Research Article

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Risk of Meningioma and Common Variation in Genes Related to Innate Immunity

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Abstract

Background: The etiology of meningioma, the second most common type of adult brain tumor in the United States, is largely unknown. Prior studies indicate that history of immune-related conditions may affect the risk of meningioma.

Methods: To identify genetic markers for meningioma in genes involved with innate immunity, we conducted an exploratory association study of 101 meningioma cases and 330 frequency-matched controls of European ancestry using subjects from a hospital-based study conducted by the National Cancer Institute. We genotyped 1,407 "tag" single nucleotide polymorphisms (SNP) in 148 genetic regions chosen on the basis of an $r^2 > 0.8$ and minor allele frequency of >5% in Caucasians in HapMap1. Risk of meningioma was estimated by odds ratios and 95% confidence intervals.

Results: Seventeen SNPs distributed across 12 genetic regions (*NFKB1* (3), *FCER1G* (3), *CCR6* (2), *VCAM1, CD14, TNFRSF18, RAC2, XDH, C1D, TLR1/TLR10/TLR6, NOS1*, and *DEFA5*) were associated with the risk of meningioma with $P < 0.01$. Although individual SNP tests were not significant after controlling for multiple comparisons, gene region–based tests were statistically significant ($P < 0.05$) for *TNFRSF18, NFKB1, FCER1G, CD14, C1D, CCR6*, and *VCAM1*.

Conclusions and Impact: Our results indicate that common genetic polymorphisms in innate immunity genes may be associated with risk of meningioma. Given the small sample size, replication of these results in a larger study of meningioma is needed. *Cancer Epidemiol Biomarkers Prev; 19(5); 1356–61. ©2010 AACR.*

Introduction

Meningioma is the second most common type of brain/central nervous system tumor in the United States, comprising ~30% of all brain/central nervous system tumors (1). Despite their largely benign histology, these tumors can cause serious morbidity by virtue of their intracranial location. Other than ionizing radiation and certain rare predisposing genetic syndromes, very little is known about the etiology of these tumors. Evidence from prior epidemiologic studies, although inconsistent, suggests a possible inverse association between the risk of meningioma and personal history of allergic disease (2,3), raising the possibility that alterations in the immune system may contribute to the etiology of these tumors.

The innate immune system is phylogenetically ancient and works closely with the adaptive immune system in an integrated process to ensure effective responses to a wide range of antigenic challenges, including tumors (4). Genetic polymorphisms as well as functional alterations in the innate immune system have been implicated in the pathogenesis of several intracranial conditions including glioma, meningioma, and neurodegenerative diseases (5-10).

Given the epidemiologic and biological evidence suggesting a link between innate immune system alterations and central nervous system disorders, we evaluated common genetic germline variants in innate immune genes to estimate the effect of low penetrance alleles on risk of meningioma. Using data from non-Hispanic whites in a hospital-based case-control study conducted by the National Cancer Institute (NCI) between 1994 and 1998, we evaluated the risk of meningioma ($n = 101$) compared with noncancer controls ($n = 330$) with respect to 1,407 tag single nucleotide polymorphisms (SNP) in 148 innate immune genes and their surrounding regions.

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Materials and Methods

Study population and setting

A detailed description of study methods can be found elsewhere (11). Briefly, the parent study was a U.S. hospital-based case-control study of the three most common brain tumor types. Eligible patients were 18 y or older with a first intracranial glioma or neuroepitheliomatous tumor (ICD-O-2 codes 9380-9473 and 9490-9506), meningioma (ICD-O-2 codes 9530-9538), or acoustic neuroma (ICD-O-2 code 9560) diagnosed during 1994 to 1998 at one of three hospitals specializing in brain tumor treatment (in Boston, Phoenix, and Pittsburgh) within the 8 wk preceding hospitalization. Ninety-two percent of eligible brain tumor patients agreed to participate and were enrolled (489 patients with glioma, 197 with meningioma, and 96 patients with acoustic neuroma). For this study, only histologically confirmed cases of meningioma were included.

Controls were chosen from individuals admitted to the same hospitals for injuries (25%), circulatory system disorders (22%), musculoskeletal disorders (22%), digestive disorders (12%), or a variety of other nonneoplastic conditions, and were frequency matched in a one-to-one ratio to a total case series (glioma, meningioma, and acoustic neuroma) based on age (18-29, 30-39, 40-49, 50-59,60-69, 70-79, 80-99 y), race/ethnicity (non-Hispanic white, Hispanic, African-American, other), sex, hospital, and residential proximity to the hospital. Seven hundred ninety-nine control patients (86% of all contacted) were enrolled.

Shortly following hospitalization, a trained research nurse administered a structured in-person interview with each subject and subjects later completed and mailed back a self-administered questionnaire. The information collected included data on use of cellular telephones, prior medical conditions, diet, and a detailed occupational history. In addition, participants were asked to provide whole blood samples. This analysis was restricted to individuals of European ancestry (89% of all study participants) who provided blood samples and for whom an adequate amount of DNA was extracted from blood samples. The study protocol was approved by the Institutional Review Board of each participating institution and written informed consent was obtained from each patient or proxy.

Laboratory methods

DNA extraction and genotyping. DNA was extracted from blood using a phenol-chloroform protocol. Samples were genotyped for 101 patients with meningioma and 330 controls of European ancestry. Genotyping was done at the NCI Core Genotyping Facility (Advanced Technology Corp.) using an Illumina GoldenGate OPA panel designed to tag 148 candidate innate immunity genes and their surrounding regions (20 kb 5′ of the start of the first exon and 10 kb 3′ of the end of the last exon of each candidate gene). The innate immunity panel was composed of genes selected from known innate immune pathways (oxidative response, pattern recognition molecules and antimicrobials, integrins and adhesion molecules, complement, chemokines with their receptors and signaling molecules, and response genes and tissue factors). Tag SNPs were chosen from the SNPs that were genotyped as part of the International HapMap (12) using the TagZilla (13) algorithm with the following parameters: minor allele frequency of >5% in HapMap Caucasian (CEU) samples, $r^2 > 0.8$, and greater weighting for SNPs with a design score of 1.1 (SNPs with a design score of <0.4 were designated as "obligate excludes").

Quality control specimens included replicate samples from 3 nonstudy participants and blinded duplicate samples from 21 participants interspersed among cases and controls. Seventy-seven of 1,536 SNPs originally chosen failed in assay manufacture or provided only monoallelic calls. For the study analyses, any SNPs that did not satisfy the Hardy-Weinberg Equilibrium at $P < 0.001$ ($n = 10$) were excluded. Additional genotype assays were excluded for low completion rates of <90% ($n = 26$) or poor concordance rates of <95% ($n = 16$). Percent agreement

Table 1. Descriptive characteristics of non-Hispanic white participants with and without genotyping: NCI Adult Brain Tumor Study, 1994 to 1998

Characteristics	Cases (n = 197)		Controls (n = 799)	
	All* (n = 163)	Genotyped (n = 101)	All* (n = 715)	Genotyped (n = 330)
Male, %	22.1	20.8	46.7	46.4
Mean age, y	56.1	54.3	50.4	49.4
Education, %				
Less than high school	8.0	6.9	10.8	10.9
High school of general equivalency diploma or 3 y of college	66.3	68.3	61.0	59.1
Complete college or graduate school or professional school	25.2	23.8	25.9	28.5
Unknown	0.6	1.0	2.4	1.5

*Limited to individuals of non-Hispanic Caucasian background.

Table 2. Tag-SNPs associated with the risk of meningioma at $P_{trend} < 0.01$ in hospital-based case-control study of meningioma, NCI Adult Brain Tumor Study, 1994 to 1998

Region Gene	SNP ID	Genotype	Control *n* (%)	Case *n* (%)	Odds ratio	(95% confidence interval)
NFKB1						
NFKB1	rs230540	TT	126 (38.3)	49 (48.5)	1.00	
		CT	162 (49.2)	48 (47.5)	0.67	(0.41-1.11)
		CC	41 (12.5)	4 (4.0)	0.16	(0.05-0.51)
		P_{trend}	—	—	0.001	—
	rs3755867	AA	140 (42.4)	52 (51.5)	1.00	—
		AG	156 (47.3)	47 (46.5)	0.74	(0.45-1.22)
		GG	34 (10.3)	2 (2.0)	0.11	(0.02-0.48)
		P_{trend}	—	—	0.002	—
	rs1585213	CC	117 (35.6)	42 (41.6)	1.00	—
		CT	164 (49.9)	55 (54.5)	0.86	(0.52-1.42)
		TT	48 (14.6)	4 (4.0)	0.16	(0.05-0.50)
		P_{trend}	—	—	0.004	—
VCAM1						
VCAM1	rs2209627	AA	222 (67.7)	54 (53.5)	1.00	—
		AG	92 (28.1)	41 (40.6)	2.60	(1.53-4.42)
		GG	14 (4.3)	6 (5.9)	2.13	(0.66-6.80)
		P_{trend}	—	—	0.001	—
FCER1G						
NDUFS2	rs4656993	GG	116 (35.3)	21 (20.8)	1.00	—
		AG	155 (47.1)	50 (49.5)	1.98	(1.08-3.61)
		AA	58 (17.6)	30 (29.7)	2.92	(1.45-5.87)
		P_{trend}	—	—	0.002	—
FCER1G	rs12094497	GG	270 (82.1)	93 (92.1)	1.00	—
		AG	52 (15.8)	8 (7.9)	0.34	(0.17-0.87)
		AA	7 (2.1)	0 (0.0)	0.00	0
		P_{trend}	—	—	0.004	—
	rs11587213	AA	224 (67.9)	80 (80.0)	1.00	—
		AG	93 (28.2)	19 (19.0)	0.53	(0.29-0.96)
		GG	13 (3.9)	1 (1.0)	0.20	(0.02-1.72)
		P_{trend}	—	—	0.008	—
CD14						
PRO1580	rs3822356	AA	208 (63.4)	49 (48.5)	1.00	—
		AG	1.09 (33.2)	47 (46.5)	2.24	(1.34-3.76)
		GG	11 (3.4)	5 (5.0)	2.15	(0.65-7.14)
		P_{trend}	—	—	0.003	—
TNFRSF18						
TNFRSF18	rs9729550	AA	180 (54.9)	68 (67.3)	1.00	—
		AC	121 (36.9)	29 (28.7)	0.56	(0.33-0.95)
		CC	27 (8.2)	4 (4.0)	0.28	(0.09-0.89)
		P_{trend}	—	—	0.003	—
RAC2						
RAC2	rs2213430	CC	103 (31.2)	38 (37.6)	1.00	
		CT	165 (50.0)	49 (48.5)	0.56	(0.32-0.96)
		TT	62 (18.8)	14 (13.9)	0.35	(0.16-0.75)
		P_{trend}	—	—	0.004	—
XDH						
XDH	rs207444	GG	291 (88.5)	97 (96.0)	1.00	—
		AG	37 (11.3)	4 (4.0)	0.26	(0.09-0.79)

(*Continued on the following page*)

Table 2. Tag-SNPs associated with the risk of meningioma at $P_{trend} < 0.01$ in hospital-based case-control study of meningioma, NCI Adult Brain Tumor Study, 1994 to 1998 (Cont'd)

Region Gene	SNP ID	Genotype	Control *n* (%)	Case *n* (%)	Odds ratio	(95% confidence interval)
		AA	1 (0.3)	0 (0.0)	0.00	0
		P_{trend}	—	—	0.005	—
C1D						
C1D	rs10203061	AA	235 (71.7)	56 (56.0)	1.00	—
		AG	85 (25.9)	40 (40.0)	1.98	(1.18-3.33)
		GG	8 (2.4)	4 (4.0)	2.81	(0.70-11.2)
		P_{trend}	—	—	0.006	—
CCR6						
CCR6	rs9459883	GG	265 (80.3)	91 (90.1)	1.00	
		CG	63 (19.1)	10 (9.9)	0.42	(0.20-0.89)
		CC	2 (0.6)	0 (0.0)	0.00	0
		P_{trend}	—	—	0.008	—
	rs3798315	CC	251 (76.1)	87 (86.1)	1.00	
		CT	72 (21.8)	13 (12.9)	0.43	(0.21-0.87)
		TT	7 (2.1)	1 (1.0)	0.31	(0.03-2.81)
		P_{trend}	—	—	0.008	—
TLR1/TLR10/TLR6						
TLR10	rs11466657	AA	306 (93.9)	97 (98.0)	1.00	—
		AG	20 (6.1)	2 (2.0)	0.19	(0.04-0.84)
		GG	—	—	—	—
		P_{trend}	—	—	0.008	—
NOS1						
NOS1	rs10850803	AA	273 (83.2)	73 (72.3)	1.00	—
		AG	54 (16.5)	24 (23.8)	1.70	(0.92-3.13)
		GG	1 (0.3)	4 (4.0)	13.50	(1.16-157)
		P_{trend}	—	—	0.009	—
DEFA5						
DEFA5	rs10503360	TT	95 (28.8)	13 (12.9)	1.00	—
		GT	160 (48.5)	56 (55.5)	2.10	(1.05-4.19)
		GG	75 (22.7)	32 (31.7)	2.74	(1.28-5.83)
		P_{trend}	—	—	0.01	—

NOTE: Odds ratios adjusted for sex, age, study hospital, and distance of residence from hospital.

between the three nonstudy replicates for the remaining 1,407 SNPs was 100% for all SNPs. Concordance for study duplicates ranged from 95% to 100% (mean, 98.8%) and the genotyping success rate ranged from 92% to 100% (mean, 99.8%). Principal component analysis of these data revealed that population stratification was negligible in this data set. A list of genes, chromosomal location, and position for the SNPs included in the analysis is available online (5).

Statistical analysis

Unconditional multivariate logistic regression models were used to estimate odds ratios and calculate 95% confidence intervals for the main effects of each individual SNP, using the homozygous wild-type genotype as the reference category. Odds ratios were estimated separately for heterozygotes and rare homozygous allele groups, adjusting for study-matching factors (age, sex, hospital, and residential distance from hospital). A likelihood ratio test of linear trend was conducted for each SNP using a three-level ordinal variable corresponding to the number of minor alleles for that SNP.

We used the rank-truncated product to adjust SNP and gene region–based findings for multiple testing while accounting for correlations among SNPs induced by linkage disequilibrium (14). The rank-truncated product, which is based on the product of the most significant *P* values within a gene or pathway, is an appropriate test in scenarios with a small set of true effects among a large number of null effects. Permutation based *P* values for the rank-truncated product statistics were computed based on 20,000 permutations of case-control status under the null hypotheses of no association with genotype.

Results

One hundred and one cases of meningioma and 330 controls were successfully genotyped for 1,407 SNPs in 148 genetic regions. Demographic characteristics did not differ appreciably between all participants and those that were genotyped, with genotyped cases being slightly more likely to be female and younger (Table 1). The observed distribution of *P* values of trend for all 1,407 SNPs did not differ significantly from the expected (uniform) null distribution, making the possibility of systematic bias in the study unlikely.

Sixty-eight SNPs in 36 genetic regions were significantly associated with the risk of meningioma at $P < 0.05$ and 17 SNPs in 12 genetic regions were associated at $P < 0.01$ (Table 2). After correcting for multiple testing, none of the SNPs from the single SNP analysis remained statistically significant at $P < 0.05$. However, gene region–based tests identified seven regions as statistically significant: *TNFRSF18* ($P = 0.003$), *NFKB1* ($P = 0.008$), *FCER1G* ($P = 0.009$), *CD14* ($P = 0.01$), *C1D* ($P = 0.03$), *CCR6* ($P = 0.03$), and *VCAM1* ($P = 0.03$).

Discussion

In our exploratory, hypothesis-generating study of risk of adult meningioma with common tagging SNPs in 148 innate immune genes and their surrounding regions, we identified seven genetic regions of particular interest within four innate immune pathways: *TNFSRF18*, *FCER1G* and *VCAM1* (integrins/cell surface receptors), *NFKB1* and *CD14* (pattern recognition and antimicrobials), *C1D* (complement), and *CCR6* (chemokines).

The gene regions for *NFKB1* and *FCER1G* were particularly intriguing given the relationship between T-cell regulation and chronic inflammation (*NFKB1*), and IgE and allergic reactions (*FCER1G*). Three statistically significant SNPs were observed in each of these regions at the $P < 0.01$ level. *NFKB1* encodes the subunit p50/p105 for a pleiotropic transcription regulator activated by a variety of intracellular and extracellular stimuli. The transcription inhibitor is part of the DNA-binding subunit of the NFKB protein complex involved with T-cell regulation and chronic inflammation (15). Epidemiologic studies have observed associations between *NFKB1* polymorphisms and risk of some cancers, including glioma, non–Hodgkin lymphoma and Hodgkin's lymphoma (5, 16, 17), and inflammatory diseases (18) but not for other cancers such as breast, colorectal, or renal cell cancers (19, 20). The *NFKB* pathway has also been associated with inflammatory conditions in the brain, such as Alzheimer's disease (7, 8). Less is known about *FCER1G* and its relevance to the etiology of meningiomas. The *FCER1G* is a subunit of the high-affinity IgE receptor mediating allergic reactions. Functional polymorphisms in *FCER1A*, which also codes for a subunit of the IgE receptor, were strongly associated with serum IgE levels in a genome-wide association study (21).

Several additional SNPs of interest lay within gene regions coding for integrin/cell surface receptors, including *TNFSRF18*, *FCER1G*, and *VCAM1*. This pathway is of particular interest given that changes in integrin pattern expression have been observed in a variety of meningiomas (9, 10) and may influence their invasive biological behavior.

The few existing studies of common genetic variation and risk of meningioma have reported statistically significant associations in genes involved in metabolism (22), DNA repair (23-25), apoptosis/cell cycle (26), folate metabolism(27, 28), p53 (25, 29, 30), and oxidative response pathways (31). To our knowledge, this is the first study of meningioma to explore a large number of genetic variants in the innate immunity pathway. In a previous candidate SNP/gene study on oxidative response and risk of meningioma, we found that the minor allele variant of SOD3 rs699473 was associated with increased risk of meningioma. This variant was not included in the tag SNPs selected for the current study (31). A small subset of the SNPs included in this study were examined in terms of interaction with lead exposure, and *XDH* rs7574920 as well as *GPX1* rs1050450 and rs18006688 were found to modify the effect of lead exposure on risk of meningioma (32).

Comparing our results for innate immunity genes and risk of meningioma with a previous examination of the same SNPs for glioma risk (5), we found that among the top 10 hits, *NFKB1* was significant in both studies ($P < 0.01$). However, gene region–based hits ($P < 0.05$) differed between glioma (*ALOX5*, *SELP*, and *SOD*) and meningioma (*TNFSRF18*, *FCER1G*, *VCAM1*, *NFKB1*, *CD14*, *C1D*, and *CCR6*).

While our results provide interesting clues, they are subject to some caveats. Although the hospital-based design of this study allowed the accrual of incident meningiomas and we imposed strict quality control criteria for blood collection and genotyping of DNA samples, the sample size for this study remains small. The SNPs in this study were chosen as tagging markers for the genetic region and not based on known function; thus, the observed associations could be due to linkage disequilibrium with the true unobserved causal SNPs. Replication of these findings with increased coverage of the identified genes of interest and larger sample size (for example, in multicenter studies of meningioma) is required to rule out the possibility of chance findings.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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