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Single-nucleotide polymorphisms of allergy-related genes and risk of adult glioma

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Abstract

Previous studies have shown an inverse association between allergies and glioma risk; however, results for associations between single nucleotide polymorphisms (SNPs) of allergy-related genes and glioma risk have been inconsistent and restricted to a small number of SNPs. The objective of this study was to examine the association between 166 SNPs of 21 allergy-related genes and glioma risk in a nested case-control study of participants from three large US prospective cohort studies. Blood collection took place between 1982 and 1994 among the 562 included Caucasian participants (143 cases and 419 matched controls) prior to case diagnosis. Custom Illumina assay chips were used for genotyping. Logistic regression analyses, controlling for age and study cohort, were used to determine associations between each SNP and glioma risk. Statistically significant associations were found between rs2494262 and rs2427824 of the *FCER1A* gene, which encodes the alpha chain of the high affinity immunoglobulin E receptor, and glioma risk (nominal trend p-values 0.01 and 0.03, respectively). Significant associations were also found between SNPs in *IL10*, *ADAM33*, *NOS1* and *IL4R* and glioma risk; however, these were not corrected for multiple comparisons and need to be interpreted with caution. Our findings with *FCER1A* SNPs provide further support for the link between allergies and risk of glioma.

Keywords

Brain tumors; glioma; allergies; single-nucleotide polymorphisms; cohort studies

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INTRODUCTION

The incidence rate of brain and central nervous system tumors in the United States is approximately 6.6 per 100,000 person-years [1], with glioma being the most prevalent type of primary malignant brain cancer. Although not common, brain tumors are responsible for considerable morbidity and carry a 5-year survival rate of only 33% [1].

The etiology of glioma is still largely unknown [2]. Previous studies have shown an inverse association between self-reported history of allergies or atopic disease and glioma risk [3,4]. There is also evidence that immunoglobulin E (IgE) levels are associated with lower glioma risk [5,6]. Atopic individuals often have elevated serum levels of IgE antibodies and respond to allergens by inducing cytokines produced by type 2 T helper (Th2) cells. It has been suggested that heightened immune response from atopic disease may protect against brain tumor development [4].

Given the consistent epidemiologic data supporting the association between allergies and gliomas, genetic susceptibility to allergies may also be related to the risk of glioma. A few studies have found that single nucleotide polymorphisms (SNPs) of inherited allergy-associated genes, such as *IL13*, *IL4*, *ORMDL3* and *STAT6*, were related to glioma risk or survival, but results have been inconsistent and few SNPs have been investigated [7–15]. More conclusive evidence on genetic susceptibility to glioma risk is needed to help determine the mechanism by which allergies may play a role in the protection against gliomas.

Therefore, we examined the association between SNPs of genes that have been associated with asthma or allergies and glioma risk in a pooled analysis of participants from three large US prospective cohort studies.

MATERIALS AND METHODS

Study populations

Data were analyzed from three independent US cohorts previously described in detail: the Physicians' Health Study (PHS), the Nurses' Health Study (NHS), and the Health Professionals Follow-up Study (HPFS) [16–18]. The PHS was a randomized controlled trial that began in 1982 to assess the efficacy of aspirin in reducing cardiovascular disease mortality and the efficacy of β-carotene in reducing overall cancer incidence. Included participants were 22,071 male physicians aged 40–84 years with no history of cardiovascular disease or cancer and were randomly assigned to receive aspirin, β-carotene or placebo. The NHS is a prospective study of lifestyle and dietary factors and chronic diseases that was started in 1976; the study includes 121,700 female US registered nurses, aged 30–55 years at baseline. The HPFS started in 1986 includes 51,529 US male health professionals, aged 40–75 years, who have been followed over time to examine lifestyle and dietary associations with major disease outcomes. Informed consent was obtained from all participants, and the present study was approved by the Human Research Committee of the Brigham and Women's Hospital.

Blood collection

Blood collection procedures were conducted as previously described [6]. Between August 1982 and December 1984, blood samples were collected from 14,916 (68%) of 22,071 PHS participants as part of the initial trial. From May 1989 through September 1990, blood samples were collected from 32,825 (55%) of 59,923 NHS cohort subjects who had indicated that they would be willing to send a blood sample. In 1993 and 1994, blood specimens were collected from 18,255 men in HPFS. Upon arrival to the laboratories, blood

samples were centrifuged, aliquoted and stored in liquid nitrogen freezers for use in future assays.

Case ascertainment and control selection

All participants were contacted yearly (PHS) or biennially (HFPS and NHS I) to ascertain outcomes. The follow-up rate for participants who provided blood samples in the cohorts was greater than 95% of the total possible person-years for incidence of cancer. For the present analysis, we included cases with any type of glioma brain tumor: astrocytoma, glioblastoma, oligodendroglioma, ependymoma, and mixed glioma subtypes; pilocytic astrocytomas were not included in this study. Deaths of cohort subjects are usually reported by family members or by the postal service in response to mailed questionnaires. The National Death Index (NDI) was also searched biennially for non-respondents, and this method has been shown to have a sensitivity of 98% [19]. Medical records and pathology reports were obtained from hospitals after permission was received from cases or requested for deceased cases identified through the NDI or other sources. Approximately 88% of potential case subjects (self-reported or deceased case subjects with glioma) were subsequently confirmed with medical, pathology, or cancer registry data. Only glioma cases confirmed from medical or pathology records, cancer registry data or a death certificate were included in the current study.

All identified and confirmed incident glioma cases who provided blood samples at baseline were selected for this study (n = 151). For each case, three controls (n = 482) were identified among the cohort participants who returned blood samples, who did not have cancer, and who were alive at the time the matched case was diagnosed; only two controls were matched with one case where the matching criteria could not be met. The controls were chosen at random and matched with each case on year of birth, cohort (which automatically matches the sex, because each cohort consists of either men or women), month of blood sample collection, and ethnic background. In the PHS cohort, controls were also matched to each case based on their original randomly assigned intervention group.

Candidate gene and SNP selection

DNA extractions were completed at the Channing Laboratory (Boston, MA) and shipped to Imperial College in London where a custom Illumina assay chip (Illumina, Inc., San Diego, CA) was designed to amplify 190 SNPs from 21 genes chosen because they have either been associated with allergy and atopy or because they are part of the IgE pathway: *AAA1, ADAM33, CD14, CTLA4, FCER1A, FLG, HLA-DPB1, IL10, IL12A, IL12B, IL13, IL4, IL4R, IL5, MS4A2, NOS1, NPSR1, ORMDL3, RAD50, STAT6,* and *TNF*.

For each gene, we chose a partially redundant set of haplotype tagging SNPs, using the HapMap data phaseIII/Rel #2 for the CEU population. We used a minor allele frequency (MAF) of 5% to avoid selecting rare alleles, and an R square cutoff of 0.8. Partial redundancy was used to protect against information loss in case one haplotype tagging SNP failed to amplify. The CEU population was chosen as the reference population for SNP tagging because the subjects in our study were Caucasian. The results from a preliminary screen, using the Illumina Preliminary Assay Design tool, allowed us to select 190 SNPs with strong validation and a high predicted amplification score.

Genotyping and quality control

DNA was obtained from all patients, and DNA concentrations were checked using Quant-iT™ PicoGreen® dsDNA reagent (Invitrogen, Carlsbad, CA) and normalized to 50ng/μl before genotyping. A total of 250ng DNA was used for the Illumina GoldenGate Assay (Illumina, Inc., San Diego, CA), which was performed according to the manufacturer's

standard three-day protocol. Each genotyping plate was prepared with both cases and controls to reduce any effects of plate-specific bias. Illumina clustering was performed on the raw data using Illumina's Genome Studio software version 2009.1. All 190 SNPs were also manually inspected to make sure the clusters were correctly called after sorting via a statistical score called Gentrain. This score varies from 1 to 0 and is based on the shape of the clusters and their relative distance to each other. The clusters were manually called for when SNPs were not correctly called by the software. All SNPs that could not be called (overlapping clusters, more than three clusters, low intensity) were zeroed (n=4, 2.1%). At least one replicate was included per plate for internal quality control, giving a total of 9 replicates across plates. The reproducibility frequency for the SNPs genotyped was 99.8%. A total of 5 HapMap Trios were also used as internal quality controls, and the data gave an overall parent-parent-child heritability percentage of 99.6%.

All individuals with <75% genotyping data (n=20), an insufficient DNA sample available (n=36) or who were not Caucasian (n=15) were excluded. Among the 190 SNPs of the 21 allergy-associated genes, those with <75% genotyping rate (n=10) or minor allele frequencies <0.05 (n=9) were excluded. Hardy-Weinberg equilibrium (HWE) in the control subjects was also assessed and the remaining SNPs with a HWE p-value <0.001 (n=5) were also excluded. The final association analysis included 143 cases, 419 controls and 166 SNPs.

IgE measurement

Frozen blood samples were sent to the Channing Laboratory (Boston, MA), which used the Pharmacia Diagnostics AB (Uppsala, Sweden) UniCAP fluorescent assay, as previously described in detail [6]. Both respiratory-specific allergens and food allergens were tested. The measured fluorescence scored against a standard curve with known quantity inputs was used to determine a continuous measure of IgE per manufacturer instructions. Results for IgE and glioma have been previously published [6].

Statistical analyses

We used conditional logistic regression analyses to examine the associations between the candidate gene SNPs and risk of glioma. The odds ratio (OR) and corresponding 95% confidence interval (CI) for the dominant and additive allele models and the Cochran-Armitage trend p-value were obtained for each SNP genotyped. Results were similar when models were reanalyzed using unconditional logistic regression and thus unconditional results are reported unless otherwise specified. Unconditional logistic regression analyses were repeated among cases who died within 12 months of diagnosis (highly fatal) and their controls, given that these case subjects most likely represent primary glioblastoma multiforme cases (n=99).

Haploview was used to generate linkage disequilibrium (LD) plots and haplotype blocks [20]. Logistic regression analyses, controlling for age and study cohort, were conducted to determine the association between glioma and haplotypes of each gene with at least one SNP that was significant in the dominant or additive models. Presented associations were not adjusted for multiple comparisons as we used a candidate-gene approach.

We also conducted one-way analysis of variance tests among cases and controls to compare levels of IgE across genotypes of SNPs from *FCER1A* and *IL13*, as these genes have been previously associated with IgE levels in previous analyses [21,15]. Total IgE measurements were log transformed to normalize them. We also compared clinically relevant categories of IgE (<25 kU/L, 25–100 kU/L and >100 kU/L) [6] across genotypes. All tests of statistical significance were two-sided, and *P* values less than 0.05 were considered statistically

significant. We applied no correction for multiple tests. All analyses were performed using SAS 9.1 (SAS Inc., Cary, NC), and were adjusted for age and study cohort.

RESULTS

The mean age at blood collection was 58.9 years for the 143 and 58.6 years for the 419 controls. The mean age at diagnosis of cases was 68.3 years. About two-thirds of both cases (66%) and controls (63%) were male.

We observed an association between rs2494262 of the *FCER1A* gene and glioma in both the dominant (OR=1.64; 95%CI: 1.01–2.67) and the additive models (trend p-value=0.01) (Table 1). A dose-response association was also observed for rs2427824 (p=0.03) and rs2427837 (p=0.06), although the association for the latter SNP was only borderline significant. These three SNPs of *FCER1A* were not in linkage disequilibrium (e.g. r^2 for rs2494262 and rs2427824 = 0.39). An association was also found between rs3024509 of the *IL10* gene and glioma (OR=1.96; 95% CI: 1.14–3.39). Other significant associations were found for the following SNPs rs3918395 (*ADAM33*), rs2293045 (*NOS1*), rs561712 (*NOS1*) and rs3024536 (*IL4R*) (Table 1).

We did not find statistically significant associations for other SNPs from allergy-associated genes, including SNPs from genes that had been previously associated with glioma risk in prior studies (Supplementary Table 1). However, in the dominant model, we did find a positive association with SNPs rs20541 (OR=1.41; 95%CI: 0.95–2.11, *IL13*) and rs1059513 (OR=1.43; 95%CI: 0.89–2.28, *STAT6*). Haplotype analyses did not add any additional significant results.

Polymorphisms of *FCER1A* were not associated with mean log(IgE) levels. For rs2494262 among controls, mean log(IgE) levels were 3.2, 3.4, and 3.0 for the CC, CA and AA genotypes, respectively (p=0.5) and 3.3, 3.0 and 3.4 among rs2427837 GG, GA and AA genotypes, respectively (p=0.5). Among controls and when using clinically relevant cut points for IgE, there was a higher percentage of participants with the common genotype, GG, for rs2427837 in the highest IgE category (>100 kU/L) compared to the rare genotype, AA (18% vs. 0% respectively for controls; 18% vs. 3% for combined). No relationship between rs2427837 and IgE level was observed among cases. IgE levels were also not associated with *IL13* genotypes rs20541 or rs1295686 in this study (results not shown).

When restricting cases with <12 month survival, the strongest association were found for rs598418 (*ADAM33*), rs324959 (*AAA1*), rs11574790 (*IL12B*) and rs172868 (*NPSR1*) (trend p=0.01 for all four SNPs) (Table 2). Associations between highly fatal gliomas and SNPs of the *NOS1* gene were borderline significant in the dominant model, but trends were not observed. Other associations between allergy-related genes and glioblastoma multiforme (GBM) were not observed, including those of genes that had been assessed in prior studies (Supplementary Table 2). In the dominant model however, a positive, albeit not statistically significant, association was observed for rs1059513 of the *STAT6* gene (OR=1.62; 95%CI: 0.96–2.72), and an OR=1.06; 95%CI: 0.66–1.71 was observed for SNP rs1805015 of the *IL4R* gene and GBM risk.

DISCUSSION

We investigated the associations between allergy gene-associated SNPs and glioma risk among participants of three large US prospective cohort studies. The strongest associations with glioma were found among rs2494262 and rs2427824 of the *FCER1A* gene. Other associations were found between glioma risk and SNPs of *IL10*, *ADAM33*, *NOS1*, and *IL4R*.

To our knowledge, this is the first study to identify variants within SNPs of *FCER1A* as potential risk factors for glioma. Previous studies have identified *FCER1A* as a risk factor for breast cancer among Korean women [22] and *FCER1G* as a risk factor of meningioma is a US study of participants with European ancestry [23]. *FCER1A*, the gene that encodes the alpha chain of the high affinity IgE receptor, has been previously associated with higher IgE levels [21]; thus, the *FCER1A*-glioma association found in our study is consistent with previous reports linking glioma risk with self-reported allergies [3,4] and borderline elevated IgE levels [6]. Previous studies have found an association between glioma risk and SNPs of *IL4*, *IL6, IL10, IL13*, *ORMDL3* and *STAT6* (Table 3). We did not find significant associations in our study among SNPs from these genes, except for rs3024509 of *IL10*. However, rs3024509 in particular has not been assessed, to our knowledge, in the existing literature and was not in LD (R^2=0.05) with rs1800896, for which an association with glioma was previously reported [7]. We assessed a number of these previously reported SNPs including rs20541 *(IL13),* rs1805015 *(IL4R)* and rs1059513 *(STAT6).* SNPs of *IL4* in our study were not in LD with those previously reported, whereas for *ORMDL3*, our tested SNPs rs8076131 and rs43788650 were in high LD with rs7216389 [9] (R^2= 0.86 and 0.85, respectively).

We also found an association between glioma risk and SNPs of *ADAM33* and *NOS1.* The *ADAM33* gene has been previously associated with asthma and decreased lung function [24,25]. NOS1 is a nitric oxide synthetase with a widespread role in many biological processes, and polymorphisms of this gene have been associated with many disease outcomes including asthma, stroke and malignant melanoma susceptibility [26–28]. Our findings suggest that these genes may also play a role in glioma risk.

We did not find statistically significant associations for IgE levels and *FCER1A* or *IL13* SNPs although these associations have been previously reported in the literature [21,15]. One study by Weidinger et al [21], found that the rare genotype of rs2427838 was associated with a decrease in IgE levels. In our study, there was a higher percentage of participants with the common allele versus the rare allele in the highest IgE category indicating a relationship between the *FCER1A* SNP and IgE consistent with the previous report. We also found a higher frequency of the rare allele among cases than controls consistent with glioma being associated with lower IgE levels. The lack of statistical significance between *FCER1A* and IgE levels in our study may be due in part to the relatively small number of participants with IgE measurements.

When restricting to glioma cases with less than 12 months survival time, we found associations between these highly fatal gliomas and SNPs of *ADAM33*, *AAA1*, *IL12B*, *NPSR1.* We did not find associations for rs1805015 (*IL4R*) or rs1059513 (*STAT6*), although associations between GBM and these SNPs have been previously reported in the literature (Table 3) [10,13]. Rs1805015 was not however, confirmed in a later study by the same authors who first reported the association [14], which is consistent with our results. While prior studies have also found significant associations for GBM and *IL4, IL13* and *IL10*, we did not find such associations.

To our knowledge, this is the most comprehensive study of glioma risk and SNPs and haplotypes of allergy-related genes to date. This study included multiple SNPs from over 20 allergy-related genes, and is the first to assess SNPs from many allergy-related genes including *FCER1A* and *NOS1.* An additional strength of this study is the pooling of data from three large prospective cohort studies, as there may be a selection bias toward cases with lower fatality in case control studies.

Because glioma is a rare cancer, even though we pooled data from three large cohort studies, our sample size was relatively low (n=143), especially when restricting to highly fatal gliomas (n=99). We were unable to assess different subtypes of glioma and may have lacked statistical power to detect associations between glioma and some SNPs and haplotypes. Presented results were not adjusted for multiple comparisons. When we did adjust for multiple comparisons, the associations were no longer statistically significant; thus, our results should be interpreted with caution as some of these unadjusted associations may have occurred due to chance. Because our analyses were restricted to Caucasian men and women from the United States, our results may not be generalizable to other populations.

In summary, we found a suggestion of an association between two polymorphisms of *FCER1A* and risk of glioma, which further supports the link with allergies and IgE. Confirmation of these findings these associations may have been missed in prior GWAS studies due to strict corrections for multiple testing comparisons [29].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Associations between allergy-related single nucleotide polymorphisms and glioma in 3 prospective cohort studies (HPFS, NHS, PHS).

Gene	SNP Genotype	Cases n (%)	Controls n (%)	OR (95% CI) [reference= wt/wt only]	OR (95% CI) [additive model]	Test for Trend P- value
FCER1A	rs2494262					
	CC	26 (18.6)	108 (26.5)	1	1	
	CA	68 (48.6)	202 (49.6)	1.64 (1.01–2.67)	1.45 (0.87–2.42)	
	AA	46 (32.9)	97 (23.8)		2.07 (1.18–3.61)	0.008
FCER1A	rs2427824					
	CC	79 (58.1)	201 (49.8)	1	1	
	CT	51 (37.5)	162 (40.1)	0.71 (0.48–1.05)	0.80 (0.53–1.21)	
	TT	6 (4.4)	41 (10.1)		0.35 (0.14–0.87)	0.03
FCER1A	rs2427837					
	GG	67 (48.2)	223 (54.7)	1	1	
	GA	56 (40.3)	157 (38.5)	1.32 (0.90–1.95)	1.20 (0.80–1.82)	
	AA	16 (11.5)	28 (6.9)		2.01 (1.02–3.96)	0.06
IL10	rs3024509					
	AA	115 (82.1)	369 (90.2)	1	1	
	AG	22 (15.7)	37 (9.0)	1.96 (1.14–3.39)	1.87 (1.05–3.31)	
	GG	3 (2.1)	3 (0.7)		3.08 (0.61–15.53)	0.01
ADAM33	rs3918395					
	CC	116 (83.5)	305 (74.0)	1	1	
	CA	21 (15.1)	99 (24.0)	0.56 (0.34–0.93)	0.56 (0.33–0.94)	
	AA	2 (1.4)	8 (1.9)		0.64 (0.13–3.06)	0.03
NOS1	rs2293045					
	CC	119 (86.2)	319 (78.4)	1	1	
	CG	18 (13.0)	81 (19.9)	0.58 (0.34–0.99)	0.59 (0.34–1.03)	
	GG	1 (0.7)	7 (1.7)		0.37 (0.04–3.02)	0.04
NOS1	rs561712					
	CC	42 (30.0)	165 (40.1)	1	1	
	CT	76 (54.3)	177 (43.1)	1.56 (1.03–2.35)	1.68 (1.09–2.59)	
	TT	22 (15.7)	69 (16.8)		1.24 (0.69–2.23)	0.2

Gene	SNP Genotype	Cases n (%)	Controls n (%)	OR (95% CI) [reference= wt/wt only]	OR (95% CI) [additive model]	Test for Trend P- value
IL4R	rs3024536[a]					
	GG	101 (76.5)	268 (67.3)	1	1	
	GA	28 (21.2)	123 (30.9)	0.63 (0.40–1.0)	0.61 (0.38–0.97)	
	AA	3 (2.3)	7 (1.8)		1.14 (0.29–4.52)	0.1

[a] rs3024547 not included in the table as it was in high linkage disequilibrium with rs3024536 (r^2=0.82)

Note. SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval; wt=wildtype

Table 2

Associations between allergy-related single nucleotide polymorphisms and highly fatal gliomas in 3 prospective cohort studies (HPFS, NHS, PHS).

Gene	SNP Genotype	Cases[a] n (%)	Controls n (%)	OR (95% CI) [reference= wt/wt only]	OR (95% CI) [additive model]	Test for Trend P- value
ADAM33	rs598418					
	GG	54 (55.1)	163 (40.0)	1	1	
	GA	34 (34.7)	186 (45.7)	0.52 (0.33–0.82)	0.53 (0.33–0.86)	
	AA	10 (10.2)	58 (14.3)		0.51 (0.24–1.07)	0.01
AAA1	rs324959					
	CC	30 (30.6)	179 (44.3)	1	1	
	CT	55 (56.1)	184 (45.5)	1.83 (1.13–2.94)	1.78 (1.09–2.91)	
	TT	13 (13.3)	41 (10.1)		2.05 (0.98–4.31)	0.02
IL12B	rs11574790					
	CC	69 (71.1)	330 (80.9)	1	1	
	CT	24 (24.7)	73 (17.9)	1.70 (1.02–2.83)	1.53 (0.90–2.62)	
	TT	4 (4.1)	5 (1.2)		4.58 (1.17–17.94)	0.02
IL12B	rs2853694					
	AA	16 (16.8)	106 (25.9)	1	1	
	AC	48 (50.5)	205 (50.1)	1.85 (1.03–3.33)	1.67 (0.90–3.10)	
	CC	31 (32.6)	98 (24.0)		2.23 (1.14–4.37)	0.03
IL12B	rs1433048					
	AA	75 (76.5)	269 (65.6)	1	1	
	AG	21 (21.4)	131 (32.0)	0.59 (0.36–0.99)	0.58 (0.34–0.99)	
	GG	2 (2.0)	10 (2.4)		0.76 (0.16–3.57)	0.07
NPSR1	rs172868					
	AA	29 (29.9)	179 (43.6)	1	1	
	AC	54 (55.7)	190 (46.2)	1.81 (1.12–2.92)	1.72 (1.05–2.84)	
	CC	14 (14.4)	42 (10.2)		2.24 (1.08–4.65)	0.01
NPSR1	rs35567595[b]					
	CC	38 (41.3)	216 (54.3)	1	1	
	CA	49 (53.3)	147 (36.9)	1.67 (1.05–2.65)	1.87 (1.16–3.01)	
	AA	5 (5.4)	35 (8.8)		0.81 (0.30–2.21)	0.1

Gene	SNP Genotype	Cases[a] n (%)	Controls n (%)	OR (95% CI) [reference= wt/wt only]	OR (95% CI) [additive model]	Test for Trend P- value
NPSR1	rs898070					
	CC	30 (30.9)	172 (42.2)	1	1	
	CT	54 (55.7)	181 (44.4)	1.61 (1.00–2.60)	1.70 (1.04–2.79)	
	TT	13 (13.4)	55 (13.5)		1.33 (0.64–2.74)	0.2
NPSR1	rs2609229					
	TT	71 (75.5)	265 (65.0)	1	1	
	TC	15 (16.0)	132 (32.4)	0.58 (0.34–0.97)	0.40 (0.22–0.73)	
	CC	8 (8.5)	11 (2.7)		2.94 (1.12–7.70)	0.4
NOS1	rs7961147					
	GG	71 (72.4)	330 (81.7)	1	1	
	GA	26 (26.5)	69 (17.1)	1.71 (1.02–2.86)	1.78 (1.05–3.00)	
	AA	1 (1.0)	5 (1.2)		0.82 (0.09–7.19)	0.09
NOS1	rs7977109[c]					
	AA	17 (18.1)	115 (28.6)	1	1	
	AG	50 (53.2)	184 (45.8)	1.81 (1.02–3.20)	1.87 (1.03–3.41)	
	GG	27 (28.7)	103 (25.6)		1.70 (0.87–3.32)	0.2

[a] Cases defined as highly fatal gliomas (<12 months survival time)

[b] rs 17776257 was not included in the table as it was in high LD with rs35567595 (r^2=0.82)

[c] rs733334 was not included as it was in high LD with rs7977109 (r^2=0.96)

Note. SNP: single nucleotide polymorphism; GBM: glioblastoma multiforme; OR: odds ratio; CI: confidence interval; wt=wildtype; LD= linkage disequilibrium

Table 3

Summary of previous studies investigating single nucleotide polymorphisms and haplotypes of allergy-associated genes.

First Author (Year)	Journal	Country	No. Cases/Controls	SNPs assessed (gene)	Outcome	Gene	SNP	Allele Comparison	OR (95% CI)[a]
Schwartzbaum (2005) [13]	Cancer Res	Sweden	111/422[b]	rs1805015, rs1801275 (IL4R); rs20541, rs1800925 (IL13); rs2280091 (ADAM33); -765GC (COX-2)	GBM	IL4R	rs1805015	TC, CC vs. TT	1.64; 1.05–2.55
							rs1801275	AG/AA vs. GG	1.61; 1.05–2.47
						IL-13	rs1800925	CC/TC vs. TT	0.56; 0.33, 0.96
Schwartzbaum (2007) [14]	Cancer Epi Biomarkers Prevention	Sweden, UK, Denmark, Finland	327/1,607[b]	rs1805015, rs1801275 (IL4R); rs20541, rs1800925 (Il13); - 765GC (COX-2); IL4Ra and IL-13 haplotypes	GBM	IL4R	rs1805015, rs1801275	T-G haplotype	2.26; 1.13, 4.52
Brenner (2007) [8]	Carcinogenesis	US	798/1,175	rs2243248, rs2243248, rs2070874 (IL4); rs1801275 (IL4R); rs2069812 (IL5); rs1800795 (IL6); rs1800871, rs1800872, rs1800896 (IL10); rs568408 (IL12A); rs20541 (IL13)	Glioma	IL4	rs2243248	GT vs. TT	1.44; 1.05, 1.97
								GT/GG vs. TT	1.49; 1.10–2.03
						IL6	rs1800795	GG vs. TT	0.70; 0.51, 0.95
					GBM	IL4	rs2243248	GT/GG vs. TT	1.47; 1.00–2.17
Dobbins (2010) [9]	Int J Cancer	UK, US	1,878/3,670	rs7216389 (ORMDL3); rs1420101 (IL1RL1); rs1588265 (PDE4D); rs7130588 (C11orf30)	Glioma	ORMDL3	rs7216389	CT vs. CC	1.16; 1.01–1.32
								TT vs. CC	1.20; 1.02–1.41
Ruan (2011) [10]	Front Biosci (Elite ed)	China	806/910	rs20541 (IL13); rs1801275 (IL4Ra); rs1059513, rs324015 (STAT6)	Glioma (never- smokers)	STAT6	rs1059513	GG vs. AA	1.691; 1.152–2.481
							rs1059513, rs324015	A-G haplotype	1.321; 1.081– 1.614
						GBM	rs1059513	GG vs. AA	1.856; 1.153– 2.987
Amirian (2010) [7]	Neuro- Oncology	US	373/365	rs2243250, rs2070874 (IL4); rs1805011, rs1805012, rs1805015, rs1801275, rs1805016 (IL4R); rs1800896, rs1800871, rs1800872 (IL10); rs20541, rs1800925 (IL13); rs16944, rs1143627(IL1B); rs2069762 (IL2); rs1800795, rs1800796, rs1800797 (IL6); rs187238 (IL18); rs20417 (COX2/PTGS2); rs1020759 (NFKB1); rs569108 (MS4A2); haplotypes for IL1, IL4, IL4R, IL6, IL10	Glioma	IL10	rs1800896	GG vs. AA/GA	1.57; 1.11–2.23
						IL13	rs20541	TT vs. CC	0.39; 0.17–0.94
								TT vs. CC/CT	0.39; 0.16–0.93
						Cox2	rs20417	CG vs. CC	1.43; 1.02, 1.98
								CG/GG vs. CC	1.41; 1.01–1.96
					GBM	IL10	rs1800896	GG vs. A/GA	1.61; 1.07–2.44
Scheuerer (2008) [11]	Clinical Cancer Res	US	694 cases	rs243250 (IL4); rs1800925 (IL13); rs1805011, rs1805012, rs1805015, rs1801275, rs1805016 (IL4R); IL4R haplotype	High- grade overall glioma survival Post 1- year high-grade glioma survival	IL4R	rs1805016	TT vs. GT/GG	0.59; 0.40–0.87
							rs1805015	TT vs. CT/CC	0.63; 0.44–0.91
							rs1805016	TT vs. GT/GG	0.44; 0.27–0.73
							rs1805011, rs1805012, rs1805015, rs1801275, rs1805016	ATTAT haplotype	0.68; 0.48–0.96
Wiemels (2007) [15]	Cancer Epi Biomarkers Prevention	US	456/541	rs1805010, rs1805011, rs1805012, rs1805015, rs1801275, rs1805016 (IL4R); rs2243250, rs2070874 (IL4); rs1800925, rs20541 (IL13); IL4, IL4R, IL13 haplotypes	Glioma	IL4	rs2243250	TC vs. CC	0.74; 0.55–1.0
						IL13	rs1800925	TC/TT vs. CC	0.77; 0.57–1.0
						IL4	rs2243250, rs2070874	C-T haplotype	0.22; 0.06–0.78

[a] Only significant ORs are reported in this table.

[b] Cases and controls from Schwartzbaum et al. 2005 are included in Schwartzbaum et al. 2007

Note: SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval; GBM: glioblastoma multiforme; UK: United Kingdom; US: United States