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Selected Human Leukocyte Antigen class II polymorphisms and risk of adult glioma

Bryan A. Bassig¹, Peter D. Inskip², Laurie Burdette³, William R. Shapiro⁴, Robert G. Selker⁵, Howard A. Fine⁶, Jay S. Loeffler⁷, Peter M. Black⁸, Robert Dubrow¹, and Alina V. Brenner²

¹Yale School of Public Health, Yale School of Medicine, 60 College Street, P.O. Box 208034, New Haven, CT 06510, USA

²Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd. MSC 7242, Bethesda, MD 20892, USA

³Core Genotyping Facility, Advanced Technology Program, SAIC-Frederick Inc., NCI-Frederick, Frederick, MD 21702, USA

⁴Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ 85013, USA

⁵Division of Neurosurgery, Western Pennsylvania Hospital, Pittsburgh, PA 15224, USA

⁶Neuro-Oncology Branch, National Cancer Institute, Bethesda, MD 20892, USA

⁷Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA 02114, USA

⁸Brigham and Women's Hospital, Boston, MA 02115, USA

Abstract

Few studies have examined the relationship between human leukocyte antigen (HLA) polymorphisms and adult glioma, particularly at class II loci. We evaluated the association between selected HLA class II polymorphisms and adult glioma in a large, hospital-based case-control study, using unconditional logistic regression. *DQB1**06 (OR=1.67, 95% CI=1.17–2.39) and *DRB1**13 (OR=1.69, 95% CI=1.08–2.64) alleles were associated with an increased risk of glioma, while the *DQB1**05 allele showed an inverse association (OR=0.63, 95% CI=0.43–0.93). These results, which were of borderline significance once controlled for the false discovery rate, suggest a potential role for the *DQB1**06, *DQB1**05, and *DRB1**13 alleles in glioma susceptibility.

Keywords

glioma; brain tumors; HLA polymorphisms; *DQB1*; *DRB1*

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Correspondence to Alina V. Brenner, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd. MSC 7362, Bethesda, MD 20892-7362; brennera@mail.nih.gov, phone: 301-402-8680.

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1. Introduction

Glioma is the most aggressive and common form of brain cancer, accounting for about 80% of primary malignant brain tumors (Central Brain Tumor Registry of the United States, 2010). The survival rate for glioma patients is characteristically poor, with less than 25% of individuals surviving past five years (Barnholtz-Sloan et al., 2007). Outcomes are much worse for patients with the most common form of glioma, glioblastoma multiforme (GBM), with a five-year survival rate of less than 5% (Barnholtz-Sloan et al., 2007). While the etiology of glioma is not well elucidated, increasing evidence has pointed to the role of immunological and genetic factors in the development and progression of these tumors ([Rajaraman et al., 2009], [Scheurer et al., 2008], [Brenner et al., 2007] and [Wensch et al., 2006]). Specifically, epidemiologic evidence has suggested a consistent inverse relationship between glioma and a prior history of allergy and, to a lesser extent, autoimmune disease ([Wiemels et al., 2008], [Brenner et al., 2002], [Schoemaker et al., 2006], [Wigertz et al., 2007] and [Il'yasova et al., 2009]). The observed relationship between glioma and immune-related disorders has been further supported by the observation that genetic polymorphisms in cytokine genes have been associated with both glioma susceptibility and survival ([Scheurer et al., 2008], [Brenner et al., 2007] and [Schwartzbaum et al., 2005]). Interestingly, specific polymorphisms associated with an increased risk of asthma were previously shown to be associated with a decreased risk of glioblastoma [Schwartzbaum et al., 2005].

It is well established that polymorphisms in human leukocyte antigen (HLA) genes, responsible for antigen presentation and initiation of immune response, are related to risk of autoimmune diseases and allergic conditions, including celiac disease (Karell et al., 2003), type I diabetes ([Gorodezky et al., 2006] and [Erich et al., 2008]), rheumatoid arthritis ([Tuokko et al., 2001] and [Seidl et al., 2001]), as well as risk of asthma (Juhn et al., 2007) and other atopic conditions ([Schubert et al., 2004] and [Sénéchal et al., 1999]). In addition to the associations with autoimmune diseases and allergies, polymorphisms in HLA genes have been found to be associated with susceptibility to several cancers, including ovarian (Kubler et al., 2006), breast (Chaudhuri et al., 2000), and cervical cancer ([Castro et al., 2009] and [Hildesheim et al., 1998]), and malignant melanoma (Bateman et al., 1998).

With regard to glioma, evidence has been limited and inconsistent, with only a few small studies that have examined polymorphisms in HLA genes as a potential susceptibility factor ([Guerini et al., 2006], [Machulla et al., 2001], [La Torre et al., 2009], [Tang et al., 2005], [Song et al., 2009] and [Nitta et al., 1994]). Each, however, has suggested an association between glioma and specific class I or class II HLA alleles or haplotypes. In particular, a study of 36 glioma patients in Italy suggested a positive association with the class II *DRB1*14* allele (Guerini et al., 2006), and a study of 65 German glioma patients demonstrated *DRB1*15* as a potential risk allele and the *DRB1*07* allele as being protective against glioma (Machulla et al., 2001). Another small Italian study confirmed an elevated frequency of the *DRB1*14* allele and, in addition, found elevated frequencies of the *DQB1*06* and *DRB3*01* alleles in 56 cases with high-grade gliomas (La Torre et al., 2009). Other larger studies (155 and 149 GBM patients, respectively), however, have observed no association between *DRB1* alleles and glioma ([Tang et al., 2005] and [Song et al., 2009]). Class I genes involving the *HLA-A*, *-B*, and *-Cw* loci have similarly been found to have both positive and negative associations with glioma ([Machulla et al., 2001], [La Torre et al., 2009], [Tang et al., 2005], [Song et al., 2009], and [Nitta et al., 1994]). The largest HLA study to date with 155 GBM cases conducted in the United States found the risk of GBM to be positively associated with the class I *B*13* allele, and negatively associated with the *Cw*01* allele (Tang et al., 2005). In addition, HLA class I *A*32* and *B*55* alleles in GBM patients were associated with slower and faster progression to death, respectively.

Furthermore, the A*32 allele was found to be negatively associated with GBM risk in a study of 149 GBM patients (Song et al., 2009).

The HLA system is known to have an important role in the adaptive immune response. This, combined with the established link between HLA polymorphisms and immune-related disorders, the inverse association between immune-related disorders and glioma risk, and the suggestive though inconsistent evidence of an association between HLA alleles and glioma, suggests that further studies of the potential role of HLA polymorphisms in glioma susceptibility are warranted. Here, we report the associations between selected HLA class II polymorphisms and adult glioma in a large, hospital-based case-control study of brain tumors in the United States.

2. Materials and Methods

2.1. Study Population

The methods for the brain tumor study conducted by the National Cancer Institute (NCI) have been described previously (Inskip et al., 1999). Briefly, the study was conducted between June 1994 and August 1998 at three hospitals in the United States, including 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 included those with a newly diagnosed, histologically confirmed intracranial glioma or neuroepitheliomatous tumor (ICD-O-2 codes 9380–9473 and 9490–9506) at one of the three hospitals. Additional eligibility criteria included age ≥ 18 years old at diagnosis, ability to understand either English or Spanish, and residence within 50 miles of the hospital (or within the state of Arizona for the Phoenix hospital). Among eligible cases, 489 (92%) agreed to participate in the study including 425 glioma cases (ICD-O-2 codes 9380–9473) with European ancestry.

Study controls consisted of individuals admitted to the same hospital for a series of nonmalignant conditions, most commonly diseases of the musculoskeletal system (ICD-9 codes 710–739), circulatory system (ICD-9 codes 390–459), digestive system (ICD-9 codes 520–579), and trauma or injuries (ICD-9 codes 800–899, V01–V82, E800–E999). In order to be eligible, the duration of symptoms for the primary control condition could not exceed five years; 90% of patients were interviewed within one year of the onset of symptoms. Controls were frequency-matched to a total case series that also included meningioma and acoustic neuroma in a 1:1 ratio by age (in 10 year strata), sex, race or ethnicity, hospital site, and distance of residence from the hospital to which they were admitted. Among eligible controls, 799 (86%) agreed to participate in the study including 715 with European ancestry. Seven controls with European ancestry admitted to the hospital for either asthma or an autoimmune disease were excluded for analysis purposes.

The study was reviewed and approved by the respective institutional review boards, and all participants signed an informed consent form upon enrollment in the study.

2.2. Interview Data

Trained research nurses administered a computer-assisted personal interview to study participants inquiring about potential risk factors for brain tumors, and obtained a detailed personal medical history. Specifically, history of allergy or autoimmune disease was assessed by inquiring about physician diagnosed asthma, eczema, hay fever, rheumatoid arthritis, lupus erythematosus, multiple sclerosis, diabetes, or pernicious anemia and grouped for analysis purposes as described elsewhere (Brenner et al., 2002). Sociodemographic characteristics collected during the interview and evaluated as potential confounders in our analyses included level of educational attainment and household income.

2.3. Collection of Blood Samples and DNA Extraction

At the time of interview, blood samples (one serum separator tube (SST) and two acid citrate dextrose tubes, ACD) were obtained from 431 (88%) consenting cases and 611 (76%) consenting controls. The processing of samples included centrifuging the SST and ACD tubes, and subsequently separating and aliquoting serum and buffy coat (Inskip et al., 1999). Both types of samples were stored at -70°C at the participating hospitals and later were shipped to the biospecimen repository at the NCI. The DNA from buffy coat samples was extracted using a phenol-chloroform method as previously described (Daly et al., 1996).

2.4. HLA Genotyping

DNA samples from 431 glioma cases and 611 controls with European ancestry were submitted for genotyping. Of these, samples from 281 cases and 370 controls had a sufficient amount of DNA and were subsequently genotyped; the remaining samples with depleted DNA (150 from cases and 241 from controls) were not genotyped. Genotyping for two class II HLA loci (*DRB1* and *DQB1*) was completed at the NCI Core Genotyping Facility (Advanced Technology Corporation, Gaithersburg, MD). *DQB1* and *DRB1* loci were chosen for genotyping as these are among the most variable and extensively studied class II loci in humans and include functionally important polymorphisms, enabling our findings to be put in the context of existing knowledge (McTernan et al., 2000). Other class II loci, including *DPB1* and *DMB1* and the loci for alpha chains (*DQA1*, *DRA1*, *DPA1*, *DMA1*), were not considered due to the relatively small number of known or functionally important polymorphisms at the time of loci selection and/or unclear relevance due to low expression levels ([McTernan et al., 2000], [Sidney et al., 2010], and [Bondinas et al., 2007]). Loci were assayed using the low-resolution reverse sequence-specific oligonucleotide method from One Lambda Inc. (Canoga Park, CA). This method involves immobilizing oligonucleotide probes on a solid-phase support, followed by the hybridization of the immobilized probes with liquid-phase PCR product (Little, 2007). Overall, the completion rate for DNA samples with sufficient DNA amount was 93.3% for the *DQB1* gene and 92.3% for the *DRB1* gene. The concordance rates for blind replicate samples were 100% for both the *DQB1* and *DRB1* genes.

2.5. Statistical Analysis

Hardy-Weinberg equilibrium (HWE) was assessed in study controls for each HLA class II locus using a chi-square test as implemented in the PROC ALLELE procedure of SAS version 9.2. Overall allele frequencies were compared between cases and controls by unconditional logistic regression, adjusting for the matching factors, using a global likelihood ratio test. Unconditional logistic regression also was used to estimate odds ratios (OR) and calculate 95% confidence intervals (CI) for the association between common *DQB1* and *DRB1* alleles ($\geq 5\%$ in the total study population) and adult glioma. All models were adjusted for the matching factors, including sex, age, hospital, and distance of residence from the hospital. Additional adjustment for education and income, as well as for prior history of allergy or autoimmune disease was also evaluated. To assess the sensitivity of ORs to the composition of the control group, separate analyses excluding one control subgroup at a time (i.e., diseases of the circulatory system, diseases of the musculoskeletal system, etc.) were conducted by refitting regression models. Likelihood ratio tests comparing nested logistic regression models that were limited to cases only were used to evaluate whether the observed associations with *DQB1* and *DRB1* alleles were different between GBM (ICD-O-2 codes 9440–9442) and other gliomas. The *HLA-DQB1-DRB1* two-loci haplotype frequencies were estimated using an expectation-maximization (EM) algorithm (Chuong and Batzoglou, 2008) and compared between cases and controls using permutation tests (Fallin et al., 2001). Analyses were limited to haplotypes with $\geq 5\%$ frequency in the total study population. Unconditional logistic regression was used to

estimate ORs and compute 95% CIs for adult glioma with inferred haplotypes. The robustness of the adjusted ORs with HLA alleles or haplotypes was assessed using the Benjamini-Hochberg approach, which accounts for multiple comparisons by controlling for the False Discovery Rate (FDR) (Ferreira and Zwinderman, 2006). The FDR method was applied to a set of 11 allele tests and a set of 7 haplotype tests at α level = 0.05. All statistical analyses were conducted using SAS version 9.1 and the SAS/Genetics program in version 9.2 (SAS Institute, Cary, NC). All statistical tests conducted were two-sided, with $p < 0.05$ considered statistically significant.

Based on a previously conducted principal components analysis of 1,397 SNPs in innate immunity genes in our study participants of European ancestry, there was little evidence of population stratification [Rajaraman et al., 2009].

3. Results

3.1. Characteristics of Cases and Controls

Selected characteristics for cases and controls of European ancestry are shown in Table 1. Among these, *DRB1* or *DQB1* genotyping data were available for 60.0% ($n=255$) of cases and for 48.0% ($n=340$) of controls. There were no major differences between cases or controls with and without HLA genotyping data with respect to sex, age, a history of allergy, or autoimmune disease. Cases with genotyping data were more likely to be diagnosed in the Boston hospital, to be more educated, and to have a higher income compared to cases without genotyping data. Similar to cases, controls with genotyping data were more likely to be diagnosed in the Boston hospital and to have a higher income. Additionally, a higher proportion of controls with genotyping data were admitted for circulatory disorders and a lower proportion were admitted for trauma/injuries compared to controls without genotyping data.

3.2. HLA Class II Polymorphisms and Risk of Adult Glioma

Neither the *DRB1* locus ($p=0.22$) nor the *DQB1* locus ($p=0.18$) showed departure from HWE in study controls. While the overall frequencies of *DQB1* alleles, adjusted for the matching factors, were significantly different between glioma cases and controls ($p=0.03$), the overall frequencies of the *DRB1* alleles were not ($p=0.18$). The associations between common class II HLA alleles and adult glioma, adjusted for matching factors, are shown in Table 2. Two *DQB1* alleles and one *DRB1* allele were significantly associated with risk of adult glioma. Specifically, the *DQB1*05* allele was significantly associated with a decreased risk of glioma (OR=0.63, 95% CI 0.43–0.93), whereas the *DQB1*06* and *DRB1*13* alleles were significantly associated with an increased risk of glioma (OR=1.67, 95% CI: 1.17–2.39 and OR=1.69, 95% CI: 1.08–2.64, respectively). When the *DQB1*05* and *DRB1*13* alleles were included in the same model, the ORs and CIs did not meaningfully change compared to the models in which they were included separately (data not shown). In contrast, the ORs for both the *DQB1*06* (OR=1.43, 95% CI: 0.94–2.19) and *DRB1*13* alleles (OR=1.44, 95% CI: 0.85–2.44) were attenuated and no longer significantly elevated when these alleles were included in the same model, suggesting that they may be linked.

Further adjustment for education and/or income as well as for history of allergy or autoimmune disease had minimal impact on the observed associations for any of the HLA class II alleles (data not shown). Similarly, excluding one control subgroup at a time revealed no meaningful effect on the observed ORs (data not shown). There were no major differences in ORs with *DQB1*05* ($p=0.43$), *DQB1*06* ($p=0.38$), *DRB1*13* ($p=0.44$) or other alleles between GBM and other gliomas. After applying the FDR method to account for multiple comparisons (Table 2), none of the observed associations with *DQB1*05*,

DQB1*06, and *DRB1*13* remained significant at $\alpha=0.05$. However, all of these associations remained noteworthy ($p=0.077$, $p=0.055$, and $p=0.077$, respectively).

3.3. HLA Class II Haplotypes and Risk of Adult Glioma

Seven *HLA-DQB1-DRB1* haplotypes had a frequency of $\geq 5\%$ in the total study population. The overall frequencies of *HLA-DQB1-DRB1* haplotypes were not significantly different between glioma cases and controls ($p=0.25$), and none of the common haplotypes was significantly associated with risk of adult glioma (Table 3). Consistent with the observed associations for individual alleles, a decreased risk of glioma was seen for the haplotype containing the *DQB1*05* allele (*DQB1*05-DRB1*01*; OR=0.54, 95% CI: 0.24–1.23), and an increased risk of glioma was observed for haplotypes containing the *DQB1*06* or *DRB1*13* allele (*DQB1*06-DRB1*13*; OR=2.19, 95% CI: 0.90–5.36 and *DQB1*06-DRB1*15*; OR=2.01, 95% CI: 0.96–4.20).

4. Discussion

The results from this hospital-based case-control study extend prior limited evidence concerning a potential role of HLA class II polymorphisms in susceptibility to adult glioma. The overall frequencies of *DQB1* alleles, but not *DRB1* alleles, significantly differed between cases and controls, suggesting that *DQB1* holds particular potential as a susceptibility locus. Furthermore, our analyses revealed significant positive associations between the *DQB1*06* and *DRB1*13* alleles, and a significant inverse association between the *DQB1*05* allele, and risk of glioma. The associations with the *DQB1-DRB1* haplotypes containing *DQB1*06*, *DQB1*05*, and *DRB1*13* alleles were consistent with the observed associations for these individual alleles, although these did not reach statistical significance. Adjustment for potential confounders, including a prior history of allergy or autoimmune disease, had no meaningful effect on the observed associations. Although the associations with the significant alleles did not withstand formal adjustment for multiple comparisons, they remained noteworthy. These results suggest that HLA class II alleles and/or haplotypes may influence susceptibility to glioma and warrant replication in large collaborative studies such as the Brain Tumor Epidemiology Consortium (Bondy et al., 2008).

Relatively few prior studies have examined the relationship between class II HLA polymorphisms and glioma, particularly for the *DQB1* locus that emerged in our study as a promising susceptibility locus. To the best of our knowledge, the only other study that evaluated the relationship between glioma and individual *DQB1* alleles similar to ours found an increased frequency of the *DQB1*06* allele among a small number of glioma cases from Italy relative to bone marrow donors and brain tumor-free patients ($p=0.005$) (La Torre et al., 2009).

The only allele from the *DRB1* locus significantly associated with risk of glioma in our study was *DRB1*13*. Interestingly, both the positive association between this allele and glioma risk and the positive association between the *DQB1*06* allele and glioma risk were attenuated when the two alleles were included in the same model simultaneously, indicating some degree of mutual confounding. The associations between *DRB1* alleles and risk of glioma in previous studies have been inconsistent. An early study of individuals with glioma in which *DRB1* alleles were typed serologically revealed an increased frequency of the *DRB1*01* allele in cases (de Moerloose et al., 1978). The frequency of the *DRB1*14* allele in two Italian studies was greater in glioma cases compared to controls ([Guerini et al., 2006] and [La Torre et al., 2009]). However, in our study population, the *DRB1*14* allele was uncommon ($<5\%$) and was not significantly associated with risk of glioma. Likewise, two previous reports of significantly decreased and increased risk associated with the

DRB1*07 ([Machulla et al., 2001] and [La Torre et al., 2009]) and *DRB1*15* alleles (Machulla et al., 2001), respectively, were not confirmed in our study.

The main challenge in interpretation of HLA studies is the existence of extensive linkage disequilibrium in the HLA region. While our data suggest that the observed associations may be related to the *DQB1* locus, we cannot rule out the possibility that these could be through linkage with other unmeasured alleles in the region. The most consistent evidence with respect to HLA class II polymorphisms in general involves autoimmune disorders. Specifically, the *DQB1*06* and/or *DRB1*13* alleles have previously been found to be associated with a reduced risk of biliary cirrhosis (Invernizzi et al., 2008), type 1 diabetes ([Guja et al., 2004] and [Buc et al., 2006]), and celiac disease ([Laadhar et al., 2009] and [Silva et al., 2000]). The *DQB1*05* allele has been associated with a reduced risk of autoimmune hypothyroidism (Rekha et al., 2007) and type 1 diabetes (Guja et al., 2004), and an increased risk of Hashimoto's thyroiditis in pediatric patients (Giza et al., 2008). However, none of the observed associations with HLA class II alleles for glioma in our study were accounted for by the protective effects of either autoimmune disease or allergy.

In recent years studies with high resolution genotyping data demonstrated that specific allele subtypes may have differing associations with the same autoimmune disease. For example, the *DQB1*0602* and *DQB1*0603* alleles have been associated with a reduced risk of type 1 diabetes ([Guja et al., 2004] and [Buc et al., 2006]), and the *DQB1*0604* allele has been associated with an increased risk [Sanjeevi, 2000]. Similarly, haplotypes containing the *DQB1*0602* and *DQB1*0603* alleles have been found to be positively and negatively associated with multiple sclerosis, respectively [Laaksonen et al., 2002]. Due to the limited resolution of our genotyping data, we were unable to evaluate which specific *DQB1*05*, *DQB1*06*, and *DRB1*13* allele subtypes may be driving the observed associations with glioma. However, if the effect of allele subtypes on risk of glioma varies, the presence of overall associations might suggest that the associations with specific allele subtypes are likely to be underestimated. Future studies with higher resolution genotyping data should be able to evaluate if this is true.

In addition to their association with autoimmune diseases, the *DQB1*06* and/or *DRB1*13* alleles have also been linked with susceptibility to Whipple's infection with central nervous system (CNS) manifestation (Martinetti et al., 2009), narcolepsy (specifically, the *DQB1*0602* and *DRB1*1501* alleles and *DRB1*1301-DQB1*0603* haplotype) ([Mignot et al., 2001], [Alaez et al., 2008]), and [Hor et al., 2010]), and Parkinson's Disease (Lampe et al., 2003). Thus, it is possible that the HLA class II region could confer independent susceptibility to a broad group of CNS disorders including glioma. Biological mechanism(s) underlying these potential associations remain to be elucidated, but may include different ability of specific HLA class II alleles to present exogenous or tumor-associated antigens to the immune system.

When considering the results of our study, several caveats should be kept in mind. While the study size is modest for evaluation of a highly polymorphic class II HLA region, it is one of the largest studies conducted to date that evaluated the relationship between *HLA-DQB1* and *HLA-DRB1* alleles and glioma. In order to reduce bias related to ethnic heterogeneity, all analyses were limited to individuals with European ancestry. While genotyping data were available for 60% of cases and 48% of controls, this was unlikely to have introduced bias, as those individuals with and without genotyping data were similar with respect to many characteristics. Additionally, adjustment for education, income, and/or prior history of allergy or autoimmune diseases had no meaningful effect on the observed associations. Our findings also do not appear to be an artifact of enrollment of hospital controls, who were admitted for a wide variety of nonmalignant diseases and conditions, as the main findings

were insensitive to exclusion of one control subgroup at a time. Even though the main associations did not withstand adjustment for multiple comparisons, they remained noteworthy and thus warrant replication in large studies to rule out the possibility of chance. Limitations of our study included the use of a low-resolution technique for HLA genotyping, lack of data for other HLA loci, and limited ability to evaluate variation in risk according to subtypes of glioma.

In summary, our hospital-based case-control study suggests a potential role of the HLA class II alleles in glioma susceptibility. However, further studies with a large number of cases, such as consortia efforts, are needed to confirm and extend these findings.

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Table 1

Selected characteristics of study participants of European ancestry from a hospital-based case-control study of adult glioma

Characteristic	With HLA results		Without HLA results		Total	
	Controls (n=340)	Cases (n=255)	Controls (n=368)	Cases (n=170)	Controls (n=708)	Cases (n=425)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sex						
Male	164 (48.2)	142 (55.7)	168 (45.7)	103 (60.6)	332 (46.9)	245 (57.7)
Female	176 (51.8)	113 (44.3)	200 (54.4)	67 (39.4)	376 (53.1)	180 (42.4)
Mean age, years	49.0 ± 16.4	52.0 ± 15.9	51.7 ± 16.5	54.1 ± 16.7	50.4 ± 16.5	52.8 ± 16.3
Site						
Phoenix	164 (48.2) ^a	111 (43.5) ^b	182 (49.5) ^a	91 (53.5) ^b	346 (48.9)	202 (47.5)
Boston	121 (35.6)	90 (35.3)	84 (22.8)	44 (25.9)	205 (29.0)	134 (31.5)
Pittsburgh	55 (16.2)	54 (21.2)	102 (27.7)	35 (20.6)	157 (22.2)	89 (20.9)
Education						
<High School	35 (10.3)	18 (7.1) ^b	42 (11.4)	26 (15.3) ^b	77 (10.9)	44 (10.4)
High School/GED	206 (60.6)	146 (57.3)	224 (60.9)	86 (50.6)	430 (60.7)	232 (54.6)
College/Grad	92 (27.1)	85 (33.3)	92 (25.0)	54 (31.8)	184 (26.0)	139 (32.7)
Other/Unknown	7 (2.1)	6 (2.4)	10 (2.7)	4 (2.4)	17 (2.4)	10 (2.4)
Income						
<\$15,000	38 (11.2) ^c	21 (8.2) ^d	60 (16.3) ^c	13 (7.7) ^d	98 (13.8)	34 (8.0)
\$15,000–\$24,999	53 (15.6)	26 (10.2)	46 (12.5)	34 (20.0)	99 (14.0)	60 (14.1)
\$25,000–\$34,999	37 (10.9)	35 (13.7)	52 (14.1)	27 (15.9)	89 (12.6)	62 (14.6)
\$35,000–\$49,999	67 (19.7)	48 (18.8)	55 (15.0)	25 (14.7)	122 (17.2)	73 (17.2)
\$50,000–\$74,999	67 (19.7)	49 (19.2)	69 (18.8)	22 (12.9)	136 (19.2)	71 (16.7)
>\$75,000	63 (18.5)	59 (23.1)	53 (14.4)	33 (19.4)	116 (16.4)	92 (21.7)
Unknown/Refused	15 (4.4)	17 (6.7)	33 (9.0)	16 (9.4)	48 (6.8)	33 (7.8)
Allergy						
None	203 (59.7)	176 (69.0)	215 (58.4)	114 (67.1)	418 (59.0)	290 (68.2)
At least One	129 (37.9)	71 (27.8)	140 (38.0)	49 (28.8)	269 (38.0)	120 (28.2)
Missing/Unknown	8 (2.4)	8 (3.1)	13 (3.5)	7 (4.1)	21 (3.0)	15 (3.5)

Characteristic	With HLA results			Without HLA results			Total		
	Controls (n=340)		Cases (n=255)	Controls (n=368)		Cases (n=170)	Controls (n=708)		Cases (n=425)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Autoimmune Disease									
None	266 (78.2)	215 (84.3)	276 (75.0)	139 (81.8)	542 (76.6)	354 (83.3)			
At least One	68 (20.0)	28 (11.0)	77 (20.9)	21 (12.4)	145 (20.5)	49 (11.5)			
Missing/Unknown	6 (1.8)	12 (4.7)	15 (4.1)	10 (5.9)	21 (3.0)	22 (5.2)			
Glioma Subtype									
Glioblastoma	--	130 (51.0)	--	96 (56.5)	--	226 (53.2)			
Other Astrocytic	--	52 (20.4)	--	36 (21.2)	--	88 (20.7)			
Oligodendroglioma	--	53 (20.8)	--	27 (15.9)	--	80 (18.8)			
Other		20 (7.8)		11 (6.5)		31 (7.3)			
Control Disorder									
Musculoskeletal	79 (23.2) ^b	--	84 (22.8) ^b	--	163 (23.0)	--			
Circulatory	94 (27.7)	--	70 (19.0)	--	164 (23.2)	--			
Trauma/Injuries	70 (20.6)	--	92 (25.0)	--	162 (22.9)	--			
Digestive	41 (12.1)	--	39 (10.6)	--	80 (11.3)	--			
Other	56 (16.5)	--	83 (22.6)	--	139 (19.6)	--			

^ap<0.001

^bp=0.05

^cp=0.02

^dp=0.03

Note: p-values comparing those with and without HLA

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for selected HLA Class II alleles and adult glioma

Allele ^a	Controls (n=340) ^b		Cases (n=255) ^b		OR ^d (95% CI)	P ^e	P ^f
	% ^c	n	% ^c	n			
DQB1		n=317		n=238			
DQB1*02	26.2%		24.6%		0.86 (0.60–1.21)	0.379	0.516
DQB1*03	33.3%		33.6%		1.15 (0.82–1.77)	0.422	0.516
DQB1*05	17.7%		13.2%		0.63 (0.43–0.93)	0.020	0.077
DQB1*06	19.9%		26.5%		1.67 (1.17–2.39)	0.005	0.055
DRB1		n=314		n=235			
DRB1*01	12.1%		9.8%		0.68 (0.44–1.05)	0.081	0.223
DRB1*03	14.3%		11.9%		0.72 (0.48–1.07)	0.106	0.233
DRB1*04	14.7%		13.6%		0.88 (0.59–1.32)	0.537	0.537
DRB1*07	14.3%		16.6%		1.29 (0.87–1.91)	0.206	0.324
DRB1*11	11.8%		10.9%		0.86 (0.55–1.33)	0.494	0.537
DRB1*13	8.9%		11.7%		1.69 (1.08–2.64)	0.021	0.077
DRB1*15	13.2%		16.6%		1.33 (0.91–1.97)	0.145	0.266

^aOnly alleles with overall frequency $\geq 5\%$ are presented.

^bIncludes individuals with genotyping data for either DQB1 or DRB1.

^cPercentages refer to allele frequencies in cases and controls.

^dAdjusted for matching factors: sex, age, hospital, and distance of residence from hospital.

^ep-value unadjusted for multiple comparisons.

^fAdjusted p-value for False Discovery Rate.

Odds ratios (OR) and 95% confidence intervals (CI) for HLA Class II haplotypes and adult glioma

Table 3

DQB1-DRB1 Haplotype ^a	Controls ^b (n=291)		Cases ^b (n=218)		OR ^d (95% CI)	P ^e	P ^f
	% ^c		% ^c				
02-03	14.8%		12.4%		0.61 (0.28-1.31)	0.204	0.357
02-07	11.2%		11.9%		1.29 (0.59-2.82)	0.530	0.618
03-04	14.8%		14.2%		0.87 (0.43-1.77)	0.696	0.696
03-11	11.3%		10.3%		0.77 (0.35-1.67)	0.502	0.618
05-01	12.5%		9.6%		0.54 (0.24-1.23)	0.142	0.331
06-13	7.4%		9.9%		2.19 (0.90-5.36)	0.086	0.301
06-15	12.4%		16.7%		2.01 (0.96-4.20)	0.064	0.301

^aOnly haplotypes with a frequency of $\geq 5\%$ in the total study population are presented.

^bIncludes only individuals with non-missing data for both DQB1 and DRB1 alleles.

^cPercentages refer to haplotype frequencies in cases and controls

^dAdjusted for matching factors: sex, age, hospital, and distance of residence from hospital.

^ep-values unadjusted for multiple comparisons.

^fAdjusted p-value for False Discovery Rate.