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An exploratory analysis of common genetic variants in the vitamin D pathway including genome-wide associated variants in relation to glioma risk and outcome

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Abstract

Purpose—Experimental and epidemiological evidence shows a beneficial role of vitamin D in cancer. In vitro evidence is consistent with a similar protective function in glioma; however, no study has yet examined the potential role of vitamin D in glioma.

Methods—We evaluated the association between common genetic variants in the vitamin D pathway and glioma risk and patient outcome in 622 newly diagnosed glioma cases and 628

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healthy controls enrolled in a clinic-based case–control study. Subjects were genotyped for 7 candidate and tagging single nucleotide polymorphisms in the vitamin D receptor and 8 additional variants in *NADSYN1*, *GC*, *CYP24A1*, *CYP2R1*, and *C10ORF88* linked in genome-wide association studies to serum concentrations of vitamin D. Unconditional logistic regression was used to estimate age- and gender-adjusted odds ratios and 95 % confidence intervals for glioma risk according to vitamin D genotypes. Proportional hazards regression was used to estimate hazard ratios for glioma-related death among 320 patients diagnosed with high-grade tumors. *P* values were uncorrected for multiple comparisons.

Results—Risk of astrocytic tumors was associated with variant alleles in rs3829251 (*NADSYN1*), rs10741657 (*CYP2R1*), rs2228570 (*Fok1*, *VDR*), and rs731236 (*Taq1*, *VDR*). No risk associations were found among oligodendroglial tumors. Survival associations were observed according to variant status for rs1544410 (*Bsm1*, *VDR*) and rs6013897 (*CYP24A1*).

Conclusion—This exploratory analysis provides limited evidence of a role for genetic variation in vitamin D pathway genes with glioma risk and survival.

Keywords

Glioma; Vitamin D; Single nucleotide polymorphism; Genotype; VDR

Introduction

Gliomas are an aggressive primary tumor of the brain with unknown etiology. The vitamin D metabolite $1,25(OH)_2D_3$ may protect against cancer by promoting cell differentiation and apoptosis and by inhibiting cell proliferation and angiogenesis (reviewed in [1]). Findings from epidemiologic studies investigating the association between serum levels of $1,25(OH)_2D_3$ and cancer risk have been inconsistent though [2–6]; the only study to consider brain cancer did not observe a significant association between plasma vitamin D levels and risk of brain tumors of all types [7]. However, the observation that there are higher incidence rates of glioma in regions with lower ambient ultraviolet B radiation [8], the principal source of vitamin D in humans, and in vitro evidence that $1,25(OH)_2D_3$ inhibits growth and induces apoptosis in glioma cell lines [9] suggests a potential role for vitamin D in glioma.

The effects of $1,25(OH)_2D_3$ are mediated through the vitamin D receptor (VDR), a transcription factor expressed in multiple tissue types including the brain [10]. Single nucleotide polymorphisms (SNPs) in the *VDR* gene, located on chromosome 12q13, influence the activity of $1,25(OH)_2D_3$. The *Fok1* (rs2228570) and *Cdx2* (rs11568820) polymorphisms alter transcription of the *VDR* gene [11], while the functional relevance of other commonly studied *VDR* polymorphisms including *Taq1* (rs731236), *Apa1* (rs7975232), and *Bsm1* (rs1544410) is unclear [12]. No study has yet examined whether genetic variants in VDR or SNPs associated with serum concentrations of 25-hydroxyvitamin D in genome-wide association (GWA) studies [13, 14] are related to glioma risk or patient outcome.

We evaluated these potential associations in a series of 622 newly diagnosed glioma cases and 628 healthy controls enrolled in the Study of Glioma in the Southeast (GliomaSE), a multi-center, clinic-based case–control study conducted at medical centers in the Southeastern United States.

Subjects and methods

Study population

A description of the study population has been published previously [15, 16]. Briefly, cases were Caucasian individuals aged 18 and older recently diagnosed (within 3 months) with a primary, non-recurrent glioma. Cases were identified at neurosurgery and neuro-oncology clinics at major medical and oncology centers in the Southeastern United States including Vanderbilt University Medical Center in Nashville, Tennessee; Moffitt Cancer Center in Tampa, Florida; the University of Alabama at Birmingham; Emory University in Atlanta, Georgia; and the Kentuckiana Cancer Institute in Louisville, Kentucky. As eligibility in the case–control study required a recent diagnosis of glioma, only primary glioblastoma multiforme (GBM) and de novo anaplastic astrocytoma were included in the case group. Controls included friends and other non-blood-related associates of the cases as well as residents from the same communities as the cases identified in white page listings. Controls were excluded if they reported a personal history of a brain tumor. Eighty-seven percent of eligible glioma patients were enrolled in the study, a median of 1.0 month following the glioma diagnosis (interquartile range: 2 weeks–1.7 months). Study protocols were approved by the institutional review committees at each participating center and all study participants provided written informed consent.

Interviewer-administered questionnaires were used to collect data on demographic characteristics and potential glioma risk factors. Genomic DNA samples were self-collected by oral rinse or the saliva method using Oragene kits (www.dnagenotek.com).

DNA processing and genotyping

DNA was extracted and stored at the Core Genotyping Facility at Vanderbilt (during the pilot phase) or at the Tissue Core laboratory of Moffitt Cancer Center (the coordinating center). For the present analysis, we examined 8 SNPs in the *VDR*, including the commonly studied restriction fragment length polymorphisms (RFLPs) *Apa1*, *Taq1*, *Bsm1*, *Fok1*, and *Cdx2*, and 3 tagging SNPs. An additional 10 SNPs linked to serum concentrations of 25-hydroxyvitamin D levels in *GC* (4q12-q13), *CYP2R1* (11p15), *CYP24A1* (20q13), *NADSYN1* (11q13), and *C10orf88* (10q26) [13, 14] were also genotyped. Genotyping was performed at the Center for Genome Technology at the Hussman Institute for Human Genomics, University of Miami using Illumina's GoldenGate technology (Illumina, San Diego, CA). Genotyping by Taqman was carried out for SNPs that failed on the Illumina array. A total of 655 glioma cases and 658 controls, all Caucasian, were submitted for genotyping. Quality control samples (water, CEPH DNA, as well as blinded and unblinded DNA samples) were included in genotyping runs. Laboratory staff was blinded to the case–control status of the samples. Two SNPs (*VDR* rs7975232 (*Apa1*) and *CYP2R1* rs2060793) failed genotyping and in one additional SNP (*GC* rs12512631) there was departure from Hardy–Weinberg Equilibrium among the controls (p value of <0.01). Concordance of genotype calls in 94 blinded duplicate pairs ranged from 89 to 100 % (mean, 99.6 %) among the 15 successfully genotyped SNPs. The genotyping success rate for individuals ranged from 91.4 to 99.7 % (mean, 97.6 %). Glioma risk has also been associated with established susceptibility variants for these tumors [17, 18] in this case–control series [15].

Statistical analysis

Risk associations were modeled using unconditional logistic regression with odds ratios (ORs) and 95 % confidence intervals (CIs) for individual genotypes adjusted for age and gender. To test for linear trend, each SNP was modeled as an ordinal term coded 0, 1, and 2 corresponding to the number of variant alleles. Multinomial logistic regression was used to examine associations between genotypes and histologic subtypes of glioma (GBM, low-

grade astrocytomas, and oligodendrogliomas). A test for heterogeneity was performed in each multinomial model to evaluate if the odds ratios for each SNP were significantly different across histology groups. Survival associations were examined among the 320 patients with high-grade tumors (GBM, anaplastic astrocytoma, and high-grade oligodendrogliomas) treated with the current standard of care (surgical resection, radiation, and temozolomide) as a first course of therapy. Cox proportional hazards regression was used to evaluate the prognostic influence of vitamin D polymorphisms on glioma survival, adjusting for age, gender, and histologic subtype of glioma (GBM; high-grade astrocytoma (non-GBM); high-grade oligodendroglioma). All p values were two sided and uncorrected for multiple comparisons. Analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, USA).

Results

Table 1 presents characteristics of glioma cases and controls. The median age among cases was 52 years (range: 18–88) and among controls was 56 years (range: 18–87). The majority of cases (63 %) and controls (57 %) were male. Subjects resided in Tennessee (30 %), Florida (25 %), Alabama (14 %), Kentucky (13 %), Georgia (11 %), and other southern states (7 %).

Associations with glioma risk under an additive model are shown in Table 2. A positive association was observed with increasing number of variant alleles in *NADSYN1* rs3829251 (OR = 1.26; 95 % CI: 1.00–1.58; $p = 0.05$); no other significant associations were evident. We further examined associations under dominant and recessive models (data not shown) and found an inverse association under a dominant model for *VDR Fok1* (OR = 0.77; 95 % CI: 0.61–0.98; $p = 0.03$) and *CYP2R1* rs10741657 (OR = 0.72; 95 % CI: 0.56–0.92; $p = 0.01$).

Risk associations according to histologic subtype of glioma are shown in Table 3. The positive association with *NADSYN1* rs3829251 was restricted to high-grade (GBM) and lower-grade astrocytic tumors (combined OR = 1.32; 95 % CI: 1.04–1.67; $p = 0.02$) with no similar association in oligodendrogliomas (OR = 0.89; 95 % CI: 0.55–1.46; $p = 0.65$) (p for heterogeneity = 0.18). There was some evidence of heterogeneity across histology types for *CYP2R1* rs10741657; an inverse association was observed in GBM and lower-grade astrocytic tumors combined (OR = 0.79; 95 % CI: 0.65–0.95; $p = 0.01$) but not in oligodendrogliomas (OR = 1.17; 95 % CI: 0.82–1.68; $p = 0.37$) (p for heterogeneity = 0.08). Homozygous variant carriers of the VDR *Taq1* variant were at significantly reduced risk of GBM only (OR = 0.58; 95 % CI: 0.35 to 0.94; $p = 0.03$) (data not shown).

We examined genotype associations with glioma survival in 320 patients with high-grade tumors treated with the current standard of care (surgical resection, radiation, and temozolomide) (Table 4). A total of 248 deaths from glioma were documented (median follow up among 72 surviving patients: 28 months). Reduced survival was observed among variant allele carriers in *VDR Bsm1* (HR = 1.34; 95 % CI: 1.01–1.77; $p = 0.04$) under a dominant model. Variant carriers of *CYP24A1* rs6013897 had significantly prolonged survival under both additive (per allele HR = 0.79; 95 % CI: 0.63–0.98; p for trend = 0.03) and recessive (HR = 0.54; 95 % CI: 0.30–0.96; $p = 0.04$) models.

We attempted to validate survival associations in the Cancer Genome Atlas (TCGA) (downloaded from http://tcga-data.nci.nih.gov/tcga) [19] among 211 TCGA GBM patients that underwent surgery, radiation, and chemotherapy. Neither of the 2 variants associated with survival in the current series (rs1544410 (*Bsm1*) and rs17217119 as a proxy for *CYP24A1* rs6013897 ($r^2 = 1.0$)) was associated with glioma survival in TCGA (not shown).

Discussion

To our knowledge, this is the first evaluation of common polymorphisms in the vitamin D pathway in relation to glioma. In this large series of incident glioma cases, suggestive associations were identified for SNPs in the *VDR* and in genes *NADSYN1*, *CYP2R1*, and *CYP24A1*. Risk associations were observed primarily for astrocytic tumors whereas no significant associations were evident for oligodendrogliomas. Associations with survival were also suggested for two of the examined variants, although neither finding was validated in the Cancer Genome Atlas data.

RFLPs *Bsm1* and *Taq1*, which are in high linkage disequilibrium in the 3′ untranslated region of the *VDR* [12], are among the *VDR* SNPs most commonly studied in relation to cancer risk. Though *Taq1* and *Bsm1* have no known functional relevance and do not change the structure of the VDR protein, they are strongly linked to a poly(A) microsatellite repeat in the 3′ untranslated region that may be associated with VDR mRNA stability [20]. Our findings suggesting a reduced risk for astrocytic tumors associated with the *Taq1* variant are consistent with findings indicating a similar pattern for melanoma [21], although no consistent association has emerged with this variant and other malignancies (reviewed in [22, 23]). The association between *Bsm1* and other cancer types is also inconclusive [22, 23]. Among studies of cancer outcome, a pooled analysis of prospective studies indicated that the *Bsm1* variant was protective for the development of more aggressive forms of breast cancer [24] whereas in the current study of glioma *Bsm1* carrier status was associated with more aggressive tumors and a worse survival outcome.

The *VDR Fok1* SNP is functionally relevant; the variant *f*(T) allele in *Fok1* produces a VDR protein that is three amino acids longer than the wild-type *F*(C) allele and is functionally less effective [11]. The association between *Fok1* and cancer risk is unclear [21–23]. In the present data, we observed a reduced glioma risk associated with the *Fok1* variant under a dominant model across all glioma subtypes.

Several of the SNPs associated with glioma risk or outcome in these analyses emerged in GWA studies as predictors of serum 25-hydroxyvitamin D [13, 14]. The *CYP2R1* gene encodes a cytochrome P450 enzyme that catalyzes the hydroxylation of vitamin D to the active form of vitamin D. The variant allele in *CYP2R1* rs10741657 has been associated with higher vitamin D levels in several studies [13, 25, 26] and was associated with reduced glioma risk in the present data. Glioma cases that were carriers of the *CYP24A1* rs6013897 variant, associated with lower serum vitamin D [13], had improved glioma survival.

Strengths of this study include the relatively large sample of cases given the rarity of glioma, rapid ascertainment of cases minimizing the potential for survival bias, and the high quality of genotype data, as evidenced by the demonstration of risk associations with established susceptibility alleles in this series of cases and controls [15]. A limitation is that we were not able to examine several variants (GC rs12512631 and CYP2R1 rs2060793) linked to serum vitamin D levels [10, 11] that failed genotyping in the present study. While the study implicated several functional variants in the VDR and provided suggestive findings for variants linked to vitamin D status, many associations were examined in this exploratory analysis and *p* values were uncorrected for multiple comparisons; therefore, significant findings may have arisen by chance. Population stratification may also have influenced our findings and results from this exploratory analysis need to be replicated in further studies.

In summary, this exploratory analysis provides some limited evidence supporting a role for vitamin D in glioma onset and survival of glioma.

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Table 1

Selected characteristics of glioma cases and controls

	Cases (*N* = 622)	**Controls (*N* = 628)**
Age, median (range)	52 (18–88)	56 (18–87)
Gender, *N*(%)		
Male	389 (63)	360 (57)
Female	233 (37)	268 (43)
State of residence, *N*(%)		
TN	163 (26)	207 (33)
FL	168 (27)	149 (24)
AL	97 (16)	80 (13)
KY	83 (13)	82 (13)
GA	72 (12)	67 (11)
Other	39 (6)	43 (7)
Histology type, *N*(%)		
Glioblastomas	341 (55)	–
Lower-grade astrocytomas	146 (23)	–
Oligodendroglial tumors	94 (15)	–
Other gliomas	41 (7)	–

Unequal column totals indicate missing data

Table 2

Associations between variants in vitamin D pathway–related genes and glioma risk

Gene	rs number	MAF	Cases	Controls	Genotype	OR (95 % CI)	P_{trend}
VDR	rs731236 (*Taq1*)	0.40	217	194	TT	Ref	0.12
			297	291	CT	0.90 (0.69, 1.16)	
			64	80	CC	0.73 (0.50, 1.08)	
					Per allele	0.87 (0.72, 1.04)	
	rs1544410 (*Bsm1*)	0.41	207	204	GG	Ref	0.17
			285	303	AG	0.90 (0.70, 1.17)	
			70	91	AA	0.77 (0.53, 1.12)	
					Per allele	0.88 (0.74, 1.05)	
	rs2107301	0.30	306	301	CC	Ref	0.96
			252	265	TC	0.95 (0.75, 1.20)	
			54	50	TT	1.06 (0.70, 1.62)	
					Per allele	1.00 (0.83, 1.19)	
	rs2228570 (*Fok1)*	0.39	234	216	GG	Ref	0.18
			251	307	AG	0.74 (0.57, 0.95)	
			79	82	AA	0.90 (0.63, 1.30)	
					Per allele	0.89 (0.75, 1.05)	
	rs2238135	0.23	317	362	CC	Ref	0.39
			216	207	GC	1.18 (0.93, 1.51)	
			32	36	GG	0.99 (0.60, 1.63)	
					Per allele	1.09 (0.90, 1.32)	
	rs4516035	0.45	166	175	TT	Ref	0.47
			296	298	CT	1.06 (0.81, 1.38)	
			117	108	CC	1.13 (0.81, 1.59)	
					Per allele	1.06 (0.90, 1.26)	
	rs11568820 (*Cdx2*)	0.20	346	356	CC	Ref	0.98
			190	179	TC	1.12 (0.87, 1.45)	
			17	26	TT	0.68 (0.36, 1.28)	
					Per allele	1.00 (0.81, 1.23)	
CYP2R1	rs10741657	0.40	227	190	GG	Ref	0.07

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Gene	rs number	MAF	Cases	Controls	Genotype	OR (95 % CI)	P_{trend}
			242	294	AG	0.69 (0.53, 0.89)	
			73	77	AA	0.83 (0.57, 1.21)	
					Per allele	0.85 (0.71, 1.01)	
CYP24A1	rs6013897	0.20	349	360	TT	Ref	0.37
			175	186	AT	1.00 (0.77, 1.29)	
			34	24	AA	1.50 (0.87, 2.59)	
					Per allele	1.10 (0.90, 1.34)	
NADSYN1	rs12785878	0.26	294	334	GG	Ref	0.28
			223	217	TG	1.19 (0.93, 1.52)	
			48	50	TT	1.10 (0.72, 1.69)	
					Per allele	1.10 (0.92, 1.32)	
	rs3829251	0.15	373	411	GG	Ref	**0.05**
			166	148	AG	1.20 (0.92, 1.57)	
			18	11	AA	1.91 (0.88, 4.12)	
					Per allele	1.26 (1.00, 1.58)	
GC	rs2282679	0.25	322	345	AA	Ref	0.33
			247	238	CA	1.11 (0.88, 1.41)	
			40	36	CC	1.17 (0.73, 1.90)	
					Per allele	1.10 (0.91, 1.32)	
	rs7041	0.43	203	210	GG	Ref	0.94
			293	281	TG	1.07 (0.83, 1.39)	
			113	122	TT	0.96 (0.70, 1.33)	
					Per allele	0.99 (0.85, 1.17)	
	rs1155563	0.25	313	339	TT	Ref	0.17
			259	246	CT	1.14 (0.90, 1.44)	
			43	35	CC	1.28 (0.80, 2.07)	
					Per allele	1.14 (0.94, 1.37)	
C10ORF88	rs6599638	0.46	153	169	GG	Ref	0.46
			246	263	AG	1.00 (0.75, 1.32)	
			129	123	AA	1.14 (0.82, 1.59)	
					Per allele	1.06 (0.90, 1.26)	

Unequal column totals for case/control counts reflect missing data

Models adjusted for age and gender

MAF minor allele frequency in controls, *OR* odds ratio, *CI* confidence interval

Bold value indicates $p \leq 0.05$

Table 3

Associations between variants in vitamin D pathway–related genes and glioma risk by histological subtype and grade

Gene	rs number	Glioblastoma Per allele OR (95 % CI)	P_{trend}	Lower-grade astrocytoma Per allele OR (95 % CI)	P_{trend}	Oligodendroglioma Per allele OR (95 % CI)	P_{trend}	P_{hetero}*
VDR	rs731236 (*Taq1*)	0.81 (0.66, 1.01)	0.06	0.87 (0.64, 1.17)	0.36	0.92 (0.63, 1.33)	0.65	0.81
VDR	rs1544410 (*Bsm1*)	0.88 (0.71, 1.08)	0.22	0.83 (0.62, 1.12)	0.22	0.91 (0.64, 1.29)	0.59	0.91
VDR	rs2107301	0.96 (0.78, 1.19)	0.73	1.08 (0.81, 1.45)	0.59	1.05 (0.74, 1.49)	0.79	0.75
VDR	rs2228570 (*Fok1*)	0.92 (0.75, 1.13)	0.45	0.88 (0.66, 1.16)	0.36	0.80 (0.56, 1.14)	0.21	0.75
VDR	rs2238135	1.12 (0.89, 1.41)	0.33	1.03 (0.75, 1.41)	0.86	1.18 (0.81, 1.70)	0.39	0.81
VDR	rs4516035	1.06 (0.87, 1.30)	0.57	0.98 (0.75, 1.30)	0.91	1.20 (0.86, 1.66)	0.28	0.61
VDR	rs11568820 (*Cdx2*)	1.06 (0.83, 1.36)	0.63	1.04 (0.74, 1.47)	0.81	0.74 (0.47, 1.18)	0.21	0.34
CYP2R1	rs10741657	**0.80 (0.65, 1.00)**	**0.05**	0.75 (0.56, 1.01)	0.06	1.17 (0.82, 1.68)	0.37	0.08
CYP24A1	rs6013897	1.07 (0.84, 1.37)	0.56	1.19 (0.86, 1.66)	0.29	1.04 (0.69, 1.58)	0.85	0.80
NADSYN1	rs12785878	1.13 (0.91, 1.39)	0.28	1.06 (0.79, 1.42)	0.70	1.00 (0.70, 1.42)	0.98	0.81
NADSYN1	rs3829251	1.26 (0.96, 1.64)	0.10	**1.49 (1.04, 2.12)**	**0.03**	0.89 (0.55, 1.46)	0.65	0.18
GC	rs2282679	1.18 (0.95, 1.47)	0.14	1.02 (0.75, 1.39)	0.89	0.93 (0.64, 1.35)	0.69	0.44
GC	rs7041	0.99 (0.82, 1.20)	0.92	1.07 (0.82, 1.39)	0.63	0.78 (0.56, 1.08)	0.13	0.25
GC	rs1155563	1.18 (0.95, 1.47)	0.13	1.12 (0.82, 1.51)	0.47	0.95 (0.65, 1.38)	0.78	0.55
C10ORF88	rs6599638	0.98 (0.80, 1.20)	0.85	1.00 (0.76, 1.32)	0.98	1.31 (0.92, 1.85)	0.13	0.30

Models adjusted for age and gender. Glioblastomas encompassed ICD-O code [27] 9440/3; lower-grade astrocytic tumors included grade 3 anaplastic astrocytomas (ICD-O 9401/3), grade 1 or 2 astrocytomas (ICD-O 9384/1, 9421/1, 9400/3, 9424/3), and astrocytoma NOS (ICD-O 9400/3); oligodendroglial tumors included mixed oligodendroglial and astrocytic tumors (ICD-O 9382/3) and pure oligodendrogliomas (ICDO 9450/3, 9451/3). Gliomas with rare or unspecified histology were excluded

OR odds ratio, *CI* confidence interval

* *P* value for heterogeneity between ORs of different histologies

Bold values indicate $p < 0.05$

Table 4

Vitamin D pathway variants and survival among high-grade glioma cases

Gene	rs number	Additive model		Dominant model		Recessive model	
		HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
VDR	rs731236 (*Taq1*)	1.15 (0.94, 1.40)	0.18	1.33 (1.00, 1.77)	0.05	0.97 (0.62, 1.50)	0.88
VDR	rs1544410 (*Bsm1*)	1.19 (0.98, 1.43)	0.08	**1.34 (1.01, 1.77)**	**0.04**	1.14 (0.77, 1.67)	0.51
VDR	rs2107301	1.01 (0.82, 1.24)	0.95	0.95 (0.73, 1.24)	0.72	1.20 (0.77, 1.88)	0.43
VDR	rs2228570 (*Fok1*)	1.19 (0.98, 1.46)	0.09	1.25 (0.95, 1.65)	0.11	1.25 (0.84, 1.86)	0.28
VDR	rs2238135	0.97 (0.76, 1.22)	0.77	0.87 (0.67, 1.14)	0.32	1.59 (0.91, 2.78)	0.10
VDR	rs4516035	1.12 (0.93, 1.36)	0.23	1.15 (0.85, 1.54)	0.36	1.19 (0.86, 1.64)	0.29
VDR	rs11568820 (*Cdx2*)	0.99 (0.77, 1.27)	0.93	1.00 (0.75, 1.33)	0.99	0.90 (0.42, 1.95)	0.80
CYP2R1	rs10741657	0.84 (0.69, 1.03)	0.09	0.86 (0.65, 1.13)	0.27	0.68 (0.44, 1.04)	0.07
CYP24A1	rs6013897	**0.79 (0.63, 0.98)**	**0.03**	0.79 (0.60, 1.05)	0.10	**0.54 (0.30, 0.96)**	**0.04**
NADSYN1	rs12785878	1.00 (0.82, 1.22)	0.98	1.00 (0.77, 1.30)	0.99	0.99 (0.63, 1.55)	0.97
NADSYN1	rs3829251	0.88 (0.70, 1.10)	0.26	0.93 (0.70, 1.23)	0.59	0.53 (0.26, 1.09)	0.08
GC	rs2282679	1.02 (0.83, 1.24)	0.86	1.06 (0.82, 1.38)	0.64	0.89 (0.55, 1.46)	0.66
GC	rs7041	0.95 (0.79, 1.14)	0.59	0.96 (0.73, 1.27)	0.79	0.90 (0.65, 1.24)	0.52
GC	rs1155563	1.01 (0.83, 1.24)	0.89	1.04 (0.81, 1.35)	0.74	0.93 (0.58, 1.50)	0.78
C10ORF88	rs6599638	1.13 (0.94, 1.36)	0.20	1.14 (0.84, 1.54)	0.39	1.24 (0.90, 1.70)	0.20

Models adjusted for age, gender, and histological subtype of glioma (glioblastomas, high-grade astrocytomas that are not glioblastoma, and high-grade oligodendrogliomas)

HR hazard ratio, *CI* confidence interval

Bold values indicate $p < 0.05$