Genetic variation in insulin-like growth factors and brain tumor risk

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Many studies support a role for insulin-like growth factors (IGFs) in the regulation of tumor cell biology. We hypothesized that single-nucleotide polymorphisms (SNPs) in IGF genes are risk factors for glioma and meningioma. To test the hypothesis, we examined associations of brain tumor risk with nine variants in five IGF genes in a hospital-based case-control study. The study was conducted at hospitals in Boston, Phoenix, and Pittsburgh between 1994 and 1998. Eligible cases were individuals (18 years or older) newly diagnosed with glioma or meningioma. Controls were selected among patients who were admitted to the same hospitals for a variety of nonmalignant conditions and frequency matched to cases by hospital, age, sex, race, and distance from residence. The present analysis was restricted to non-Hispanic whites. DNA was extracted from blood samples collected from 354 glioma cases, 133 meningioma cases, and 495 control individuals. We evaluated nine SNPs in five IGF genes (*IGF1*, *IGF1R*, *IGF2*, *IGF2R*, and *IGFBP3*). The majority of the analyzed IGF SNPs did not display statistically significant associations with glioma or meningioma. For glioma, one *IGF1R* SNP (rs2272037) indicated a possible association. No indications of association were seen for glioblastoma, but for low-grade gliomas, the odds ratio under a dominant model was 0.56 (95% confidence interval [CI], 0.35–0.90) for *IGF1* rs6220, 2.98 (95% CI, 1.65–5.38) for *IGF1R* rs2272037, and 1.60 (95% CI, 0.90–2.83) for *IGF1R* rs2016347. Overall, our results do not provide strong evidence of associations of brain tumor risk with IGF polymorphic variants but identify several associations for glioma that warrant further examination in other, larger studies.
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The insulin-like growth factor (IGF) system comprises two ligands (IGF-1 and IGF-2), the IGF-1 and IGF-2 receptors, six binding proteins (IGFBP-1 to -6), and various IGFBP-related peptides.[1] IGF-1 is the major physiological mediator of the effect of growth hormone and therefore has a strong influence on cell proliferation and differentiation. It also inhibits apoptosis by blocking initiation of the apoptotic pathway.[1] The IGF-1 receptor (IGF-1R) mediates the action of IGF-1 and is involved in oncogenic transformation processes.[1] IGFBPs modulate the interaction between IGF-1 and IGF-1R but also have independent effects on

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cell growth.[1–3] IGFBP-3 has an inhibitory effect on IGF-1 activity and also acts as an apoptotic agent.[1] IGFBP-3 also has been recognized to exhibit a number of growth-promoting effects.

Experimental studies have shown that alterations in IGF function can influence cellular transformation and tumor cell proliferation. *IGF1*, *IGF2*, and *IGF1R* genes have all been reported to be overexpressed in glioma and meningioma as well as in a wide range of other human cancers, including breast, leukemia, lung, thyroid, and prostate.[4] IGFs, together with their receptors and binding proteins, have been reported to be associated with cancer risk.[5,6] Epidemiological studies have suggested that genetic variation in *IGF1*, *IGF1R*, and *IGFBP3* may be related to breast, prostate, and colorectal cancer risk.[7–10] In vitro studies have demonstrated that IGF receptors and binding proteins promote mitogenesis and differentiation in glial cells, oligodendrocytes, neuronal cells, adult stem cells, and brain explants and regulate axon myelination.[4] Furthermore, observations in the literature suggest that IGF gene pathways show similar expression and functional features during fetal development and tumorigenesis.[11] There is, however, little epidemiologic data concerning the possible involvement of IGF signaling in the development of brain tumors in humans. A recent small prospective study indicated an inverse association between glioma and IGF-1 serum levels.[12] We hypothesized that polymorphisms in IGF genes are risk factors for glioma and meningioma. To test the hypothesis, we examined associations with several IGF gene variants in the context of a case-control study.

Materials and Methods

The methods for this case-control study have been described in detail previously.[13] In brief, the study was conducted at hospitals in Boston, Phoenix, and Pittsburgh between 1994 and 1998. Each of the three hospitals is a referral center for the diagnosis and treatment of brain tumors. The study was restricted to adults (18 years or older) who received care at one of the participating hospitals, resided within 50 miles of the hospital (or within Arizona, in the case of the Phoenix center), and could understand English or Spanish. Institutional review boards at the National Cancer Institute and all participating hospitals approved the protocol, and written informed consent was obtained from each participant.

Cases and Controls

Eligible cases were defined as patients with a primary intracranial glioma or meningioma during the study period. All cases had to be diagnosed with a microscopically confirmed tumor within the 8 weeks preceding hospitalization at a participating hospital; most (80%) were enrolled within 3 weeks of initial diagnosis. In total, 88% of the glioma cases (n = 489) and 98% of the meningioma cases (n = 197) participated in the study. DNA extracted from blood samples was available for 388 glioma cases and 162 meningioma cases, of which 354 and 133, respectively, were non-Hispanic whites. We restricted the present analysis to non-Hispanic whites.

The controls were patients who were admitted to the same hospitals as the cases for a variety of nonmalignant conditions. The most common reasons for hospitalization among the controls were injuries (25%) and disorders of the circulatory (22%), musculoskeletal (22%), digestive (12%), and nervous (7%) systems. They were frequency matched to the total group of patients with tumors (including acoustic neuroma) according to hospital, age (in 10-year strata), sex, race or ethnic group, and proximity of their residence to the hospital. Of the eligible controls, 86% (n = 799) participated. DNA extracted from blood samples was available for 553 controls, of which 495 were non-Hispanic whites.

All participating cases and controls were interviewed by trained nurses. The structured, computerized, in-person interview included detailed questions related to medical and reproductive history, including exposure to diagnostic and therapeutic radiation, and various environmental risk factors, including occupational exposures, cellular telephone use, and sociodemographic characteristics.

Selection of Polymorphisms and Laboratory Analyses

Single-nucleotide polymorphisms (SNPs) in IGF genes were selected initially based on the allele frequency, potential functional importance as indicated by a nonsynonymous amino acid change, occurrence in an exon or promoter region, or associations with other cancers in the literature;[6–8] however, several intronic SNPs also were included as potential markers. Nine SNPs in five IGF genes were evaluated (Table 1).

DNA was extracted from peripheral white blood cells from blood samples by GenoType, Ltd. (United Kingdom) using a phenol-chloroform method as described by Daly et al.[14] Genotyping was conducted by the Core Genotyping Facility at the National Cancer Institute (Gaithersburg, MD, USA), using TaqMan (Applied Biosystems, Foster City, CA, USA) methods. Descriptions for assay-specific methods can be found at the National Cancer Institute SNP500Cancer Web site (http://snp500cancer.nci.nih.gov).

Quality-control measures included 75 study duplicates (two samples for each individual, all of whom were study subjects) interspersed throughout the batches for all assays and in 68 samples from three individuals who were not study subjects (processed in identical fashion as samples from study subjects). In addition, laboratory assay-specific positive controls for the three possible genotypes and one DNA-negative control were included on each assay plate.

Statistical Analysis

Allele frequencies in SNPs among controls were assessed for deviation from Hardy-Weinberg equilibrium (HWE). Associations between SNPs and risk of brain tumors were assessed using unconditional logistic regression to

Table 1. Basic information for single-nucleotide polymorphisms analyzed in the study

Gene	dbSNP ID	Locus	Amino Acid Change	Chromosomal Location	*p*-Value HWE[a]	Percent Agreement[b]
IGF1	rs6220	Ex4+1830 G>A	No change	12q22–q23	0.02	99.7%
IGF1	rs2162679	IVS1–1682 A>G	N/A	12q22–q23	0.96	98.9%
IGF1R	rs2272037	IVS7–20 T>C	N/A	15q25–q26	0.001	98.5%
IGF1R	rs2137680	IVS2+61405 G>A	N/A	15q25–q26	0.80	98.5%
IGF1R	rs2016347	3128bp 3′ of STP T>G	N/A	15q25–q26	0.14	99.5%
IGF2	rs3213216	IVS1+1280 A>G	N/A	11p15.5	0.43	99.0%
IGF2	rs2230949	Ex4–233 C>T	No change	11p15.5	0.17	99.7%
IGF2R	rs629849	Ex34–93 A>G	R1619G	6q26	0.92	99.0%
IGFBP3	rs9282734	Ex3+70 A>C	H158P	7p13–p12	0.89	99.5%

[a]*p*-Value for the deviations from expectation under the assumptions of Hardy-Weinberg equilibrium (HWE) in controls.

[b]Percent agreement among replicates and duplicate samples in the quality-control assay.

estimate odds ratios (ORs) and calculate associated 95% likelihood-based confidence intervals (CIs). All SNPs were analyzed under a dominant model, but a codominant relationship was assumed when numbers permitted (homozygous variant frequency >1% among the controls). The analyses were restricted to non-Hispanic whites and adjusted for the matching variables (hospital, age, sex, and proximity of their residence to the hospital).

Stratified analyses were performed by sex and age (two groups: <50 years and ⩾50 years). Glioblastomas and low-grade gliomas were analyzed separately. The tumor grade of gliomas was classified according to the guidelines of Kleihues et al.[15] There were 171 glioblastoma cases (48% of all gliomas) and 98 low-grade gliomas (28% of all gliomas). The low-grade glioma group included 34 oligodendrogliomas, 29 astrocytomas, 14 neuronal-glial tumors, 12 mixed gliomas, and 9 other low-grade gliomas.

Results

Genotyping was successful on an average of 89% of all variants of the total collected blood samples analyzed. Missing values, primarily the result of insufficient quantity or concentration of high-quality DNA, or poor amplification for a specific locus, were equally likely to be from case or control samples. We achieved 98%–100% agreement among replicates and duplicate samples for all assays (Table 1). Two of the analyzed SNPs showed significant deviations from HWE (Table 1). The *IGF1* rs6220 SNP had more than expected heterozygotes, and the *IGF1R* rs2272037 SNP had fewer than expected heterozygotes. The concordance in the quality-control measures for the two SNPs with significant departure from HWE was high (Table 1).

Frequencies of characteristics of brain tumor cases and controls are presented in Table 2. Meningioma cases were more often female compared with controls or

Table 2. Distribution of cases and controls with respect to selected characteristics

	Controls (*n* = 495)	Glioma[a] (*n* = 354)	Meningioma (*n* = 133)
Sex			
Male	232 (47%)	194 (55%)	29 (22%)
Female	263 (53%)	160 (45%)	104 (78%)
Age at enrollment (years)			
18–39	149 (30%)	88 (25%)	20 (15%)
40–59	198 (40%)	138 (39%)	60 (45%)
60–90	148 (30%)	128 (36%)	53 (40%)
Location of hospital			
Phoenix, AZ	236 (48%)	154 (44%)	62 (47%)
Boston, MA	176 (36%)	131 (37%)	60 (45%)
Pittsburgh, PA	83 (17%)	69 (19%)	11 (8%)

[a]Includes 171 glioblastomas, 42 oligodendrogliomas, 25 mixed gliomas, 47 anaplastic astrocytomas, 34 other astrocytomas, 14 neuronal-glial tumors, and 21 other gliomas.

glioma cases. The glioma and meningioma cases tended to be older than the controls.

The risks of glioma and meningioma associated with IGF polymorphic variants are presented in Table 3. The majority of the analyzed IGF genes did not display statistically significant associations with glioma or meningioma. For glioma, only one SNP (*IGF1R* gene rs2272037) indicated an association for both heterozygous and homozygous carriers (p for trend = 0.04); however, the OR was greater for heterozygotes than for homozygous variants. The OR under the dominant model was 1.58 (95% CI, 1.15–2.15). Under the dominant model, the *IGF1* (rs6220) variant was significantly associated with glioma risk (OR 0.74; 95% CI, 0.56–0.98). Meningioma was not strongly associated with any of the genotypes examined.

Table 4 displays the results for gliomas separately for glioblastoma and low-grade glioma. No statistically significant associations between glioblastoma and the analyzed SNPs were detected, but indications

Table 3. Risk of brain tumors in relation to insulin-like growth factor (IGF) polymorphic variants

Gene/ SNP ID	Genotype	Controls	Glioma	OR[a]	95% CI	Meningioma	OR[a]	95% CI
IGF1	TT	214	185	1.00		62	1.00	
rs6220	CT	219	131	0.69*	0.51–0.92	56	0.86	0.56–1.33
	CC	33	29	1.09	0.63–1.89	8	0.89	0.37–2.15
				p for trend = 0.15			p for trend = 0.52	
	CT & CC	252	160	0.74*	0.56–0.98	64	0.86	0.57–1.31
IGF1	AA	300	235	1.00		78	1.00	
rs2162679	AG	103	69	0.90	0.63–1.24	28	1.05	0.63–1.77
	GG	9	7	1.01	0.36–2.82	3	1.29	0.28–5.94
				p for trend = 0.47			p for trend = 0.74	
	AG & GG	112	76	0.91	0.64–1.28	31	1.07	0.65–1.78
IGF1R	CC	170	93	1.00		38	1.00	
rs2272037	CT	177	160	1.64**	1.17–2.29	53	1.42	0.86–2.33
	TT	87	68	1.35	0.89–2.05	24	1.04	0.56–1.93
				p for trend = 0.04			p for trend = 0.37	
	CT & TT	264	228	1.58**	1.15–2.15	77	1.26	0.80–2.00
IGF1R	GG	207	166	1.00		60	1.00	
rs2137680	AG	185	121	0.84	0.62–1.15	42	0.78	0.49–1.24
	AA	39	31	1.00	0.59–1.69	13	1.27	0.60–2.72
				p for trend = 0.47			p for trend = 0.78	
	AG & AA	224	152	0.86	0.64–1.15	55	0.85	0.55–1.32
IGF1R	TT	123	77	1.00		22	1.00	
rs2016347	GT	201	169	1.37	0.96–1.96	65	1.67	0.95–2.92
	GG	109	78	1.10	0.72–1.67	27	1.15	0.58–2.27
				p for trend = 0.50			p for trend = 0.31	
	GT & GG	310	247	1.28	0.92–1.79	92	1.49	0.88–2.54
IGF2	GG	161	124	1.00		48	1.00	
rs3213216	AG	213	150	0.91	0.66–1.26	47	0.73	0.45–1.18
	AA	60	46	1.05	0.66–1.69	18	1.30	0.67–2.52
				p for trend = 0.83			p for trend = 0.65	
	AG & AA	273	196	0.93	0.69–1.26	65	0.83	0.53–1.29
IGF2	CC	384	266	1.00		109	1.00	
rs2230949	CT & TT	74	69	1.36	0.94–1.97	17	0.79	0.44–1.44
IGF2R	GG	333	255	1.00		89	1.00	
rs629849	AG & AA	98	63	0.89	0.62–1.28	25	0.85	0.50–1.45
IGFBP3	AA	431	318	1.00		116	N/A	
rs9282734	AC	4	5	1.91	0.50–7.28	0	N/A	

Abbreviations: SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval. Totals for variables are not equal because of missing information.

[a]Adjusted for matching variables (hospital, age, sex, and residence).

*p-value <0.05.

**p-value <0.01.

of associations were seen between low-grade glioma and one *IGF1* SNP (rs6220) and two *IGF1R* SNPs (rs2272037 and rs2016347). The OR under a dominant model was 0.56 (95% CI, 0.35–0.90) for rs6220, 2.98 (95% CI, 1.65–5.38) for rs2272037, and 1.60 (95% CI, 0.90–2.83) for rs2016347. The rs2272037 was the only SNP that displayed a statistically significant trend ($p = 0.03$); however, the OR was greater for the heterozygous carriers than for the homozygous carriers.

For several SNPs, the gender-specific analysis yielded a stronger association among men compared to women. Although data were sparse in the gender-specific analysis, the positive association observed for *IGF1R* (rs2272037) with low-grade glioma was stronger among

Table 4. Insulin-like growth factor (IGF) polymorphic variants and risk of glioblastoma (GBM) and low-grade glioma (LGG)

Gene/ SNP ID	Genotype	Controls	GBM	OR[a]	95% CI	LGG[b]	OR[a]	95% CI
IGF1	TT	214	83	1.00		52	1.00	
rs6220	CT	219	71	0.91	0.61–1.35	28	0.42**	0.25–0.72
	CC	33	13	1.10	0.53–2.31	13	1.54	0.70–3.38
					p for trend = 0.58			p for trend = 0.67
	CT & CC	252	84	0.93	0.64–1.36	41	0.56*	0.35–0.90
IGF1	AA	300	112	1.00		64	1.00	
rs2162679	AG	103	32	0.98	0.60–1.60	19	0.72	0.40–1.30
	GG	9	3	1.30	0.31–5.41	1	0.33	0.04–2.83
					p for trend = 0.46			p for trend = 0.46
	AG & GG	112	35	1.01	0.63–1.61	20	0.69	0.39–1.23
IGF1R	CC	170	54	1.00		17	1.00	
rs2272037	CT	177	63	0.99	0.63–1.55	53	3.59***	1.92–6.72
	TT	87	37	1.24	0.72–2.11	17	1.85	0.85–4.05
					p for trend = 0.25			p for trend = 0.03
	CT & TT	264	100	1.08	0.72–1.63	70	2.98***	1.65–5.38
IGF1R	GG	207	77	1.00		40	1.00	
rs2137680	AG	185	63	1.01	0.66–1.54	37	1.01	0.60–1.69
	AA	39	12	0.76	0.36–1.64	11	1.47	0.67–3.25
					p for trend = 0.53			p for trend = 0.43
	AG & AA	224	75	0.94	0.63–1.40	48	1.08	0.66–1.75
IGF1R	TT	123	40	1.00		19	1.00	
rs2016347	GT	201	78	1.05	0.65–1.68	54	1.79	0.99–3.27
	GG	109	38	0.82	0.46–1.43	16	1.11	0.52–2.38
					p for trend = 0.77			p for trend = 0.98
	GT & GG	310	116	0.98	0.63–1.53	70	1.60	0.90–2.83
IGF2	GG	161	56	1.00		33	1.00	
rs3213216	AG	213	76	1.01	0.65–1.55	40	0.95	0.55–1.62
	AA	60	22	1.12	0.60–2.11	15	1.35	0.64–2.85
					p for trend = 0.85			p for trend = 0.72
	AG & AA	273	98	1.00	0.67–1.51	55	0.98	0.59–1.62
IGF2	CC	384	126	1.00		72	1.00	
rs2230949	CT & TT	74	34	1.33	0.81–2.17	20	1.47	0.81–2.63
IGF2R	GG	333	129	1.00		63	1.00	
rs629849	AG & AA	98	25	0.70	0.41–1.17	24	1.30	0.74–2.25
IGFBP3	AA	431	152	1.00		88	1.00	
rs9282734	AC	4	3	4.58	0.93–22.48	1	1.13	0.12–10.46

Abbreviations: SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval. The tumor grade of gliomas was classified according to the guidelines of Kleihues et al.[15] Totals for variables are not equal because of missing information.

[a]Adjusted for matching variables (hospital, age, sex, and residence).

[b]The LGG group included 34 oligodendrogliomas, 29 astrocytomas, 14 neuronal-glial tumors, 12 mixed gliomas, and 9 other low-grade gliomas.

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$.

men with OR 5.35 (95% CI, 1.97–14.57) for heterozygous carriers and OR 3.09 (95% CI, 0.95–10.00) for homozygous carriers compared to women with OR 2.51 (95% CI, 1.09–5.80) and OR 1.21 (95% CI, 0.39–3.70), respectively. Indication of a possible stronger association among men compared to the combined analysis was also present for *IGF1* (rs2162679) and another *IGF1R* gene (rs2137680). Stratifying the analysis by age (<50 years, ⩾50 years) did not indicate heterogeneity of risk for glioblastoma, low-grade glioma, or meningioma (results not shown).

The estimated ORs were similar in the crude and adjusted analysis, indicating that the matching variables had limited influence on the results. The results did not change materially when the analysis included all racial or ethnic groups. Sequentially excluding subgroups of controls based on reasons for hospitalization did not change any overall results.

Discussion

Several environmental factors have been suggested to increase the risk of brain tumors,[16,17] but few have been studied with strong or consistent evidence of causality. Variation in IGF function should be considered as a possible candidate in brain tumor etiology. To our knowledge, no previous epidemiologic study has investigated genetic variation in the IGF pathway in relation to brain tumor risk, and our results therefore cannot be compared directly with other studies. A recent small prospective epidemiologic study indicated an inverse association between glioma and serum levels of IGF-1,[12] and experimental data support the possibility that IGFs are related to glioma development and progression.[4] Our investigation did not indicate an association between meningioma and IGF polymorphic variants. For glioma, no association was seen between glioblastoma and IGF polymorphic variants, but a possible association was detected for low-grade glioma. The associations were mainly seen for the *IGF1R* gene. IGF-1R binds IGFs with a high affinity and plays a critical role in transformation events.[18] It is highly overexpressed in most malignancies, where it functions as an antiapoptotic agent by enhancing cell survival.

This is the first study exploring the hypothesis that alterations in IGF pathways are risk factors for brain tumors, and the study has several notable strengths. The results are based on one of the largest brain tumor case-control studies with DNA. Cases were identified continuously during the study period through collaboration with the treating clinics, and a rapid recruitment of cases was therefore possible. The rapid ascertainment is essential in a study of brain cancers because of the severity of the disease and the relatively short survival time. The participation rate was high, and the collection of blood samples very soon after brain tumor diagnosis minimizes the influence of a survival bias associated with IGF genotypes.

The study has several limitations as well, and there is reason for caution in interpreting the results. Two of the analyzed SNPs showed significant departure from HWE, and these included SNPs with non-null associations. It has been reported that HWE-violating SNPs more often show significant associations than SNPs without HWE violation.[19] There are several reasons why HWE may be violated, including genotyping error, chance, and population structure. In the present study, the quality-control data indicate high reproducibility of results for the two SNPs with HWE-violation. It is not likely that the HWE violation is a chance finding, but we cannot exclude the possibility. If we assume HWE for controls in the two SNPs according to the strategy presented by Chen et al.,[20] the OR shifts toward unity but still indicates an association between IGF and low-grade glioma. In addition, discrepant HWE results do not mean that postulated associations should be dismissed, but they should hint at the need for caution in interpretation and more evidence and replication. We evaluated nine SNPs in four tumor groups or subgroups, and the only significant associations were only marginally significant, so they may well be due to chance; replication is clearly needed. The selected SNPs in our study did not fully cover the IGF pathway and additional SNPs should be analyzed, including more IGF genes, for example, *IGFBP2* and *IGFBP5*. Selection bias could be a source of spurious associations in a hospital-based case-control study if one or more of the gene variants evaluated is associated with one or more of the diseases constituting the control series; however, sequential removal of each major control group based on reason for hospitalization did not materially change the results.

In conclusion, we report a possible association between IGF polymorphic variants and the risk of low-grade glioma. Our results are not robust, and the association between IGF polymorphisms and brain tumors needs to be considered further in large, well-designed studies with more comprehensive coverage of the IGF genes.

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