Neuro-Oncology

21(10), 1297–1309, 2019 | doi:10.1093/neuonc/noz094 | Advance Access date 6 July 2019

Genetic variants and cognitive functions in patients with brain tumors

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Abstract

Background. Patients with brain tumors treated with radiotherapy (RT) and chemotherapy (CT) often experience cognitive dysfunction. We reported that single nucleotide polymorphisms (SNPs) in the *APOE*, *COMT*, and *BDNF* genes may influence cognition in brain tumor patients. In this study, we assessed whether genes associated with late-onset Alzheimer's disease (LOAD), inflammation, cholesterol transport, dopamine and myelin regulation, and DNA repair may influence cognitive outcome in this population.

Methods. One hundred and fifty brain tumor patients treated with RT ± CT or CT alone completed a neurocognitive assessment and provided a blood sample for genotyping. We genotyped genes/SNPs in these pathways: (i) LOAD risk/inflammation/cholesterol transport, (ii) dopamine regulation, (iii) myelin regulation, (iv) DNA repair, (v) blood–brain barrier disruption, (vi) cell cycle regulation, and (vii) response to oxidative stress. White matter (WM) abnormalities were rated on brain MRIs.

Results. Multivariable linear regression analysis with Bayesian shrinkage estimation of SNP effects, adjusting for relevant demographic, disease, and treatment variables, indicated strong associations (posterior association summary [PAS] ≥ 0.95) among tests of attention, executive functions, and memory and 33 SNPs in genes involved in: LOAD/inflammation/cholesterol transport (eg, *PDE7A*, *IL-6*), dopamine regulation (eg, *DRD1, COMT*), myelin repair (eg, *TCF4*), DNA repair (eg, *RAD51*), cell cycle regulation (eg, *SESN1*), and response to oxidative stress (eg, *GSTP1*). The SNPs were not significantly associated with WM abnormalities.

Conclusion. This novel study suggests that polymorphisms in genes involved in aging and inflammation, dopamine, myelin and cell cycle regulation, and DNA repair and response to oxidative stress may be associated with cognitive outcome in patients with brain tumors.

Key Points

1. Genetic polymorphisms influence cognitive function in brain tumor patients.
2. Variants in aging, dopamine, myelin, and DNA repair genes are associated with cognition in brain tumors.

Brain tumor patients often experience cognitive dysfunction associated with their disease and radiotherapy (RT) and/or chemotherapy (CT)[1]; however, little is known about individual factors that may influence the vulnerability for treatment-related neurotoxicity and the heterogeneity in cognitive outcome in this population. A novel focus of research involves the study of inherited polymorphisms in genes related to neural, vascular, myelin, and DNA repair

Importance of the Study

Brain tumor patients often develop cognitive dysfunction related to their disease and the adverse effects of radiotherapy and chemotherapy. However, little is known about individual factors that may impact the vulnerability for treatment-related neurotoxicity and the heterogeneity in cognitive outcome in this population. A novel focus of research involves the study of inherited polymorphisms that may influence cognitive function in cancer patients. In this study of a large cohort of brain tumor patients, we found significant associations of polymorphisms in genes involved in aging/inflammation/cholesterol transport, dopamine, myelin and cell cycle regulation, DNA repair, and response to oxidative stress with cognitive functions including attention, executive functions, and memory. This line of research would ultimately help predict which patients are at increased risk for treatment-related neurotoxicity and guide the implementation of targeted interventions.

that may contribute to the patient's increased or decreased constitutive response,[2] as both individual factors and exposures (ie, treatment) could modify neurotoxicity risk and the magnitude of the side effects. In this regard, recent studies began to investigate the contribution of genetic variants to neurocognitive outcome in brain tumor patients.[3] We reported previously that among brain tumor patients treated with RT ± CT, carriers of the apolipoprotein E epsilon 4 (*APOE* ε4) allele, a risk factor for late onset Alzheimer's disease (LOAD), had significantly lower memory scores in comparison to non-ε4 carriers.[4] Variants in the *COMT*, *BDNF*, and *DTNBP1* genes were also associated with cognitive functions in this cohort.[5] Variants in genes involved in inflammation, DNA repair, and metabolism were reported in association with cognition in patients with newly diagnosed glioma.[6]

To investigate the role of genetics in cognitive functions, we examined additional polymorphisms associated with LOAD risk, including those identified in candidate loci and in genome-wide association studies.[7,8] We also included polymorphisms in genes involved in cholesterol transport[9] and inflammation[10] given their reported role in modulating LOAD risk. Given the known adverse effects of RT and CT, including demyelination and changes in blood vessels and blood–brain barrier (BBB) permeability,[11] DNA damage, and oxidation,[12] we investigated genes involved in myelin regulation,[13] BBB disruption,[14] DNA repair,[15] cell cycle regulation, and response to oxidative stress.[16] We also examined genes involved in dopamine regulation reported to modulate working memory.[17,18] In this study, we investigated the association of polymorphisms in the aforementioned pathways with cognitive and neuroimaging outcomes in brain tumor patients.

Materials and Methods

Subjects

One hundred and fifty brain tumor patients were recruited from a cohort of patients followed at Memorial Sloan Kettering Cancer Center between 2009 and 2012. Study eligibility included: no evidence of active disease on MRIs prior to accrual; RT or CT completed at least 3 months prior to enrollment; no history of psychiatric or other neurological disorders; fluency in English. The research protocol was approved by the institutional review board, and all patients signed informed consent. This patient cohort participated in our previous studies.[4,5]

Table 1 shows patient demographics and disease and treatment variables. Among patients treated with RT ± CT, 85 had focal RT (57%) and 20 had whole-brain RT (14%); RT dose ranged from 2340 to 6840 cGy. All patients had a neuropsychological evaluation and provided a blood sample for genotyping. *APOE* genotyping was obtained previously for all participants,[4] and 35 (23%) were carriers of at least one ε4 allele.

Measures

Neuropsychological assessment

Tests with reported sensitivity to the adverse effects of cancer therapy[1] were selected to evaluate the following cognitive domains:

- Attention: Digit Span subtest (Digit Span Forward [DSF]; Digit Span Backward [DSB]); Wechsler Memory Scale Third Edition (WMS-III); Brief Test of Attention (BTA).
- Graphomotor Speed and Executive Functions: Trail Making Test Parts A and B (TMT-A, TMT-B); Phonemic Verbal Fluency Test (VF).
- Verbal Memory: Hopkins Verbal Learning Test Revised–Learning (HVLT-L), Delayed Recall (HVLT-D), Discrimination Index (HVLT-DI).

Raw cognitive test scores were compared with age-corrected published normative values[19] and converted into *z*-scores (mean = 0; standard deviation [SD] = 1). A negative *z*-score value indicates that a score is lower than the mean, which corresponds to worse cognitive test performance.

Selection of polymorphisms

Polymorphisms in candidate genes and pathways were selected based on their known or anticipated functional impact in healthy and clinical populations according to published in vitro, in vivo, and association studies for the following pathways: (i) LOAD risk/inflammation/cholesterol transport, (ii) dopamine regulation, (iii) myelin regulation, and (iv) DNA repair. Given the early stages of this research area and the paucity of published studies, we considered it important to also investigate the role of SNPs

Table 1 Demographic characteristics and disease/treatment history ($N = 150$)

Characteristics	
Male, *n*	68 (45%)
Right handed, *n*	131 (87%)
Caucasian, *n*[1]	133 (89%)
Age at study entry, y	
Mean (SD)	51 (13.4)
Median (range)	52 (21–83)
Mean education, y	16 (2.8)
Mean estimated verbal IQ	112 (8.6)
Tumor type	
Low grade glioma	34 (23%)
High grade glioma	57 (38%)
Primary CNS lymphoma	42 (28%)
Other	17 (11%)
Tumor location	
Frontal/frontal-temporal/ frontal-parietal	81 (54%)
Temporal/parietal/occipital	36 (24%)
Cortical/subcortical	33 (22%)
Predominant tumor side	
Left	53 (36%)
Right	68 (45%)
Bilateral	29 (19%)
Treatment type[2]	
RT ± chemotherapy	105 (70%)
Chemotherapy	45 (30%)
Time since treatment completion, mo	
Mean (SD)	45 (50.7)
Median (range)	27 (6–370)[3]
Smoking history	
Yes	66 (44%)
Vascular risk	
Yes	58 (39%)
Antiepileptics[4]	
Yes	76 (51%)

[1]Additional ethnicity: Asian = 5%, black = 4%, other = 2%.
[2]Treatment history = all therapy received including at relapse, if applicable.
[3]Two patients had longer time since treatment completion compared with others (ie, highest values = 370 and 314 mo; third highest value = 155 mo).
[4]Medication at the time of the cognitive evaluation.

in genes involved in these additional pathways: (v) BBB disruption, (vi) cell cycle regulation, and (vii) response to oxidative stress. We selected SNPs predicted to overlap with seed miRNA regions or transcription factor binding sites and tagged SNPs with a correlation (r^2) greater than 0.80 with other SNPs (as reported in the Single Nucleotide Polymorphism Database [dbSNP] for Caucasians). In general, we selected SNPs with 15% minimum minor allele frequency (MAF) in Caucasians. For tagging SNPs and for the DNA repair SNPs we set a minimum cutoff MAF of 25%. A few polymorphisms were included regardless of the MAF (rs3796530; rs446037; rs2227902; rs1018381; rs2214102), due to their functional relevance.

Genotyping

Germline DNA was previously extracted and available for this study.[4,5] Briefly, DNA was extracted from frozen whole blood using the Gentra Puregene Blood kit (Qiagen) following manufacturer's protocols and then normalized to a final concentration of 50 to 100 ng/μL. SNPs were first typed using the GoldenGate assay (Illumina). A set of 51 SNPs, including SNPs that failed at the design or wet testing stages when using the GoldenGate assay, were typed in 4 multiplexed assays or "wells" using the MassArray iPLEX platform (Agena Bioscience, formerly Sequenom) with methods and quality control measures as previously described.[20] Assays were considered optimal according to the degree of clustering, specificity, and reproducibility. Supplementary Table 2 shows the PCR and extension primers used for the MassArray-based assays. *COMT* rs165599 was typed by PCR-based fragment size analysis, with primers and assay conditions listed in Supplementary Table 3. The frequencies obtained in our study were compared with those expected according to dbSNP and the literature. Hardy–Weinberg equilibrium (HWE) was calculated to identify major genotyping issues; however, absence of HWE in a cohort consisting solely of cases with the disease can be observed for SNPs conferring true risk for the condition. SNPs that were mono-allelic, had >5% missing data, or showed poor clustering and/or reproducibility were excluded from further analysis.

For SNPs in high linkage disequilibrium (LD), we retained only one of the SNPs in the analysis. The following polymorphisms were successful assays but subsequently removed to avoid multicollinearity as they were in very strong association (posterior association summary [PAS] ≥ 0.95): rs3744260 (cell cycle pathway), rs737865 (dopamine pathway), rs624366, rs1060915, rs16940, rs16941, rs16942, rs1799966, rs3092994, rs799917, rs8176318, rs565416, rs579325, rs4647269, rs748766 (DNA repair pathway), rs11556505 and rs2075650 (mitochondrial neurotoxicity, LOAD risk), rs670101713 (LOAD risk, inflammation), and rs2271398 (myelin regulation). Three DNA repair SNPs and one SNP associated with the neural/vascular repair were removed due to MAF <10% in our cohort: rs7468, rs1573638, and rs446037. A total of 357 SNPs remained in our final analyses. Supplementary Table 1 lists the selection criteria, reference sequence (RefSeq), and other SNP attributes.

Neuroimaging

White matter (WM) abnormalities were rated on a fluid-attenuated inversion recovery (FLAIR) sequence brain MRI scan performed within 3 months of the cognitive evaluation. The ratings were performed by 2 neuroradiologists (S.K., J.L.), who were blind to the cognitive test results. Radiographic endpoints were measured according to the

modified Fazekas scale[21] and included: no/minimal WM abnormalities (grade 0), punctate WM foci (grade 1), start of confluence of WM (grade 2), and large confluent areas (grade 3). One score (range: 0–3) was obtained for each patient.

Statistical Analyses

The primary outcomes of interest were the 9 cognitive tests *z*-scores, treated as continuous outcomes (listed in "Materials and Methods"). The secondary outcome was WM rating, treated as a binary variable: no/minimal WM abnormalities (grades 0–1) and moderate/severe WM abnormalities (grades 2–3). Our main risk factors of interest were SNPs from 7 gene pathways (listed in "Materials and Methods").

We used multivariable linear regression analysis to examine the association between multiple SNPs in each pathway and each primary outcome, resulting in a total of 63 sets of analyses. We treated each SNP as a risk factor having 2 or 3 categories based on the following rule. If the frequencies of each of the 3 genotype categories were at least 10%, we considered the SNP as having 3 categories. We entered 2 dummy variables for that SNP in the model by treating one homozygous genotype category as the baseline. If the frequency of any genotype category was less than 10%, we combined it with another genotype category and treated that SNP as a binary variable.

We adjusted all analyses for age (continuous), education level (continuous), treatment (binary: RT ± CT yes, no), time since treatment (continuous), and tumor location (categorical). There were significant associations ($P \leq 0.05$) between age and DSF, education and DSB, VF, and HVLT Revised, and tumor location and TMT-A. We also adjusted for APOE ε4 status (binary: yes, no) when analyzing SNPs from the LOAD risk/inflammation/cholesterol transport and the dopamine regulation pathways, in view of our previous findings.[4,5] Regression analysis results for each cognitive outcome versus tumor type, adjusting for age, education, and treatment, showed that tumor type was not significantly associated with any of the cognitive tests ($P > 0.05$); therefore, this variable was not included in the multivariate regression analyses with the SNPs. Time since treatment completion did not differ among the 4 tumor histology subgroups (Kruskal–Wallis, $P = 0.52$).

We used a Bayesian shrinkage approach to estimate the effects of SNPs from each of the 7 pathways in the corresponding multivariable regression models, considering the large number of SNPs and limited sample size. This approach builds on our prior work where we demonstrated its superior sensitivity and specificity relative to standard multivariable analyses.[22] Briefly, the analysis of each cognitive outcome and SNPs from each pathway proceeded by first specifying a likelihood function using the multivariable model relating an outcome, the multiple SNPs, and the adjustment variables. Next, we specified independent *a priori* normal distributions with mean zero and an unknown variance for the SNP effects to shrink the effects of seemingly null SNPs toward zero. We obtained shrinkage estimates of the effects of the SNPs via a Markov chain Monte Carlo procedure.[23]

To determine whether an SNP (or one of the 2 categories of an SNP) is associated with a cognitive test, we derived a novel measure known as the *posterior association summary* (PAS), which can be interpreted as the complement of local false discovery rate,[24,25] or the probability that the effect of that SNP is not equal to 0, given the observed data, adjusted for evaluating multiple SNPs. PAS takes value between 0.5 (= no association with outcome) and 1 (= strong association with outcome). We report SNPs with PAS ≥ 0.95 as being strongly associated with the outcomes. When an SNP has 3 genotype categories and, hence, has 2 effect estimates, we report the estimated effects and standard error of both the genotype categories even if the effect of only one genotype category had PAS ≥ 0.95.

We analyzed WM ratings using logistic regression analysis, adjusting for the same variables described above. We fitted separate multivariable logistic regression models for each pathway and derived Bayesian shrinkage estimates of the odds ratio parameters using a Markov chain Monte Carlo technique as described above. The only difference was that the likelihood function was derived using the logistic regression model for these analyses.

All the analyses were performed using the R programming language version 3.0.1 (http://www.R-project.org/).[26] We implemented Bayesian shrinkage estimation via Markov chain Monte Carlo using the rjags software package with an interface to the R programming language. Supplementary Table 4 describes the rjags program and technical details related to implementing the estimation approach.

Data Availability

The de-identified data that support the study findings are available upon reasonable request from the corresponding author. The data are not publicly available because of information that could compromise the privacy of the research participants.

Results

Table 2 summarizes the number of genes and SNPs in each pathway included in the statistical analysis. Data were missing for *APOE* ε4 in one patient and for *REST*-rs7680799 in another patient. Since only 2 patients have missing data in 2 genetic factors, we imputed the missing genotypes for these individuals as the genotype having the largest frequency. The sample size was 150 patients for all pathways, except for the BBB pathway, which included 105 patients treated with RT ± CT. Supplementary Table 5 lists cognitive test *z*-scores for all patients; 23–56% had *z*-scores at least 0.5 SD below normative values for a given test.

Multivariable regression shrinkage analyses adjusting for age, education, tumor location, treatment with RT ± CT, time since treatment, and *APOE* ε4 status for the LOAD and dopamine pathways showed strong associations (PAS ≥ 0.95) between at least one cognitive test and alleles in (i) 7 SNPs in 7 LOAD/inflammation/cholesterol transport genes, (ii) 8 SNPs in 4 dopamine regulation genes, (iii) 8

Table 2 Pathways, genes, and SNPs investigated in the current study

Pathways	Number of Genes in Analysis	Number of SNPs in Analysis
LOAD+	22	38
Dopamine	7	24
Myelin	6	91
DNA repair	37	171
Cell cycle	2	19
Response to oxidative stress	4	8
Blood–brain barrier disruption	3	6
Total	**81**	**357**

LOAD+ = includes genetic variants known to be associated with late-onset Alzheimer's disease risk, and SNPs in the inflammation and cholesterol transport pathways.

SNPs in 4 myelin regulation genes, (iv) 6 SNPs in 6 DNA repair genes, (v) 2 SNPs in one cell cycle regulation gene, and (vi) 2 SNPs in 2 response to oxidative stress genes (Tables 3–6).

LOAD/inflammation/cholesterol transport pathway (Table 3)

PDE7A-rs10808746 was strongly associated with the cognitive outcomes, with GG carriers having higher scores in executive function and memory, and AG carriers having *lower* scores in attention. Alleles in *SORCS1*-rs12219216, *APOE*-rs584007, *IL-6*-rs1474348, and *ABCC1*-rs8187858 were strongly associated with higher scores in attention and executive functions. *IL-1*-rs1143634 and *ABCA7*-rs3764650 were strongly associated with memory, with carriers of variant alleles having *lower* scores.

Dopamine regulation pathway (Table 4)

Alleles in *DRD1*-rs4532 and *DRD4*-rs3758653 were strongly associated with higher scores in executive functions. *ANKK1*-rs34863235 was strongly associated with memory, with carriers of the variant allele having *lower* scores. Four SNPs in the *COMT* gene were strongly associated with attention and executive functions, with carriers of the variant alleles having *lower* scores. Carriers of the variants allele in *COMT*-rs165815 also had *lower* scores in memory.

Myelin regulation pathway (Table 5)

LINGO1-rs12898861-GG was strongly associated with *lower* scores in attention. *LINGO1*-rs11072660 was strongly associated with memory, with higher scores among AG carriers and *lower* scores among GG carriers. Alleles in *TNFRSF19/TROY*-rs9507406 and 3 SNPs in the *TCF4* gene (rs1217569, rs3760609, rs3760620) were strongly associated with higher scores in attention and/or executive functions. *TNFRSF19/TROY*-rs7989554-AC was strongly associated with reduced graphomotor speed, and *TNFRSF19/TROY*-rs9511424-GG was strongly associated with *lower* scores in memory.

DNA repair, cell cycle regulation, response to oxidative stress pathways (Table 6)

Alleles in *MGMT*-rs7075748, *TDP1*-rs1286254, and *XPC*-rs12493301 in the DNA repair pathway were strongly associated with *lower* scores in executive functions. Alleles in *RAD51*-rs12593359, *XRCC5*-rs670818, and *XRCC6*-rs12484029 were strongly associated with *lower* scores in memory. Alleles in *SESN1*-rs1951358 and *SESN1*-rs911475 in the cell cycle regulation pathway, and *GSTP1*-rs947895 in the response to oxidative stress pathway were strongly associated with *lower* scores in executive functions. *GSTM3*-rs11807 was associated with higher scores on processing speed.

White matter ratings

WM abnormalities were rated as moderate/severe (grade ≥ 2) in 65 (43%) patients, and none/minimal (grades 0–1) in 85 (57%) patients. The results of logistic regression analyses adjusting for the same variables as in the primary multivariate regression analyses showed that none of the SNPs in the 7 pathways were significantly associated with WM abnormalities.

Discussion

We provide new evidence that polymorphisms in pathways involved in LOAD/inflammation/cholesterol transport, dopamine, myelin, and cell cycle regulation, DNA repair, and response to oxidative stress are associated with neurocognitive function in brain tumor patients treated with RT ± CT. We found 33 polymorphisms in 23 genes with significant associations, and to the best of our knowledge, only one of these SNPs was previously reported in relation to cognition in this population. Variants in the dopamine and myelin regulation pathways were primarily associated with attention and executive functions, while variants in the LOAD/inflammation/cholesterol transport, cell cycle regulation, DNA repair, and response to oxidative stress were associated primarily with executive functions and memory. We have previously reported that in this patient cohort, *APOE* ε4 allele carriers had significantly lower scores in memory compared with non-ε4 carriers,[4] and that *COMT*, *BDNF*, and *DTNBP1* variants were also associated with cognitive outcome.[5] This more comprehensive study suggests that additional relevant genetic variants and pathways are associated with cognition in this clinical population.

LOAD/inflammation/cholesterol transport pathway

Our results suggest that polymorphisms in LOAD risk genes other than APOE[4] may also be associated with cognitive outcome. The *PDE7A*-rs10808746 GG genotype conferred better executive function and memory, while the AG genotype conferred worse attention. This SNP has been reported

Table 3 Multivariable regression shrinkage analyses results: associations between LOAD/inflammation/cholesterol transport SNPs and cognitive test *z*-scores

		N	DSF	DSB	TMT-A	TMT-B	BTA	VF	HVLT-L	HVLT-D	HVLT-DI
rs10808746	AA (ref)	40									
PDE7A	AG	78	–0.25(0.19)*	**–0.33(0.19)****	0.03(0.21)Δ	0.14(0.23)Δ			0.04(0.21)Δ	0.27(0.21)Δ	0.32(0.21)*
	GG	32	–1.0(0.22)Δ	0.08(0.22)Δ	**0.43(0.24)****	**0.46(0.26)****			**0.53(0.24)****	**0.54(0.25)****	0.34(0.25)*
rs12219216	AA (ref)	28									
SORCS1	AG	68			0.35(0.22)*	**0.46(0.25)****		0.34(0.23)*	0.30(0.23)*	0.37(0.23)*	
	GG	54			0.02(0.22)Δ	0.66(0.25)Δ		0.19(0.24)Δ	0.09(0.23)Δ	0.13(0.24)Δ	
rs584007	AA (ref)	26									
APOE	AG	66						0.07(0.24)Δ			
	GG	58						**0.60(0.26)****			
rs1143634	AA (ref)	65									
IL-1	AG	85						–0.38(0.23)		**–0.38(0.23)****	
rs1474348	CC (ref)	19									
IL-6	GC	62	0.27(0.22)Δ	0.01(0.22)Δ		–0.10(0.25)Δ	0.03(0.24)Δ	0.02(0.24)Δ	0.04(0.24)Δ		
	GG	69	0.32(0.22) Δ	**0.41(0.21)****		**0.47(0.25)****	0.32(0.23)*	0.38(0.24)*	0.36(0.24)*		
rs3764650	GT,G(ref)	31									
ABCA7	TT	119			0.32(0.23)*						**–0.43(0.24)****
rs8187858	CC (ref)	118									
ABCC1	TC,TT	32			**0.39(0.21)****						

Δ, PAS < 0.90; *PAS ≥ 0.90; ****PAS** ≥ **0.95**

DSF = Digit Span Forward; DSB = Digit Span Backward; TMT-B = Trail Making Test, Part B; BTA = Brief Test of Attention; VF = Verbal Fluency Test; HVLT-L = Hopkins Verbal Learning Test–Learning; HVLT-D = Hopkins Verbal Learning Test–Delayed Recall; HVLT-DI = Hopkins Verbal Learning Test–Discrimination Index.

Beta and standard error values for 7 SNPs retained in the multivariate regression models, controlling for age, education, treatment with RT ± CT, time since treatment, and tumor location.

Blank cells indicate that the SNP was not associated with the given cognitive test. SNPs and cognitive tests showing very strong (PAS ≥ 0.95) and strong (PAS ≥ 0.90) associations are included.

For SNPs with 3 categories, the effects and standard error of both categories are included even if only one category had PAS ≥ 0.95.

Table 4 Multivariable regression shrinkage analyses results: associations between dopamine regulation SNPs and cognitive test *z*-scores

		N	DSF	DSB	TMT-A	TMT-B	BTA	VF	HVLT-L	HVLT-D	HVLT-DI
rs4532	CC (ref)	18									
DRD1	CT	69		0.38(0.24)*	0.28(0.26)*		**0.59(0.27)****				
	TT	63		0.18(0.24)Δ	**0.49(0.27)****		**0.45(0.27)****				
rs3758653	TC,CC (ref)	65									
DRD4	TT	85			0.27(0.19) *		–0.24(0.18)*	**0.36(0.19)****			
rs34863235	CC (ref)	102									
ANKK1	TC,TT	48						0.29(0.20)*			**–0.34(0.20)****
rs165774	AG,AA (ref)	68									
COMT	GG	82	**–0.49(0.21)****								
rs165815	AA (ref)	101									
COMT	AG,GG	49	–0.37(0.23)*	–0.33(0.22)*				**–0.66(0.26)****	**–0.61(0.25)****	**–0.42(0.26)****	–0.33(0.25)*
rs174696	AA (ref)	95									
COMT	AG,GG	55					**–0.43(0.24)****				
rs740603	AA (ref)	29									
COMT	AG	68	0.36(0.26)*			0.31(0.30)*	**0.46(0.28)****	0.38(0.29)*			
	GG	53	0.12(0.30)Δ			–0.56(0.36)*	–0.08(0.33)Δ	–0.03(0.34)Δ			
rs9332377	AG,AA (ref)	54									
COMT	GG	96	–0.35(0.22)*			–0.35(0.26)*	–0.37(0.23)*	**–0.49(0.25)****	–0.34(0.23)*		

Δ, PAS < 0.90; *PAS ≥ 0.90; ****PAS** ≥ **0.95**

DSF = Digit Span Forward; DSB = Digit Span Backward; TMT-B = Trail Making Test, Part B; BTA = Brief Test of Attention; VF = Verbal Fluency Test; HVLT- L = Hopkins Verbal Learning Test–Learning; HVLT-D = Hopkins Verbal Learning Test–Delayed Recall; HVLT-DI = Hopkins Verbal Learning Test–Discrimination Index.

Beta and standard error values for 8 SNPs retained in the multivariate regression models, controlling for age, education, treatment with RT ± CT, time since treatment, and tumor location.

Blank cells indicate that the SNP was not associated with the given cognitive test. SNPs and cognitive tests showing very strong (PAS ≥ 0.95) and strong (PAS ≥ 0.90) associations are included.

For SNPs with 3 categories, the effects and standard error of both categories are included even if only one category had PAS ≥ 0.95.

Table 5 Multivariable regression shrinkage analyses results: associations between myelin regulation SNPs and cognitive test *z*-scores

		N	DSF	DSB	TMT-A	TMT-B	BTA	VF	HVLT-L	HVLT-D	HVLT-DI
rs12898861	AA(ref)	25									
LINGO-1	AG	72					0.01(0.22)$^{\Delta}$				
	GG	53					**–0.46(0.23)****				
rs11072660	AA(ref)	32									
LINGO1	AG	74							**0.36(0.22)****	0.32(0.23)$^{\Delta}$	
	GG	44							–0.10(0.25)*	–0.14(0.26) *	
rs1217569	AG,A(ref)	55									
TCF4	GG	95			**0.38(0.20)****						
rs3760609	AA(ref)	20									
TCF4	AG	70	–0.19(0.21)$^{\Delta}$	–0.21(0.22)$^{\Delta}$							
	GG	60	**0.39(0.24)****	0.32(0.22)*							
rs3760620	AA(ref)	92									
TCF4	GG,AG	58		**0.39(0.19)****		**0.38(0.22)****	0.28(0.20)*	0.28(0.21)*			
rs7989554	AA(ref)	23									
TNFRSF19	AC	71	–0.04(0.22)$^{\Delta}$		**–0.48(0.23)****						
	CC	56	–0.36(0.25)*		–0.18(0.25)$^{\Delta}$						
rs9507406	AA(ref)	111									
TNFRSF19	AG,GG	39		**0.39(0.21)****	**0.49(0.23)****						
rs9511424	AG,AA(ref)	56									
TNFRSF19	GG	94							**–0.32(0.21)****	**–0.36(0.22)****	

Δ, PAS < 0.90; *PAS ≥ 0.90; ****PAS** ≥ **0.95**

DSF = Digit Span Forward; DSB = Digit Span Backward; TMT-B = Trail Making Test, Part B; BTA = Brief Test of Attention; VF = Verbal Fluency Test; HVLT- L = Hopkins Verbal Learning Test– Learning; HVLT-D = Hopkins Verbal Learning Test–Delayed Recall; HVLT-DI = Hopkins Verbal Learning Test–Discrimination Index.

Beta and standard error values for 8 SNPs retained in the multivariate regression models, controlling for age, education, treatment with RT ± CT, time since treatment, and tumor location.

Blank cells indicate that the SNP was not associated with the given cognitive test. SNPs and cognitive tests showing very strong (PAS ≥ 0.95) and strong (PAS ≥ 0.90) associations are included. For SNPs with 3 categories, the effects and standard error of both categories are included even if only one category had PAS ≥ 0.95

Table 6 Multivariable regression shrinkage analyses results: associations between DNA repair, cell cycle regulation, and response to oxidative stress SNPs and cognitive test *z*-scores

		N	DSF	DSB	TMT-A	TMT-B	BTA	VF	HVLT-L	HVLT-D	HVLT-DI
rs7075748	AA (ref)	68									
MGMT (DNA repair)	AG,GG	82	–0.27(0.19)*					**–0.45(0.21)****			
rs12593359	AA (ref)	42									
RAD51 (DNA repair)	AC	72			–0.01(0.19)$^{\Delta}$	–0.10(0.20)$^{\Delta}$			–0.16(0.19)$^{\Delta}$	–0.09(0.20)$^{\Delta}$	–0.08(0.19)$^{\Delta}$
	CC	36		.	–0.30(0.21)*	–0.35(0.23)*			–0.36(0.22)*	–0.34(0.23)*	**–0.38(0.21)****
rs1286254	AA (ref)	46									
TDP1 (DNA repair)	AG	72						**–0.36(0.21)****			
	GG	32						–0.01(0.23)$^{\Delta}$			
rs12493301	AA (ref)	43									
XPC (DNA repair)	AG	64			**–0.39(0.20)****	–0.28(0.21)*		–0.22(0.20)$^{\Delta}$			
	GG	43			–0.13(0.20)$^{\Delta}$	–0.15(0.20)$^{\Delta}$		–0.26(0.20)*			
rs6708185	AA (ref)	35									
XRCC5 (DNA repair)	AG	77							–0.01(0.21)$^{\Delta}$		0.20(0.20)$^{\Delta}$
	GG	38							–0.29(0.22)*		**–0.37(0.21)****
rs12484029	AA (ref)	71									
XRCC6 (DNA repair)	AG	62			–0.27(0.19)*				**–0.38(0.20)****		–0.28(0.18)*
	GG	17			–0.20(0.23)$^{\Delta}$				–0.24(0.23)$^{\Delta}$		–0.06(0.22)$^{\Delta}$
rs1951358	AA,AG (ref)	53									
SESN1 (Cell Cycle)	GG	97						**–0.57(0.32)****			
rs911475	AA,AG (ref)	33									
SESN1 (Cell Cycle)	GG	117						**–0.58(0.33)****			
rs11807	AA (ref)	105									
GSTM3 (Oxidative)	AG,GG	45			**0.41(0.20)****						
rs947895	AA,AC (ref)	77									
GSTP1 (Oxidative)	CC	73				**–0.64(0.32)****					

Δ, PAS < 0.90; *PAS ≥ 0.90; ****PAS ≥ 0.95**

DSF = Digit Span Forward; DSB = Digit Span Backward; TMT-B = Trail Making Test, Part B; BTA = Brief Test of Attention; VF = Verbal Fluency Test; HVLT-L = Hopkins Verbal Learning Test–Learning; HVLT-D = Hopkins Verbal Learning Test–Delayed Recall; HVLT-DI = Hopkins Verbal Learning Test–Discrimination Index.

Beta and standard error values for 6 SNPs (DNA Repair); 2 SNPs (Cell Cycle); 2 SNPs (Oxidative Stress) retained in the multivariate regression models, controlling for age, education, treatment with RT ± CT, time since treatment, and tumor location.

Blank cells indicate that the SNP was not associated with the given cognitive test. SNPs and cognitive tests showing very strong (PAS ≥ 0.95) and strong (PAS ≥ 0.90) associations are included.

For SNPs with 3 categories, the effects and standard error of both categories are included even if only one category had PAS ≥ 0.95.

in association with cognitive decline in older adults and in Alzheimer's disease (AD) patients, particularly in the domains of episodic memory, working memory, and processing speed.[8] In our study, *SORCS1*-rs12219216 was associated with executive function and memory. Other *SORCS1* variants were found to influence pathology[27] and memory[28] in AD. *APOE*-rs584007 was associated with executive function, consistent with our prior report that other variants in this gene may modulate cognitive outcome in this population.[4]

Recent studies have described a role for the immune system in AD and suggested that inflammation may contribute to neurodegeneration.[29] Genome-wide association studies have identified several LOAD risk genes involved in inflammation.[7] We found that *IL-1*-rs1143634-AG carriers had worse memory and executive function. Other gene variants in *IL-1* have been described in association with inflammatory diseases and LOAD risk.[10] A variant in *IL-6* (rs1912124) was reported previously in association with executive function in newly diagnosed glioma.[6] Although rs1912124 was not significant in our study, another *IL-6* variant, rs1474348, was associated with attention, executive functions, and memory. This SNP is in high LD ($r > 0.8$) with rs1800795 (–174G > C), which has been reported to modulate the release of inflammatory cytokines in the brain and influence neurodegeneration.[30]

ABCA7-rs3764650, which was associated with worse memory, is likely to affect binding of transcription factors and weaken transcription (RegulomeDB,[31] Supplementary Table 1). Associations with processing speed were evident for SNPs in the *ABCC1* and *ABCA7* genes, including *ABCC1*-rs8187858, which was reported in association with processing speed in newly diagnosed glioma.[6] Variants in *ABC* transporter genes have been reported to influence neuroinflammation, cholesterol homeostasis, and LOAD risk,[7] and the *ABCC1* and *ABCA7* genes were also linked to AD.[9]

These findings suggest that polymorphisms in this pathway were associated primarily with executive functions and memory, with variants in genes involved in inflammation and cholesterol transport having adverse effects on memory.

Dopamine regulation pathway

There is evidence that dopaminergic genes influence receptor densities in the prefrontal cortex,[32] and that dopamine availability plays an important role in modulating attention and working memory.[33] In our study, SNPs in the *DRD1* and *DRD4* genes were associated with better attention and executive function. SNP rs3758653 in the *DRD4* gene, which is widely expressed in the frontal cortex, was found to be associated with processing speed in healthy adults,[34] suggesting it has an important role in modulating executive functions. SNPs in dopamine receptor genes *DRD1*, *DRD2/ANKK1*, and *DRD4* have been found to influence prefrontal neural networks[35] and to modulate memory in older adults.[36] In our patients, we found that *ANKK1*-rs34863235 was associated with worse memory. This SNP has not been reported previously; however, it is in LD ($r^2 = 0.4$) with rs1800497 (https://www.broadinstitute.org/snap/, accessed in March 2018), a widely studied polymorphism reported in association with reduced striatal D2 receptor density, with disorders of reward deficiency,[37] and associative memory in older adults.[36]

COMT is an important regulator of prefrontal dopamine levels,[38] and studies have reported that carriers of the G (Val) allele of *COMT*-rs4680 degrade dopamine faster[18] and perform worse on executive function tests than carriers of the A (Met) allele.[38] In this study, *COMT* SNPs were associated with worse attention and executive functions and SNP rs165815 was also associated with worse memory, which is consistent with the results from our prior report.[5]

Our data provide further evidence that SNPs in dopamine regulation genes are associated primarily with attention and executive functions. The underlying mechanisms are unknown; however, it is possible that in those carrying certain genotypes/alleles, particularly in the *COMT* and *ANKK1* genes, disease and treatment further disrupt the availability of dopamine and diminish the efficiency of cognitive functions mediated in part by the frontal lobes.

Myelin regulation pathway

The haplotype tagging SNP rs12898861 (GG) was associated with worse attention. SNP rs11072660 was associated with memory, with AG carriers having higher scores and GG carriers having lower scores. These SNPs are located on the leucine rich repeat and immunoglobulin domain containing 1 (*LINGO-1*) gene, which is expressed selectively in the CNS on oligodendrocytes and neurons.[39] LINGO-1 is a component of the neurite outgrowth inhibitor (Nogo) receptor complex and a negative regulator of oligodendrocyte differentiation, axonal formation, and myelination.[13] LINGO-1 is overexpressed in WM lesions in multiple sclerosis.[40]

TNFRSF19/TROY SNPs were associated with attention and executive functions, with rs7989554-AC carriers having slower processing speed and worse attention, and *TNFRSF19*-rs9511424-GG carriers having worse memory. TNFRSF19/TROY is a tumor necrosis factor (TNF) receptor family member selectively expressed in the adult nervous system. With Nogo and LINGO-1, it forms a functional receptor complex and inhibits myelin formation.[41] The Nogo complex modulates plasticity, and decreased Nogo messenger RNA levels have been observed in the hippocampus of aged rats.[42] SNPs in the *TCF4/TCF712* gene were associated with better attention and executive functions, while rs3760609-AG carriers had worse attention. To our knowledge, there is no functional evidence for the impact of these SNPs. TCF4/TCF712 is an oligodendroglial transcription factor that regulates myelin gene expression during myelination and remyelination, and inhibits oligodendrocyte differentiation and remyelination in multiple sclerosis.[43]

The findings suggest that genes involved in myelin regulation were associated primarily with attention and executive functions. Demyelination has been widely reported as a delayed adverse effect of RT and CT,[11] and further investigation of the role of polymorphisms in genes that inhibit oligodendrocyte differentiation and myelination on modulating the risk for treatment-related neurotoxicity is warranted. It is noteworthy that in our study, ratings of WM abnormalities were not associated with myelin regulation

polymorphisms, despite the associations with cognitive function. This may be in part due to reduced sensitivity and restricted range of the scale.

DNA repair, cell cycle regulation, and response to oxidative stress pathways

RT and CT achieve therapeutic effect in part through DNA damage by introducing interstrand DNA and DNA-protein crosslinks, single- and double-stranded DNA breaks, methylation, and oxidation and by increasing formation of reactive oxygen species. Nontumor cells are also affected, and the accumulation of DNA damage in neuronal and glial cells can result in neurodegeneration.[12] In our cohort, *TDP1*-rs1286254, *MGMT*-rs7075748, and *XPC*-rs12493301 SNPs were associated with worse executive functions. We found no other reports regarding the haplotype tagging SNP in *TDP1* and the intronic *MGMT* SNP. It is possible that certain genotypes or alleles in these genes result in greater accumulation of posttreatment damage, systemic or in the CNS, resulting in cognitive dysfunction. In silico predictions suggest that rs12493301 in *XPC* overlaps with the translation factor sex determining region Y box 5 (Matrix ID V$SOX5_01), although the functional implications are not yet understood.

XRCC5-rs6708185 and *XRCC6*-rs12484029 were associated with worse memory. SNPs in the *XRCC* genes were described in association with susceptibility to glioma and other cancers,[44] and reported to be potential biomarkers of RT efficacy.[45] *RAD51* is involved in double-stranded DNA break repair after exposure to ionizing radiation, and has also been associated with resistance to CT in glioblastoma.[46] The rs12593359-CC, associated with worse memory and executive functions in our cohort, is located within the 3′ untranslated region of the *RAD51* gene, potentially affecting miRNA-binding sites and RAD51 mRNA expression.[47]

Two *SESN1* SNPs, reported to influence cellular response to DNA damage, including oxidative stress and radiation,[16] were associated with worse executive function. The tagging SNP rs1951358 is likely to be functional (RegulomeDB score 2b, Supplementary Table 1). A recent study reported that variants in genes related to response to oxidative stress, including *GSTP1*, were associated with attention difficulties in childhood leukemia survivors.[48] SNP rs947895 in the *GSTP1* gene was associated with worse executive function in our cohort, although the underlying mechanism is not yet known. Thus, our findings suggest that polymorphisms in these pathways may be associated with worse cognitive outcome, particularly in executive function and memory.

There are several limitations to the present study. First, considering the cross-sectional design, we cannot exclude the possibility that some of the lower cognitive test scores seen in association with several SNPs and genotypes were related to preexisting cognitive dysfunction in risk allele carriers, or to an interaction with other factors inherent to the disease and treatment modalities. Although a relatively small number of patients had cognitive scores in the impaired range, there was a range of scores, with several falling below expected levels considering the estimated high average mean IQ (1 SD above norms) and education level of this cohort. Our goal was to assess the association of SNPs and cognitive performance, but it is possible that the number of low scores influenced the ability to detect significant associations. Second, the relatively small sample size limited the power to detect small to moderate size effects, and assess the associations with disease-related factors, such as tumor grade and type, location and treatment with RT or CT, and time elapsed since treatment. Also, due to the limited sample size, we did not examine interactions among SNPs in our analyses. Third, it is possible that the sensitivity of the WM rating scale was inadequate to detect associations between the severity and distribution of WM lesions and the genetic variants. Measurements of brain volume and WM integrity may provide greater sensitivity to detect the involvement of these genes in the development of treatment-related changes in brain structure. Fourth, it is possible that some of the observed effects in our study were due to other linked, yet not tested, polymorphisms. This would likely explain the opposite direction of the effects for some of the genetic variants that were observed across cognitive tests. A follow-up study on a larger cohort will permit confirmation of our findings.

Despite these limitations, this is the first comprehensive investigation addressing several relevant pathways, and our findings demonstrate that polymorphisms in genes involved in aging, inflammation, cholesterol transport, dopamine and myelin regulation, and DNA repair may also be important in modulating cognitive outcome in patients with brain tumors, and may contribute to individual patient vulnerability to treatment-related neurotoxicity. Although these associations may not be specific to brain tumor patients, our data suggest that these patients may be at greater risk for cognitive dysfunction through several mechanisms involved in aging and less efficient neuroplasticity, regulation of dopamine and myelin, and repair of DNA damage related to their disease and its treatment. A large prospective study would be required to validate the role of the SNPs described, and to investigate additional relevant genes. The understanding of the mechanisms and risk factors for cognitive dysfunction associated with the adverse effects of cancer treatments is becoming increasingly relevant as many patients are living longer. This research would ultimately contribute to the identification of patients at increased risk for treatment-related neurotoxicity, guide the implementation of targeted interventions to prevent or reduce their negative impact, such as the use of emerging therapies with neuroprotective effects for treating inflammation[49] and demyelinating disorders,[50] and assist in individualized treatment planning through an assessment of neurotoxicity risk.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

brain tumors | cognitive | genes | polymorphisms | SNP

Funding

Funding for this project was provided by The Brain Tumor Center, Survivorship Outcomes and Risk (P30 CA008748 Core Grant), and The Society of MSK (to D.D.C. and I.O.). Partial support for analytic contributions was provided by the National Cancer Institute (R01 CA197402) (to J.S.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Acknowledgments

The study findings were presented in part at the Society for Neuro-Oncology Annual Meeting in November 2017, and at the International Cancer and Cognition Task Force Annual Meeting in April 2018.

Conflict of interest statement. Dr Correa serves on the editorial board of *Neuro-Oncology Practice*. Dr DeAngelis serves on the editorial boards of *Neurology, Journal of Neuro-Oncology, Open Clinical Cancer Journal, CNS Oncology, Neuro-Oncology, and Neuro-Oncology Practice*. Dr Karimi is the principal investigator on a grant from Bayer Pharmaceuticals. No other authors have conflicts of interest.

Authorship statement. The authors were involved in various components of the study, including: conceptualization and design (D.D.C. and I.O.), patient identification (D.D.C., L.M.D.), data collection (D.D.C., E.B., M.K-L., I.O.), cognitive data processing and tabulation (D.D.C., E.B., M.K-L.), design of genetic assays (I.O., S.D.), laboratory experiments and compilation of data (K.C., A.S., S.D., K.O., S.L.), MRI ratings (S.K., J.L.), and biostatistical analyses (J.S. and A.M.). All authors contributed to the interpretation of the findings, manuscript preparation and editing, and approval of the final version.

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