



Original Contribution

Interaction Between 5 Genetic Variants and Allergy in Glioma Risk

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The etiology of glioma is barely known. Epidemiologic studies have provided evidence for an inverse relation between glioma risk and allergic disease. Genome-wide association data have identified common genetic variants at 5p15.33 (rs2736100, *TERT*), 8q24.21 (rs4295627, *CCDC26*), 9p21.3 (rs4977756, *CDKN2A-CDKN2B*), 11q23.3 (rs498872, *PHLDB1*), and 20q13.33 (rs6010620, *RTEL1*) as determinants of glioma risk. The authors investigated whether there is interaction between the effects of allergy and these 5 variants on glioma risk. Data from 5 case-control studies carried out in Denmark, Finland, Sweden, and the United Kingdom (2000–2004) were used, totaling 1,029 cases and 1,668 controls. Risk was inversely associated with asthma, hay fever, eczema, and “any allergy,” significantly for each factor except asthma, and was significantly positively associated with number of risk alleles for each of the 5 single nucleotide polymorphisms. There was interaction between asthma and rs498872 (greater protective effect of asthma with increasing number of risk alleles; per-allele interaction odds ratio (OR) = 0.65, $P = 0.041$), between “any allergy” and rs4977756 (smaller protective effect; interaction OR = 1.27, $P = 0.047$), and between “any allergy” and rs6010620 (greater protective effect; interaction OR = 0.70, $P = 0.017$). Case-only analyses provided further support for atopy interactions for rs4977756 and rs498872. This study provides evidence for possible gene-environment interactions in glioma development.

allergy and immunology; case-control studies; glioma; polymorphism, single nucleotide

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

Gliomas account for approximately 80% of malignant tumors of the central nervous system and have a very poor prognosis (1). The etiology of glioma is largely unknown. High-dose ionizing radiation is known to increase risk. However, this is likely to account for only a small proportion of cases. Several rare genetic syndromes are associated with increased risk, but these collectively account for only a small proportion of the 2-fold increased risk seen in relatives of glioma cases (2, 3). Hence, it has been postulated that much of the familial risk is a consequence of the coinheritance of multiple low-risk genetic variants. Epidemiologic case-control studies have found reduced glioma risks in subjects with a self-reported history of allergic disease (4), hypoth-

esized to be due to increased tumor immunosurveillance (5, 6).

We conducted 5 case-control studies of glioma in 4 countries—Denmark, Finland, Sweden, and the United Kingdom—to investigate environmental and genetic risk factors and have previously reported on the association of glioma risk with allergic disease (7, 8). The United Kingdom and Swedish studies recently contributed to the identification of 5 single nucleotide polymorphisms (SNPs) associated with glioma risk, and results were replicated in 3 independent case-control series (9). The risk loci were 5p15.33 (rs2736100, *TERT*), 8q24.21 (rs4295627, *CCDC26*), 9p21.3 (rs4977756, *CDKN2A-CDKN2B*), 11q23.3

(rs498872, *PHLDB1*), and 20q13.33 (rs6010620, *RTEL1*). As with other cancers, the risk of glioma is likely to be a complex result of interactions between genetic and environmental/lifestyle factors.

To investigate potential gene-environment interactions between the effects of allergic disease and genotype for these 5 susceptibility SNPs in glioma risk, we analyzed 1,029 glioma cases and 1,668 controls for whom both types of data were available.

MATERIALS AND METHODS

The case-control studies from which the data were derived were conducted in several regions of Sweden and the United Kingdom, nearly all of Finland, and all of Denmark (see Web Table 1, which appears on the *Journal's* Web site (<http://aje.oxfordjournals.org/>)). They all followed the core protocol of the INTERPHONE Study, coordinated by the International Agency for Research on Cancer (10), with several extensions to the study design, and included several types of intracranial tumors.

Cases were patients with glioma (*International Classification of Diseases for Oncology*, Third Edition, morphology codes 9380–9411, 9420–9451, 9460, 9480, and 9505 (11) and *International Classification of Diseases*, Tenth Revision, topography code C71 (12)) who resided in one of the study areas and were first diagnosed at ages 18–69 years between 2000 and 2004 (age range and study period varying by center). Cases were recruited continuously through collaboration with treating clinics. For all study centers except Finland, any additional cases identified from cancer registries who had not been ascertained through the clinics were also included in the study, to achieve complete population-based ascertainment. Controls were defined as subjects with no previous diagnosis of brain tumor, with the same age and regional criteria as the cases. They were selected from general practice lists in the United Kingdom and from the population register in other countries and were frequency-matched to all brain tumor cases on age (5-year age groups), sex, and region within-study or individually matched to cases in the United Kingdom–North study.

Eligible cases were approached by letter, or personally at the clinic, with accompanying written information about the study. Controls were first approached by letter. Written informed consent was obtained from all participants. Each study was approved by the appropriate local ethics committee. Persons who consented were interviewed by trained research nurses or medical students. The interview included questions on a wide range of possible risk factors, with a main focus on mobile telephone use but also questions on allergies.

In Denmark, Sweden, and the United Kingdom, we attempted to collect a blood sample from all participants, whereas in Finland we collected blood samples from a convenience sample of predetermined size from patients in 3 hospitals and controls living in the area served by those hospitals. For the United Kingdom and Sweden, all available controls, including those selected as controls for non-glioma cases, were genotyped. For Denmark and Finland, a subset of all controls was available for genotyping, selected by randomly frequency-matching on sex; this

Table 1. Characteristics of Glioma Cases and Controls, Nordic-UK Brain Tumor Study, 2000–2004

Factor	Cases		Controls	
	No.	%	No.	%
Sex				
Male	634	61.6	792	47.5
Female	395	38.4	876	52.5
Age at reference date, years ^a				
18–29	99	9.6	93	5.6
30–39	198	19.2	234	14.0
40–49	232	22.6	413	24.8
50–59	328	31.9	601	36.0
60–69	172	16.7	327	19.6
Study center				
Denmark	125	12.2	151	9.1
Finland	97	9.4	98	5.9
Sweden	200	19.4	374	22.4
United Kingdom–North	375	36.4	646	38.7
United Kingdom–South	232	22.6	399	23.9
Tumor histology ^b				
Glioblastoma	480	46.7		
Nonglioblastoma	549	53.3		
Total	1,029	100	1,668	100

^a Date of diagnosis for cases and calculated censoring date for controls.

^b Glioblastoma was defined according to *International Classification of Diseases for Oncology*, Third Edition (11), morphology codes 9440–9442, and nonglioblastoma was defined as codes 9380–9411, 9420–9430, 9443–9451, 9460, 9480, and 9505.

accounted for 25% of all Danish controls and 89% of all Finnish controls who provided a blood sample.

Between the 5 study centers, 1,863 cases and 4,073 controls were interviewed, with participation proportions of 64% (range, 37%–81%) and 48% (range, 42%–66%), respectively (Web Table 1). We excluded subjects who did not provide a blood sample and those from Denmark and Finland who were not selected for genotyping (822 cases, 2,360 controls), subjects with non-Western European ancestry (3 cases, 36 controls), subjects with failed genotyping (8 cases, 9 controls), and subjects with no allergy information (1 case). The final study included data on 1,029 cases and 1,668 controls. These persons represented 55% and 41% of all interviewed cases and controls, respectively, or 60% of interviewed cases and 59% of controls after exclusion of Danish and Finnish subjects.

The 5 SNPs in the study (rs4295627, rs2736100, rs4977756, rs6010620, and rs498872) were selected on the basis of pooled analyses of results from 2 genome-wide association studies carried out in the United Kingdom and the United States, which were verified in Swedish, German, and French samples (9). British cases and Swedish cases and

Table 2. Odds Ratios for Risk of Glioma in Relation to Number of Risk Alleles per Single Nucleotide Polymorphism, Nordic-UK Brain Tumor Study, 2000–2004

Single Nucleotide Polymorphism	Chromosome	Gene	Ancestral Allele	Frequency (Proportion) in Controls	Risk Allele	Frequency (Proportion) in Controls	Per-Allele Odds Ratio ^a	95% Confidence Interval	P Value
rs2736100	5	<i>TERT</i>	T	0.49	G	0.51	1.31	1.17, 1.47	4.7×10^{-6}
rs4295627	8	<i>CCDC26</i>	T	0.82	G	0.18	1.24	1.08, 1.42	2.7×10^{-3}
rs4977756	9	<i>CDKN2A/B</i>	A	0.58	G	0.42	1.27	1.14, 1.43	2.6×10^{-5}
rs498872	11	<i>PHLDB1</i>	C	0.70	T	0.30	1.21	1.07, 1.36	2.4×10^{-3}
rs6010620	20	<i>RTEL1</i>	G	0.77	G	0.77	1.43	1.24, 1.64	8.3×10^{-7}
Sum of all risk alleles (range, 0–9)							1.27	1.20, 1.35	5.9×10^{-17}

Abbreviations: *CCDC26*, coiled-coil domain containing 26; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *CDKN2B*, cyclin-dependent kinase inhibitor 2B; *PHLDB1*, pleckstrin homology-like domain, family B, member 1; *RTEL1*, regulator of telomere elongation helicase 1; *TERT*, telomerase reverse transcriptase.

^a Odds ratio per unit increase in the risk allele, adjusted for study center, sex, and age at reference date (5-year groups).

controls described in the current study were included in the above genome-wide association study. Genotyping for the United Kingdom cases was conducted, as part of the parent genome-wide association study, using Illumina Infinium HD Human610-Quad BeadChips (Illumina, Inc., San Diego, California). United Kingdom controls, as well as Danish, Swedish, and Finnish cases and controls, were genotyped by KBiosciences for the 5 SNPs using competitive allele-specific polymerase chain reaction KASPar chemistry (KBiosciences Ltd., Hoddesdon, United Kingdom). Genotyping quality control was evaluated through inclusion of duplicate DNA samples in SNP assays. For all SNP assays, greater than 99% concordant results were obtained.

Statistical methods

Departure of the genotype frequencies in the controls from frequencies expected under Hardy-Weinberg equilibrium was assessed by means of a Pearson chi-squared test, or by a Fisher's exact test where any expected cell count was less than 5. There was no evidence for departure from Hardy-Weinberg equilibrium among controls, except for rs4295627 in the United Kingdom–North study center ($P = 0.009$) (Web Table 2). Combining both United Kingdom data sets provided little evidence of population stratification or genotyping problems ($P = 0.36$).

Odds ratios for being a case in relation to a past diagnosis of allergy or genotype were obtained from an (unconditional) logistic regression model adjusting for study center, sex, and age at reference date (in 5-year categories). The case reference date was defined as the diagnosis date. Control reference dates were assigned as previously described for the United Kingdom–North study center (7) and other centers (8). For the United Kingdom–North center, we chose to break the matching, since restriction of analyses to subjects with available DNA would have resulted in the loss of many case-control pairs.

The allergic conditions analyzed were physician-diagnosed asthma, hay fever, eczema, and all allergies combined. Data collection at all study centers included questions on past diagnosis of asthma, hay fever, and eczema, and all

centers except United Kingdom–North collected additional details on diagnosis of nonseasonal or seasonal allergic rhinitis and conjunctivitis, food or contact allergy, and “other allergy.” Because the term “hay fever” might have been used differently in different countries and because there might have been changes in terminology over time, seasonal and nonseasonal allergic rhinitis and conjunctivitis were included under the term “hay fever” in the analysis for the centers for which that was possible. The risk factor “any allergy” was defined in the analysis as asthma, hay fever, or eczema and, for all centers except United Kingdom–North, food or contact allergy and other specified allergy (commonly allergy to pets or medicines).

SNP genotypes were categorized as having 0, 1, or 2 risk alleles, with “risk allele” being defined as the allele associated with increased risk of glioma. Per-allele odds ratios were fitted assuming an additive genetic model.

To test for heterogeneity (interaction), we assessed the effect of allergic disease on glioma risk according to SNP-specific genotype. We did this by fitting a model with the main effects of allergy and genotype (0, 1, or 2 risk alleles), as well as an interaction term between them, examining statistical significance by means of a log likelihood ratio test comparing the model against a model with only the main effects of allergy and genotype. Odds ratios and 95% confidence intervals in relation to allergy for subjects with 0, 1, or 2 risk alleles were then obtained. We also tested whether the linear trend of glioma risk in relation to number of SNP-specific risk alleles was significantly different between subjects with allergic disease and those without allergic disease by fitting an interaction term between allergic disease and genotype, with genotype fitted as a linear term. The total number of risk alleles of all 5 SNPs was also calculated, and allergy-associated odds ratios were assessed according to 3 allele groups (0–3, 4–5, or 6–9 risk alleles), with the boundaries aimed at creating equal-sized groups.

Analyses were repeated for glioblastoma cases only, as a single homogeneous group of tumors, and after exclusion of SNPs from centers that did not meet Hardy-Weinberg equilibrium. We also tested for between-study heterogeneity in the main effects, as a background check on the results, but

Table 3. Odds Ratios for Risk of Glioma in Relation to Allergic Disease in Subjects with 0, 1, or 2 Risk Alleles per Single Nucleotide Polymorphism, Nordic-UK Brain Tumor Study, 2000–2004

Allergic Disease and SNP	No. of Cases With Disease	No. of Controls With Disease	0 Risk Alleles		1 Risk Allele		2 Risk Alleles		P for Heterogeneity	P for Interaction Trend ^b
			OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI		
Asthma	92	182								
rs2736100			0.89	0.49, 1.61	0.72	0.49, 1.05	0.94	0.55, 1.61	0.686	0.805
rs4295627			0.74	0.52, 1.04	0.93	0.57, 1.53	0.97	0.28, 3.40	0.717	0.436
rs4977756			0.77	0.46, 1.26	0.71	0.47, 1.07	1.19	0.67, 2.10	0.337	0.297
rs498872			1.13	0.77, 1.67	0.56	0.36, 0.86	0.67	0.28, 1.60	0.048	0.041
rs6010620			2.61	0.84, 8.07	0.84	0.51, 1.39	0.70	0.50, 0.99	0.108	0.085
Hay fever	186	369								
rs2736100			0.76	0.47, 1.22	0.62	0.46, 0.82	1.11	0.76, 1.62	0.052	0.120
rs4295627			0.76	0.59, 0.99	0.77	0.54, 1.10	0.61	0.25, 1.52	0.891	0.782
rs4977756			0.58	0.39, 0.86	0.83	0.62, 1.12	0.99	0.64, 1.53	0.154	0.063
rs498872			0.83	0.61, 1.12	0.78	0.57, 1.06	0.59	0.32, 1.11	0.641	0.403
rs6010620			1.11	0.36, 3.36	0.99	0.69, 1.43	0.68	0.53, 0.88	0.210	0.080
Eczema	107	259								
rs2736100			0.86	0.48, 1.52	0.62	0.44, 0.87	0.63	0.39, 1.00	0.619	0.472
rs4295627			0.58	0.42, 0.80	0.81	0.53, 1.24	1.00	0.28, 3.62	0.383	0.164
rs4977756			0.80	0.51, 1.26	0.58	0.40, 0.84	0.69	0.41, 1.16	0.567	0.622
rs498872			0.60	0.41, 0.88	0.73	0.51, 1.05	0.59	0.29, 1.19	0.735	0.824
rs6010620			0.68	0.21, 2.25	0.65	0.39, 1.10	0.61	0.45, 0.82	0.969	0.807
Any allergy ^c	343	724								
rs2736100			0.82	0.56, 1.20	0.56	0.44, 0.71	0.71	0.52, 0.98	0.174	0.790
rs4295627			0.59	0.48, 0.73	0.77	0.57, 1.04	0.89	0.41, 1.92	0.264	0.107
rs4977756			0.57	0.42, 0.78	0.62	0.49, 0.80	0.94	0.66, 1.34	0.086	0.047
rs498872			0.70	0.54, 0.90	0.65	0.50, 0.84	0.53	0.32, 0.89	0.633	0.370
rs6010620			1.05	0.48, 2.33	0.83	0.61, 1.14	0.56	0.45, 0.69	0.055	0.017

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

^a Odds ratio for the allergic condition relative to not having the condition for subjects with 0, 1, or 2 risk alleles, adjusted for study center, sex, and age at reference date (5-year groups).

^b Test for difference in linear trend of glioma risk per unit increase in the risk allele between subjects with allergic disease and those without allergic disease.

^c "Any allergy" was defined as asthma, hay fever, eczema, or other allergy, where asked.

none was found. We further evaluated potential interactions with respect to glioma risk using a case-only design (13). The use of this design is dependent on the assumption that the frequency of the environmental exposure does not vary according to genotype in the population. We tested this assumption with a chi-squared test in controls. The statistical package Stata was used for all analyses (14), except for estimation of statistical power, for which we used the Espresso-CC power calculator (15) for R, version 2.9.1 (R Foundation for Statistical Computing (<http://www.r-project.org/foundation/>)). Statistical significance was defined as a 2-sided *P* value less than 0.05.

RESULTS

Table 1 shows the characteristics of the 1,029 cases and 1,668 controls included in the study. In most study centers,

controls were matched for all forms of primary brain tumors rather than specifically for glioma. This had the consequence that in this analysis, the glioma cases tended to be more likely to be male and younger than controls.

Allelic odds ratios were significantly raised for each of the SNPs in the entire data set (Table 2). Because the Danish and Finnish genotype data were not included in the previously published genome-wide association study (9), we considered these data separately in a subanalysis. Odds ratios were somewhat higher for each of the SNPs in comparison with the overall results in Table 2 and were significantly raised, except for rs4977756, for which the odds ratio was lower and not significantly different from 1.0 (odds ratio (OR) = 1.17, 95% confidence interval (CI): 0.90, 1.51) (data not shown).

Consistent with parent analyses (8), the risk of glioma was reduced in relation to past diagnosis of asthma (OR = 0.79, 95% CI: 0.60, 1.04), hay fever (OR = 0.77, 95% CI:

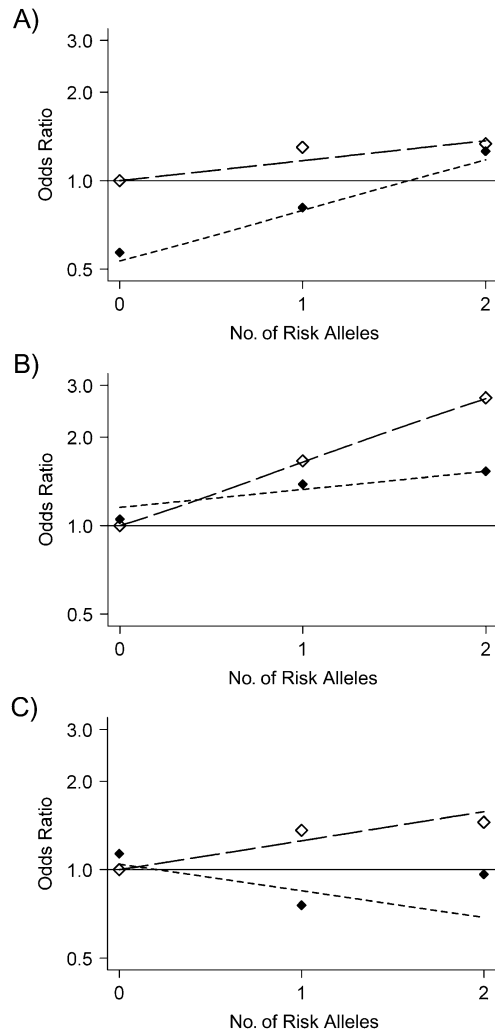


Figure 1. Odds ratios for risk of glioma in relation to number of risk alleles for A) rs4977756 and “any allergy” (asthma, hay fever, eczema, or other allergy), B) rs6010620 and “any allergy,” and C) rs498872 and asthma, Nordic-UK Brain Tumor Study, 2000–2004. Odds ratios fitted separately for 0, 1, and 2 risk alleles are shown for subjects with allergy (solid diamonds) and subjects with no allergy (open diamonds) (see Table 3). Lines represent odds ratios obtained from a per-allele log-linear trend model for subjects with allergy (short dashes) and subjects with no allergy (long dashes). The reference group (odds ratio = 1.0) was persons with no allergy and 0 risk alleles.

0.63, 0.95), eczema (OR = 0.66, 95% CI: 0.51, 0.84), or “any allergy” (OR = 0.66, 95% CI: 0.55, 0.78). There were no statistically significant interactions between the effects of hay fever and eczema and each of the SNPs with respect to glioma risk (Table 3). The relative protective effect of “any allergy” with respect to glioma risk increased with number of risk alleles of rs6010620 (Table 3); to consider it another way, glioma risk increased less strongly with the number of risk alleles in persons with allergy than in those without allergy (per-allele interaction OR = 0.70 (1.15/1.65 = 0.70; see Web Table 3), $P = 0.017$) (Figure 1 and Web Table 3). Similarly, the relative protective effect of asthma on glioma risk increased with number of risk alleles for

rs498872 (interaction OR = 0.65, $P = 0.041$). Evidence for interaction was also observed for rs4977756 and “any allergy,” with allergy-associated odds ratios converging with increasing number of risk alleles or, to consider it another way, per-allele odds ratios being greater in persons with “any allergy” than in those with no allergy (interaction OR = 1.27, $P = 0.047$). Analyses by number of risk alleles showed no significant effect modification of allergy-associated odds ratios between subjects with 0–3, 4–5, and 6–9 alleles and no evidence for interaction in linear trend across the total number of risk alleles (Web Table 4). Repetition of analyses for rs4295627 without the data from the United Kingdom–North center, because of deviation from Hardy-Weinberg equilibrium, showed no material difference in results.

Analyses restricted to glioblastoma cases and controls did not provide significant evidence for interaction (Web Table 5). The protective effect of “any allergy” on glioblastoma risk appeared to decrease with the number of risk alleles for rs4977756, but not significantly so (P -interaction trend = 0.093). The results for rs6010620 and rs498872 did not show significant evidence for interaction. Analyses restricted to nonglioblastoma cases showed significant interaction between rs498872 and asthma (P -interaction trend = 0.034) and between rs6010620 and “any allergy” (P -interaction trend = 0.034) but not between rs4977756 and “any allergy” ($P = 0.109$) (results not shown in table).

The case-only analysis (Table 4) provided support for an inverse interaction between asthma and rs498872, albeit nonsignificant, and a positive interaction between “any allergy” and rs4977756. Odds ratios based on case-only analyses can be interpreted as the synergy index of interaction (the factor by which the combined effect of gene and environment is enhanced or reduced above that expected from a multiplicative effect of the individual factors) (13), conditional on independence between the 2 factors in the population. Estimates of this synergy were comparable to those in the main analyses; the per-allele odds ratio for rs498872 was 0.74 in the case-only analysis and 0.65 (0.81/1.25 = 0.65; Web Table 3) in the main analyses. For rs4977756, these values were 1.21 and 1.27, respectively. For “any allergy” and rs6010620, the frequency of allergy was not independent of the rs6010620 genotype among controls (chi-squared test: $P = 0.04$), and therefore the assumption of a case-only design was invalidated.

To gain insight into our ability to identify main-effect interactions, we computed our study’s statistical power. On the basis of the obtained numbers of cases and controls and the prevalence of “any allergy” among controls (44%), statistical power was 79%–94% to detect an interaction odds ratio of 1.5, 62%–82% to detect an odds ratio of 1.4, and 43%–62% to detect an odds ratio of 1.3, assuming minor allele frequencies of 18%–49%. For individual allergic conditions, for which prevalences were 11%–22% among controls, power was lower.

DISCUSSION

In this large case-control study of glioma risk, there was evidence for modification of the effect of asthma with

Table 4. Odds Ratios for Risk of Allergic Disease According to Number of Risk Alleles per Single Nucleotide Polymorphism in Glioma Cases and Controls (Case-Only Analysis), Nordic-UK Brain Tumor Study, 2000–2004

Allergic Disease, SNP, and No. of Risk Alleles	No Allergy		Allergy		Chi-Squared <i>P</i> Value	Adjusted OR ^a	95% Confidence Interval or <i>P</i> Value
	No.	%	No.	%			
Cases							
Asthma							
rs498872							
0	391	42.0	48	52.2		1.00	
1	429	46.1	35	38.0		0.67	0.42, 1.07
2	111	11.9	9	9.8	0.17	0.63	0.30, 1.35
Per-allele OR and <i>P</i> -trend						0.74	<i>P</i> = 0.09
Any allergy ^b							
rs4977756							
0	196	28.9	87	25.6		1.00	
1	338	49.8	160	47.1		1.13	0.81, 1.56
2	145	21.4	93	27.4	0.10	1.48	1.01, 2.16
Per-allele OR and <i>P</i> -trend						1.21	<i>P</i> = 0.045
rs6010620							
0	21	3.1	14	4.1		1.00	
1	187	27.3	95	27.9		0.74	0.35, 1.56
2	476	69.6	231	67.9	0.65	0.71	0.34, 1.46
Per-allele OR and <i>P</i> -trend						0.91	<i>P</i> = 0.48
Controls							
Asthma							
rs498872							
0	725	49.6	85	47.2		1.00	
1	597	40.8	79	43.9		1.10	0.78, 1.52
2	141	9.6	16	8.9	0.73	0.97	0.55, 1.71
Per-allele OR and <i>P</i> -trend						1.03	<i>P</i> = 0.83
Any allergy ^b							
rs4977756							
0	319	34.6	238	33.9		1.00	
1	426	46.2	335	47.7		1.03	0.81, 1.30
2	178	19.3	129	18.4	0.81	0.93	0.69, 1.25
Per-allele OR and <i>P</i> -trend						0.97	<i>P</i> = 0.73
rs6010620							
0	65	7.0	43	6.1		1.00	
1	328	35.5	215	30.2		1.01	0.66, 1.58
2	532	57.5	453	63.7	0.04	1.35	0.88, 2.10
Per-allele OR and <i>P</i> -trend						1.22	<i>P</i> = 0.013

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

^a Odds ratio for allergic disease, adjusted for study center, sex, and age at reference date (5-year groups). The analysis in cases corresponds to a case-only analysis of interaction between allergic disease and SNP with respect to risk of glioma, conditional on independence of these 2 factors among controls.

^b "Any allergy" was defined as asthma, hay fever, eczema, or other allergy, where asked.

respect to glioma risk by rs498872 genotype and the effect of “any allergy” by rs4977756 and rs6010620 genotypes. These results were based on tests for difference in linear trend with only modestly significant *P* values, and they could have been false-positive findings due to multiple testing. On the other hand, statistical power was weak-to-moderate for individual allergic diseases, and it is possible that other, weak associations could not be detected. In addition, case-only analyses confirmed our findings for asthma and rs498872 and for “any allergy” and rs4977756. Such analyses can be useful, since they avoid biases related to control selection. There was no evidence for effect modification according to the total number of risk SNPs, but this analysis included SNPs that did not show evidence for effect modification with allergy.

Glioma constitutes a heterogeneous group of tumors. Restriction of analyses to the relatively homogeneous group of glioblastoma multiforme tumors produced results somewhat different from those for glioma overall. This may be partly a consequence of smaller numbers and therefore less power, but in the original genome-wide association study, Shete et al. (9) reported evidence for a different risk profile for glioblastoma multiforme. Analyses restricted to nonglioblastoma tumors suggested that some of the main results were driven by this group. Larger studies of homogeneous subtypes of glioma are required to address whether any gene-environment interactions are histology-specific.

An inverse association of glioma risk with allergic disease is the most consistently reported association in etiologic epidemiologic studies of this tumor (4), besides the uncommon exposures of certain genetic syndromes and high-dose radiation. Inverse associations of glioma with autoimmune disease (16) and of immunoglobulin G positivity with varicella-zoster virus (17) have also been reported. Cases were reported to have lower immunoglobulin E levels than controls (18), and higher immunoglobulin E levels have been associated with longer survival (19). It has therefore been hypothesized that people with atopy have better anti-tumor responses (5, 6). However, most studies of the relation of glioma risk to allergic disease have been case-control studies, and results from the few cohort studies have been inconsistent (20). The allergy association could therefore be due to reverse causality—that is, due to immunologic changes induced by the tumor (21, 22), or other types of bias, including interviewer bias, selection bias in controls, and underreporting of allergies by cases due to their glioma diagnosis (7). It is interesting, however, that inverse associations with atopy have also been observed in relation to risk of central nervous system tumors in children (23), where such biases are likely to be less of an issue.

The 5 SNPs investigated in this study account for an excess familial risk of glioma of approximately 7%–14% (9). The SNP rs4295627 maps to intron 3 of the *CCDC26* (coiled-coil domain containing 26) gene and encodes a retinoic acid modulator of differentiation and death (24). Retinoid acid induces caspase-8 transcription through phosphorylation of cyclic adenosine monophosphate response element-binding and increases apoptosis in glioblastoma cells with down-regulation of telomerase activity (25).

The SNP rs2736100 localizes to intron 2 of the *TERT* (telomerase reverse transcriptase) gene, the reverse transcriptase component of telomerase, which is required for maintaining telomeres and cell immortalization. *TERT* expression is associated with glioma grade and prognosis (26). The SNP rs4977756 maps 59 kilobases telomeric to *CDKN2B* (cyclin-dependent kinase inhibitor 2B), a region that encompasses the *CDKN2A-CDKN2B* tumor suppressor genes, with a distinct role in gliogenesis (26–28). The SNP rs6010620 localizes to intron 12 of the RAD3-like helicase gene *RTEL1* (regulator of telomere elongation helicase 1), mapping within a 65-kilobase region of linkage disequilibrium at 20q13.33, a region which shows amplification in approximately 30% of gliomas, with copy number change correlating with *RTEL1* expression (9). Finally, rs498872 maps to the 5′-untranslated region of the *PHLDB1* (pleckstrin homology-like domain, family B, member 1) gene; there is no direct evidence for a role of this gene in gliogenesis, although this region (11q23.3) is frequently deleted in patients with neuroblastoma (29). None of the 5 risk SNPs are positioned in close proximity to an SNP known to be associated with allergy (30, 31); therefore, linkage disequilibrium with allergy SNPs cannot explain our findings. While genetic variation in these genes may not play a direct role in influencing immune function, it is conceivable that they may have an impact on immune function and hence atopy through epitopic effects.

To our knowledge, this is the first study to have investigated the effect of interaction between allergic phenotype and risk SNPs on glioma, a highly fatal disease of which little is known. The merit of using SNPs identified through genome-wide association studies is that the SNPs have convincingly been associated with glioma risk at a very high level of significance ($P < 10^{-7}$). The search for main-effect interactions is likely to be hypothesis-generating at this juncture, as power considerations dictate that the identification of gene-environment interactions is contingent on very large data sets. However, this study did show evidence that such interactions might play a role in glioma development. This merits follow-up in further studies, including replication studies and research into biologic pathways.

In conclusion, our study provides some evidence that the protective effect of allergy with respect to glioma risk is influenced by genetic variation. Larger studies are needed to reinvestigate these findings, which, if confirmed, are likely to be highly informative regarding glioma development.

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Web Table 1. Details of Study Design and Participation by Study Center, Nordic-UK Brain Tumor Study, 2000-2004.

	Denmark	Finland	Sweden	UK-South	UK-North	All centers combined
Study population	Nationwide	Excluding northern Lapland and Åland	Stockholm, Göteborg, Lund and Umeå	Thames regions of Southeast England	Trent, West Midlands, West Yorkshire and Southern Scotland	
Age range (yrs)	20-69	20-69	20-69	18-59	18-69	
Study period	September 2000-August 2002	November 2000-September 2002	September 2000-August 2002	December 2000-February 2004	December 2000-June 2003	
<i>Cases</i>						
Total number eligible interviewed subjects	252	267	364	376	604	1,863
Participation rate	71	81	74	37	63	64
Number with DNA SNP data available	125	97	200	232	375	1,029
% with available DNA SNPs	50	36	55	62	62	55
<i>Controls</i>						
Total number eligible interviewed subjects	824	870	632	630	1117	4,073
Participation rate	52	42	66	43	48	48
Number with DNA SNP data available	151	98	374	399	646	1,668
% with available DNA SNPs	18	11	59	63	58	41

Abbreviation: UK, United Kingdom.

Web Table 2. Distribution of Genotypes by Case-control Status and Center, Nordic-UK Brain Tumor Study, 2000-2004.

Country	SNP	risk allele	Cases						Controls						P(HWE) ^a
Denmark	rs2736100	G	TT	22	TG	58	GG	39	TT	31	TG	74	GG	41	0.82
	rs4295627	G	TT	76	TG	40	GG	7	TT	98	TG	46	GG	3	0.57
	rs4977756	G	AA	37	GA	55	GG	29	AA	54	GA	64	GG	27	0.30
	rs498872	T	CC	54	TC	57	TT	10	CC	82	TC	53	TT	10	0.72
	rs6010620	G	AA	1	GA	38	GG	83	AA	8	GA	56	GG	83	0.72
Finland	rs2736100	G	TT	8	TG	56	GG	33	TT	23	TG	53	GG	19	0.25
	rs4295627	G	TT	47	TG	34	GG	16	TT	58	TG	31	GG	6	0.51
	rs4977756	G	AA	26	GA	51	GG	18	AA	36	GA	38	GG	22	0.06
	rs498872	T	CC	34	TC	48	TT	15	CC	48	TC	34	TT	12	0.14
	rs6010620	G	AA	4	GA	22	GG	69	AA	3	GA	30	GG	63	0.99
Sweden	rs2736100	G	TT	29	TG	107	GG	57	TT	101	TG	171	GG	90	0.30
	rs4295627	G	TT	130	TG	63	GG	6	TT	241	TG	117	GG	14	0.97
	rs4977756	G	AA	42	GA	97	GG	57	AA	110	GA	177	GG	80	0.58
	rs498872	T	CC	93	TC	82	TT	24	CC	178	TC	155	TT	38	0.62
	rs6010620	G	AA	4	GA	52	GG	144	AA	25	GA	116	GG	230	0.05
UK-North	rs2736100	G	TT	59	TG	198	GG	118	TT	143	TG	317	GG	175	0.98
	rs4295627	G	TT	237	TG	122	GG	16	TT	434	TG	156	GG	27	0.009
	rs4977756	G	AA	108	GA	182	GG	85	AA	216	GA	301	GG	110	0.77
	rs498872	T	CC	148	TC	179	TT	48	CC	301	TC	272	TT	66	0.69
	rs6010620	G	AA	18	GA	106	GG	252	AA	44	GA	212	GG	376	0.06
UK-South	rs2736100	G	TT	53	TG	105	GG	74	TT	86	TG	202	GG	107	0.61
	rs4295627	G	TT	137	TG	83	GG	12	TT	266	TG	119	GG	11	0.59
	rs4977756	G	AA	70	GA	113	GG	49	AA	141	GA	181	GG	68	0.45
	rs498872	T	CC	111	TC	98	TT	23	CC	201	TC	162	TT	31	0.84
	rs6010620	G	AA	8	GA	65	GG	159	AA	28	GA	129	GG	233	0.09

Abbreviation: HWE, Hardy-Weinberg Equilibrium; UK, United Kingdom.

^aTest for departure from Hardy-Weinberg Equilibrium (HWE) among controls with Pearson's Chi-square, or Fisher's exact test when expected cell count <5.

Web Table 3. Per-allele Odds Ratios by Allergic Condition, Nordic-UK Brain Tumor Study, 2000-2004.

Allergic disease (no. of cases/controls with disease)	SNP	No allergy ^a		With allergy ^a		P int trend ^c
		Trend OR ^b	95% CI	Trend OR ^b	95% CI	
Asthma (92/182)	rs2736100	1.30	1.15, 1.47	1.37	0.93, 2.01	0.805
	rs4295627	1.22	1.05, 1.41	1.47	0.94, 2.29	0.436
	rs4977756	1.25	1.11, 1.41	1.53	1.06, 2.19	0.297
	rs498872	1.25	1.11, 1.42	0.81	0.54, 1.21	0.041
	rs6010620	1.49	1.28, 1.73	0.98	0.64, 1.52	0.085
Hay fever (186/369)	rs2736100	1.25	1.10, 1.43	1.59	1.21, 2.10	0.120
	rs4295627	1.25	1.07, 1.47	1.19	0.88, 1.62	0.782
	rs4977756	1.21	1.07, 1.37	1.59	1.23, 2.06	0.063
	rs498872	1.24	1.08, 1.41	1.09	0.83, 1.43	0.403
	rs6010620	1.52	1.30, 1.77	1.09	0.79, 1.52	0.080
Eczema (107/259)	rs2736100	1.33	1.18, 1.51	1.17	0.83, 1.65	0.472
	rs4295627	1.19	1.03, 1.38	1.63	1.08, 2.47	0.164
	rs4977756	1.29	1.15, 1.46	1.19	0.86, 1.64	0.622
	rs498872	1.21	1.06, 1.37	1.26	0.90, 1.76	0.824
	rs6010620	1.45	1.25, 1.69	1.37	0.90, 2.10	0.807
Any allergy ^d (343/724)	rs2736100	1.32	1.14, 1.53	1.28	1.05, 1.55	0.790
	rs4295627	1.13	0.95, 1.35	1.43	1.14, 1.80	0.107
	rs4977756	1.17	1.02, 1.35	1.49	1.23, 1.79	0.047
	rs498872	1.26	1.08, 1.47	1.12	0.92, 1.37	0.370
	rs6010620	1.65	1.38, 1.97	1.15	0.91, 1.45	0.017

Abbreviations: CI, confidence interval; OR, odds ratio; UK, United Kingdom.

^aAllergic condition specified in column 1.^bPer-allele odds ratio, adjusted for study center, sex, age at reference date (5-yr groups).^cTest for difference in linear trend of glioma risk per unit increase in risk allele between those with allergic disease and those without.^dAny allergy defined as any of asthma, hay fever, eczema, or other allergy, where asked.

Web Table 4. Odds Ratios for Risk of Glioma in Relation to Allergic Disease by Total Number of Risk Alleles for the Five Susceptibility-associated SNPs, Nordic-UK Brain Tumor Study, 2000-2004.

Allergic disease	0-3 risk alleles		4-5 risk alleles		6-9 risk alleles		P het	P int trend ^c	Overall	
	OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI			OR	95% CI
Asthma	1.36	0.79, 2.36	0.65	0.43, 0.99	0.89	0.52, 1.53	0.114	0.305	0.79	0.60, 1.04
Hay fever	0.91	0.58, 1.44	0.70	0.51, 0.94	0.84	0.57, 1.23	0.562	0.787	0.77	0.63, 0.95
Eczema	0.62	0.32, 1.18	0.62	0.43, 0.87	0.69	0.43, 1.10	0.930	0.493	0.66	0.51, 0.84
Any allergy ^b	0.76	0.52, 1.11	0.57	0.44, 0.73	0.74	0.53, 1.02	0.294	0.920	0.66	0.55, 0.78

Abbreviations: CI, confidence interval; OR, odds ratio; UK, United Kingdom.

^aORs for those with allergic condition relative to those without the condition, for subjects with 0, 1, or 2 risk alleles, adjusted for study center, sex, age at reference date (5-yr groups).

^bAny allergy defined as any of asthma, hay fever, eczema, or other allergy, where asked.

^cTest for difference in linear trend of glioma risk per unit increase in risk allele between those with allergic disease and those without.

Web Table 5. Odds Ratios for Risk of Glioblastoma in Relation to Allergic Disease in Subjects With 0, 1 or 2 Risk Alleles per SNP, Nordic-UK Brain Tumor Study, 2000-2004.

Factor (no. of cases/ controls with condition) ^a	SNP	0 risk alleles		1 risk allele		2 risk alleles		P het	P int trend ^c
		OR ^b	95% CI	OR ^b	95% CI	OR ^b	95% CI		
Asthma (33/182)	rs2736100	0.86	0.35, 2.12	0.57	0.33, 1.01	0.88	0.42, 1.85	0.592	0.797
	rs4295627	0.63	0.39, 1.01	0.80	0.37, 1.71	1.03	0.19, 5.49	0.781	0.472
	rs4977756	0.77	0.37, 1.62	0.58	0.32, 1.06	0.90	0.42, 1.94	0.655	0.798
	rs498872	0.92	0.54, 1.59	0.47	0.24, 0.91	0.73	0.23, 2.33	0.297	0.302
	rs6010620	2.47	0.26, 23.24	0.75	0.37, 1.53	0.61	0.38, 0.99	0.535	0.340
Hay fever (89/369)	rs2736100	1.17	0.62, 2.21	0.64	0.43, 0.94	1.34	0.83, 2.14	0.041	0.370
	rs4295627	0.89	0.64, 1.23	0.85	0.52, 1.41	0.68	0.20, 2.33	0.909	0.723
	rs4977756	0.58	0.33, 1.03	0.99	0.68, 1.44	1.18	0.69, 2.01	0.160	0.075
	rs498872	1.06	0.73, 1.54	0.82	0.54, 1.25	0.55	0.23, 1.35	0.346	0.149
	rs6010620	0.00		1.27	0.80, 2.00	0.76	0.54, 1.06	0.027	0.134
Eczema (40/259)	rs2736100	1.04	0.46, 2.33	0.40	0.23, 0.68	0.65	0.35, 1.21	0.140	0.654
	rs4295627	0.56	0.36, 0.85	0.60	0.30, 1.19	0.32	0.04, 2.91	0.856	0.861
	rs4977756	0.50	0.23, 1.08	0.59	0.36, 0.97	0.57	0.28, 1.14	0.941	0.841
	rs498872	0.57	0.34, 0.98	0.52	0.29, 0.91	0.60	0.23, 1.56	0.955	0.976
	rs6010620	0.00		0.57	0.27, 1.20	0.53	0.35, 0.80	0.280	0.827
Any allergy ^d (150/724)	rs2736100	0.88	0.51, 1.53	0.52	0.38, 0.72	0.79	0.53, 1.18	0.140	0.854
	rs4295627	0.60	0.45, 0.79	0.80	0.53, 1.22	0.74	0.26, 2.10	0.494	0.300
	rs4977756	0.55	0.35, 0.86	0.63	0.46, 0.87	0.95	0.61, 1.47	0.192	0.093
	rs498872	0.78	0.57, 1.08	0.59	0.42, 0.84	0.47	0.24, 0.95	0.304	0.123
	rs6010620	0.29	0.03, 2.51	0.86	0.57, 1.29	0.58	0.44, 0.77	0.207	0.255

Abbreviations: CI, confidence interval; OR, odds ratio; UK, United Kingdom.

^aOverall odds ratios were 0.69 (95% CI: 0.46-1.02) for asthma, 0.89 (95% CI: 0.68-1.16) for hay fever, 0.55 (95% CI: 0.39-0.79) for eczema and 0.66 (95% CI: 0.53-0.83) for any allergy.

^bORs for allergic condition relative to not having the condition, for subjects with 0,1, or 2 risk alleles, adjusted for study center, sex, age at reference date (5-yr groups).

^cTest for difference in linear trend of glioma risk per unit increase in risk allele between those with allergic disease and those without.

^dAny allergy defined as any of asthma, hay fever, eczema, or other allergy (where asked).