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Short communication

SWI/SNF gene variants and glioma risk and outcome

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ABSTRACT

Background: The human SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex plays essential roles in a variety of cellular processes and has been implicated in human cancer. However, the role of germline genetic variants in this complex in relation to cancer risk is not well studied. *Methods*: We assessed the association of 16 variants in the catalytic subunits (*SMARCA2* and *SMARCA4*) of the SWI/SNF complex with the risk of glioma subtypes (lower grade astrocytoma, oligodendroglioma and glioblastoma [GBM]) and with mortality from high-grade tumors (GBM) in a multicenter US case–control study that included 561 cases and 574 controls. Associations were estimated with odds ratios (OR, for risk) or hazards ratios (HR, for mortality) with 95% confidence intervals (CI). False discovery rate (FDR-*q*) was used to control for multiple testing in risk associations. *Results*: None of the investigated SNPs was associated with overall glioma risk. However, analyses according to histological subtypes revealed a statistically significant increased risk of oligodendroglioma in association with *SMARCA2* rs2296212 (OR = 4.05, 95%CI = 1.11–14.80, $P = 0.030$, $q = 0.08$) and rs4741651 (OR = 4.68, 95%CI = 1.43–15.30, $P = 0.011$, $q = 0.08$) and *SMARCA4* rs11672232 (OR = 1.90, 95%CI = 1.01–3.58, $P = 0.048$, $q = 0.08$) and rs12232780 (OR = 2.14, 95%CI = 1.06–4.33, $P = 0.035$, $q = 0.08$). No significant risk associations were observed for GBM or lower grade astrocytoma. Suggestive associations with GBM mortality were not validated in the Cancer Genome Atlas. *Conclusion*: Our findings suggest that genetic variants in *SMARCA2* and *SMARCA4* influence the risk of oligodendroglioma. Further research is warranted on the SWI/SNF complex genes and epigenetic mechanisms more generally in the development of glioma in adults.

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1. Introduction

Glioma is the most common central nervous system tumor comprising approximately 80% of malignant brain tumors. Despite improvements in diagnosis and treatment, the prognosis of glioma remains dismal with a 5-year survival rate of less than 30% [1]. There is a paucity of information on the etiology of glioma. Familial aggregation [2] and the identification of common [3,4] and rare [5] genetic susceptibility variants suggest a genetic predisposition to this disease. However, the currently known genetic variants may collectively account for a small proportion of cases and more variants remain to be identified.

Chromatin structure plays an important role in the regulation of gene expression and perturbation in chromatin structure is important in cancer development [6]. The human SWItch/Sucrose Non-Fermentable (SWI/SNF) complex modulates the structure of chromatin and thus plays an important role in cancer development [6]. Somatic mutations in subunits of the complex including, BRM/*SMARCA2* and BRG1/*SMARCA4*, have been observed in several human cancers including brain tumors [6,7]. BRG1 expression is elevated in human glioma tumor tissue samples compared to normal brain tissue [8]. Furthermore, *SMARCA2* is expressed in proliferating neural stem cells and the conversion of rat oligodendrocyte precursor cells to multipotent neural stem-like cells is mediated, in part, by *SMARCA2* [9].

Because of the important role of *SMARCA2* and *SMARCA4* in neural development and cancer, we investigated for the first time whether genetic variants in these genes are associated with the risk of glioma subtypes and mortality in 561 cases and 574 controls in a clinic-based case–control study in the United States.

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2. Materials and methods

2.1. Study population

Details of the study protocols are reported elsewhere [10]. The study population comprised Caucasian participants (United States residents only) in a clinic-based case–control study in the Southeastern United States. The present analysis included participants enrolled between 2004 and 2010 and followed up till March 2012. Cases had histologically confirmed primary glioma and were enrolled a median of one month following tumor diagnosis. Controls were friends, in-laws and other associates of the cases and persons from the same communities as the cases with no previous history of brain tumor. Controls were frequency matched to cases on age, gender and residence. Eighty-seven percent of eligible glioma cases participated in the study and 49.6% of confirmed eligible households yielded a control participant.

The study was approved by Investigational Review Committees at each participating center and all subjects provided written informed consent.

2.2. Biospecimen and data collection and genotyping

DNA samples were self-collected by oral rinse or the saliva method using Oragene kits (www.dnagenotek.com) and extracted using standard protocols [10]. Information on demographic characteristics and risk factors for glioma were obtained *via* in-person interview.

SNPs in *SMARCA2* ($N = 8$) and *SMARCA4* ($N = 9$) were selected based on SNP information from unrelated Caucasian samples in Hapmap using a minor allele frequency (MAF) ≥ 0.05. Genotyping was attempted on 599 glioma cases and 619 controls using the Taqman Open Array system under previously described conditions [10]. A total of 83 participants (38 cases [6.3%] and 45 controls [7.3%]) were excluded due to low (<80%) call rates, leaving 561 cases and 574 controls in the final analysis. All of the 17 SNPs in *SMARCA2/4* were successfully genotyped. The mean sample call rate was 98.6% and the mean concordance for 70 duplicate samples was 99.7%. One SNP in *SMARCA4* (rs1801514) was monomorphic and was therefore excluded from further analysis.

2.3. The Cancer Genome Atlas data

We attempted to validate mortality associations using independent data from The Cancer Genome Atlas (TCGA). TCGA has genotype, demographic and clinical data on various cancer sites (including GBM) that are freely available and widely used by cancer researchers [11]. For comparability to our data, we limited analysis of the TCGA data to Caucasians aged 19–89 years. Seven of the SNPs were genotyped, and 8 other SNPs had suitable proxies ($r^2 = 0.8$) in TCGA, whereas no counterpart could be identified for one SNP (rs11672232).

2.4. Statistical analysis

Genotypes among participants were used to estimate allele frequencies and departure from Hardy–Weinberg equilibrium (HWE) was assessed among control subjects using Fisher's exact test. The association between each SNP and glioma risk (overall or histological subtypes) was estimated with odds ratios (OR) and 95% confidence intervals (CI) using unconditional logistic regression. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% CIs for the association between SNPs and mortality among patients with GBM (the most prevalent histological subtype). A total of 262 GBM-related deaths occurred in a median of 13.3 months (range: 0.79–62.0 months) following diagnosis. The 43 surviving patients were followed a median of 30.5 months (range: 7.4–55.7 months). Survival time was defined as the time from GBM diagnosis to death or last contact among surviving cases.

Three inheritance genetic models (log-additive, dominant and recessive) were tested for each outcome and the model with the minimum *P*-value was considered as the best genetic model [12]. All regression models included terms for age and gender. Statistical analysis was performed using SAS Version 9.1 (SAS Institute, Inc., Cary, NC) and statistical significance was defined as a two-sided *P*-value < 0.05. False discovery rate (FDR) *q*-values were calculated to adjust for multiple testing.

3. Results

Descriptive information on study populations is shown in Table 1. None of the SNPs was associated with overall glioma risk (Supplementary Table 1). Analyses according to histological subtypes revealed a statistically significant increased risk of oligodendroglioma in association with *SMARCA2* rs2296212 (OR = 4.05, 95%CI = 1.11–14.80, $P = 0.030$, $q = 0.08$) and rs4741651 (OR = 4.68, 95%CI = 1.43–15.30, $P = 0.011$, $q = 0.08$) and *SMARCA4* rs11672232 (OR = 1.90, 95%CI = 1.01–3.58, $P = 0.048$, $q = 0.08$) and rs12232780 (OR = 2.14, 95%CI = 1.06–4.33, $P = 0.035$, $q = 0.08$) (Table 2). The two SNPs in *SMARCA2* were perfectly correlated ($r^2 = 1.0$), but no correlation was observed for the two *SMARCA4* SNPs. No significant risk associations were observed for GBM or lower grade astrocytoma (Table 2).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2012.12.001.

SMARCA2 rs13288443 (HR = 0.36, 95%CI = 0.13–0.99, $P = 0.049$) was associated with increased GBM mortality in our data (Supplementary Table 2). This SNP was not genotyped in TCGA, but results for a highly correlated ($r^2 = 0.85$) SNP (*SMARCA2* rs12003289) did not validate our finding in the TCGA data (Supplementary Table 2).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2012.12.001.

Table 1
Characteristics of study participants.

	GliomaSE[a]		TCGA[b]
	Cases ($N = 561$)	Controls ($N = 574$)	Cases ($N = 281$)
Age, median (range)	51 (18–88)	55 (19–87)	58 (19–89)
Gender, *N* (%)			
Male	352 (62.8)	327 (57.0)	178 (63.4)
Female	209 (37.3)	247 (43.0)	103 (36.6)
State of residence, *N* (%)			
Tennessee	151 (26.9)	187 (32.6)	–
Florida	149 (26.6)	138 (24.0)	–
Alabama	94 (16.8)	78 (13.6)	–
Kentucky	69 (12.3)	75 (13.1)	–
Georgia	64 (11.4)	60 (10.5)	–
Other[c]	34 (6.1)	36 (6.3)	–
Histological subtype,[d] *N* (%)			
Glioblastoma	305 (54.4)	–	281 (100.0)
Lower grade astrocytoma	138 (24.6)	–	–
Oligodendroglioma	83 (14.8)	–	–
Other gliomas	35 (6.2)	–	–
Vital status for GBMs only			
Living	43 (14.1)	–	56 (19.9)
Deceased	262 (85.9)	–	225 (80.1)

[a] Southeastern study of glioma in adults.
[b] The Cancer Genome Atlas.
[c] Includes US residents in all the other states of the US.
[d] Histological subtypes were defined as previously reported [16].

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