of a variety of physiological and pathological processes in the central nervous system (32,33) and key messengers in bidirectional communication between neural and immune cells (34).

We had adequate statistical power to detect strong to modest main effects of the common genetic polymorphisms. The SNPs for candidate cytokine genes were carefully selected based on prior evidence and potential relevance to glioma, increasing the prior probability of true association. In the analyses, we controlled for FDR. We believe that accurate genotyping according to a standardized approach in both studies minimized misclassification, further enhancing our ability to detect modest effects.

Although among the largest glioma studies to date, our study had limited statistical power to detect modest to weak associations. If glioma survival was associated with the SNPs under consideration, this could introduce survival bias given that blood samples were available for 41% of all NIOSH cases compared with 88% of NCI cases. However, findings from the two studies were consistent, both for all gliomas combined and for glioblastoma, where the potential for such survival bias is highest. We evaluated only one to three SNPs per gene and, therefore, our conclusions pertain to specific genotypes and not the entire gene or region. Furthermore, additional regulation at the level of transcription or translation, or complex interactions among the cytokines, would not be captured in our results.

In summary, using data from two large, independent case–control studies, we found suggestive associations between glioma and *IL4* (rs2243248, −1098T>G) and *IL6* (rs1800795, −174G>C) polymorphisms. Further studies with sufficient power focusing on dense genotyping and haplotype estimation of the cytokine genes are warranted. Our findings underscore the importance of pooled analyses in genetic association studies and, if confirmed, could imply that genetic polymorphisms in cytokine genes are important susceptibility factors for glioma.

Supplementary material

Supplementary material can be found at http://carcin.oxfordjournals.org/

Funding

NCI study by Intramural Research program of the National Institutes of Health (National Cancer Institute, Division of Cancer Epidemiology and Genetics). NIOSH study by NIOSH Initiative for Cancer Control for Farmers and in part by Centers for Disease Control and Prevention/NIOSH operating funds.

Acknowledgements

Conflict of Interest Statement: None declared.

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Received June 14, 2007; revised August 24, 2007; accepted September 12, 2007