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ORIGINAL ARTICLE

Glioma mutational signatures associated with haloalkane exposure are enriched in firefighters

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Abstract

Background: Glioma is the most common malignant primary brain tumor and is associated with significant morbidity and mortality. Modifiable risk factors remain unidentified. New advances in exposure assessment, genomic analyses, and statistical techniques permit more accurate evaluation of glioma risk associated with exogenous occupational or environmental exposures.

Methods: By using whole-exome sequencing data from matched germline and glioma tumor samples, the authors compared tumor mutational signatures for 17 persons with glioma and a documented occupational history of firefighting with those of 18 persons with glioma without an occupational history of firefighting. All 35 individuals were participants in the University of California, San Francisco Adult Glioma Study.

Results: There was a positive correlation among firefighters between the median number of sample variants attributable to single-base substitution signature 42, a single-base substitution mutational signature associated with haloalkane exposure (from the Catalogue of Somatic Mutational Signatures in Cancer) and firefighting years ($p = .04$; $R^2 = 0.29$). Among nonfirefighters, the individuals with the highest number of median variants attributable to single-base substitution signature 42 also had occupations that possibly exposed them to haloalkanes, such as painting and being a mechanic.

Conclusions: In summary, the authors identified gliomas that had mutational signatures associated with haloalkane exposure that were enriched in firefighters and other occupations.

KEYWORDS
epidemiology, firefighters, glioma, haloalkane, mutation, occupation, signature

INTRODUCTION

Gliomas are associated with significant morbidity and mortality, motivating attempts to discover risk factors through large-scale epidemiology, genetic, and neuropathology collaborations.[1–6] To date, with the exception of ionizing radiation[7] and possibly air pollution,[8,9] results are inconsistent for environmental factors, and most identified genetic variants conferring significant risk are rare.[7]

We recently identified specific mutational signatures matched to those reported in the Catalogue of Somatic Mutational Signatures in Cancer (COSMIC; Wellcome Sanger Institute) using 1000 gliomas available from The Cancer Genome Atlas (TCGA) and Glioma Longitudinal Analysis (GLASS).[1] Although most glioma mutation signatures were related to the aging process single-base substitution signature 1 (SBS1), signatures from environmental haloalkane exposures were present in some gliomas, particularly in men. This mutational signature (single-base substitution signature 42; SBS42) was first identified in association with occupational cholangiocarcinoma among the workers from a printing company in Japan.[10] Haloalkanes are widely used commercially (as well as in the home) in flame retardants, fire extinguishants, and pesticides and are an intriguing finding given the observed increased glioma risk noted in firefighters from the Adult Glioma Study (AGS).[5] Recently, in one of the first efforts to directly assess chemical exposure and glioma cell toxicity, researchers treated oligodendrocyte progenitor cells with a panel of almost 2000 chemicals and observed that organophosphate flame retardants prematurely arrested oligodendrocyte maturation, lending further support to the role of this exposure in gliomagenesis.[11]

MATERIALS AND METHODS

Because no data on occupational or environmental exposure histories were available for the TCGA/GLASS patient samples used in our prior analysis[1] and to validate our findings in a separate group of patients, we now compare mutational signatures for 17 individuals with glioma and a documented occupational history of firefighting versus those of 18 individuals who had glioma without an occupational history of firefighting. Individuals with glioma were drawn from the case–control University of California, San Francisco (UCSF) Adult Glioma Study (AGS), between 1991 and 2013.[5] The AGS included greater than 3000 adults aged 18 years and older who had a newly diagnosed glioma between 1991 and 1994 (series 1), 1997 and 1999 (series 2), 2001 and 2004 (series 3), 2006 and 2010 (series 4), and 2010 and 2013 (series 5). Population-based individuals with glioma (series 1–4) resided in the San Francisco Bay Area, and clinic-based patients (series 3–5) were recruited to participate while seeking care at the UCSF Neuro-Oncology Clinic, regardless of their place of residence. Participants were interviewed about various factors, including occupational history and treatment, and provided blood specimens at the time of the interview for research purposes. Pathology was centrally reviewed by a UCSF neuropathologist during the original recruitment period, and tumor specimens were obtained from consenting patients. Various tumor marker assays, including *IDH* mutation and 1p/19q co-deletion, were later conducted; World Health Organization 2016 diagnoses were later assigned to most of these patients.[3,12] From this patient cohort, we identified 17 firefighters with glioma for whom blood and tumor samples were available. Individuals with glioma ($n = 18$) who reported no occupational history of firefighting were matched to the firefighter group on age, sex, blood collection year, race, dexamethasone use, chemotherapy and radiation exposure before the collection of blood, days since chemotherapy, days since radiation, and glioma subtype.[6] Paired blood and treatment-naive tumor DNA samples from each patient were prepared at UCSF and sent to the Yale Center for Genomic Analysis for whole-exome sequencing.[13] Next-generation sequencing libraries were prepared from 100 ng each of paired normal whole-blood and formalin-fixed, paraffin-embedded tumor-derived DNA using the IDT xGen formalin-fixed, paraffin-embedded DNA library Prep Kit (Integrated DNA Technologies, Inc.). Paired-end, 100-base-pair sequencing was performed on the NovaSeq S4 platform to a depth of 50x for normal libraries and 100x for tumor-derived libraries (Illumina, Inc.).

Molecular data were prepared and analyzed with the cancereffectsizeR package,[14] which uses the MutationalPatterns package[15] for signature refitting and reports the number of substitutions within a sample attributable to each detectable signature. Data were filtered in accordance with the steps outlined by Cannataro et al. in 2022,[16] wherein all variants in >0.04% of any gnomAD subpopulation were dropped, along with variants not at a statistically different variant allele frequency with the paired normal sample (Boschloo exact test; dropped if $p > .05$). Variants within one or two base pairs of one another were also dropped because these variants are likely not independent (e.g., double-base substitutions). COSMIC signatures previously identified within glioblastoma multiforme (GBM)[17] were refit to all nonrecurrent single nucleotide variants within our data set.[18] Signatures were refitted 1000 times per sample using the bootstrapping functionality of MutationalPatterns. To highlight probable driver genes within our data that have a high likelihood of being attributable to the COSMIC SBS42 signature, GBM data from GLASS[19] and TCGA[20] were combined with our data and the dndscv package,[21] informed with GBM-specific covariates of mutation rate,[22] and used to detect genes with significantly more variants than expected under assumptions of neutrality. The probability that the SBS42 signature contributed to each variant, given the variant's trinucleotide context and the mutational weights within the tumor calculated in each bootstrap resampling, were calculated using cancereffectsizeR.[18]

RESULTS

The 17 firefighters and 18 nonfirefighters with glioma were primarily men (94%) who reported being White and of non-Hispanic ethnicity (Table 1). They worked as firefighters for an average of 22 years and were diagnosed approximately 7 years after the last reported firefighter exposure, on average. Most tumors were *IDH1/IDH2* wild type and of high grade (glioblastoma). Most participants received chemotherapy (temozolomide) and radiation prior to blood collection.

TABLE 1 Characteristics of University of California, San Franciso Adult Glioma Study participants diagnosed from 1991 to 2013 included in this report.

	Firefighters with glioma, $n = 17$		Nonfirefighters with glioma, $n = 18$[a]		
Characteristic	**No.**	**%**	**No.**	**%**	***p***
Age at diagnosis, years					
30–39	1	5.9	1	5.6	
40–49	3	17.6	3	16.7	
50–59	4	23.5	8	44.4	
60–69	8	47.1	4	22.2	
≥70	1	5.9	2	11.1	
Age: Average ± SD, years	56.3 ± 8.8		55.9 ± 9.6		.90
Sex					
Male	16	94.1	17	94.4	1.00
Female	1	5.9	1	5.6	
Race					
White	17	100.0	18	100.0	1.00
Non-White	0	0.0	0	0.0	
Ethnicity					
Hispanic	1	5.9	0	0.0	.49
Non-Hispanic	16	94.1	18	100.0	
Firefighting exposure, total years					
1–9	3	17.7	NA	—	
10–19	2	11.8	NA	—	
20–29	8	47.1	NA	—	
30–39	4	23.5	NA	—	
Average ± SD	22.2 ± 10.0				
Time from last firefighting exposure to diagnosis, years					
0-4	9	52.9	NA	—	
5-9	3	17.6	NA	—	
10-19	1	5.9	NA	—	
20-29	1	5.9	NA	—	
30-39	1	5.9	NA	—	
Unknown	2	11.8	NA	—	
Average ± SD	7.3 ± 10.9		—	—	
Histologic diagnosis					
Glioblastoma	12	70.6	12	66.7	.79
Astrocytoma, grade 3	1	5.9	1	5.6	
Astrocytoma, grade 2	2	11.8	2	11.1	
Oligodendroglioma, grade 3	1	5.9	0	0.0	
Oligodendroglioma, grade 2	0	0.0	2	11.1	
Oligoastrocytoma, grade 2	0	0.0	1	5.6	
Other	1	5.9	0	0.0	

(Continues)

TABLE 1 (Continued)

Characteristic	Firefighters with glioma, *n* = 17		Nonfirefighters with glioma, *n* = 18[a]		
	No.	%	No.	%	*p*
IDH1 mutation					
Wild type	14	82.4	14	77.8	1.00
Mutated	3	17.7	4	22.2	
1p/19q status[b]					
Not co-deleted	13	76.5	15	83.3	.00
Co-deleted	2	11.8	3	16.7	
Unknown	2	11.8	0	0.0	

	Median	IQR (min/max)	Median	IQR (min/max)
Tumor mutational burden, mutations/Mb	56.0	11.0 (26.0/69.0)	55.5	31.75 (25.0/102.0)
Mean contribution to mutation burden of SBS1[c]	0.369		0.382	

Abbreviations: IQR, interquartile range; max, maximum; min, minimum; NA, not applicable.; SBS1, single-base substitution signature 1 (glioma mutation signatures related to the aging process); SD, standard deviation.

[a]Two nonfirefighters with glioma were matched to the firefighter who had a noted *IDH* mutation but had unknown 1p/19q status. For this patient, we selected both a nonfirefighter with a low-grade *IDH*-mutant astrocytoma and another with an *IDH*-mutant oligodendroglioma.

[b]Some of these patients were classified as not co-deleted based on our Adult Glioma Study 1p/19q imputation algorithm.[3]

[c]Values indicate the clock-like Catalogue of Somatic Mutational Signatures mutational signature mean value among samples of the median SBS1 signature contribution after bootstrapping.

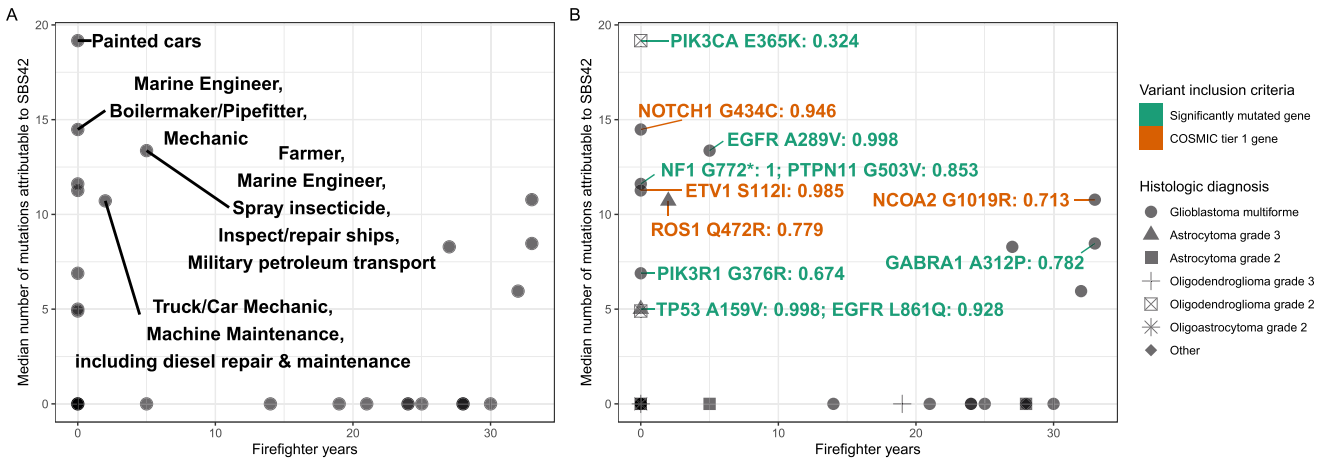

FIGURE 1 The median number of mutations attributable to SBS42 among 1000 bootstrap resamplings of variant data, with (A) occupations and (B) variants highlighted. (A) Points correspond to firefighters with a nonzero median SBS42 attribution who had <10 firefighting years and nonfirefighters who had the two greatest median attributable SBS42 mutations and had self-reported occupation. (B) Variants considered significantly mutated are highlighted ($Q < 0.1$; green text, with median probability [across 1000 bootstrap samplings] that each variant is attributable to SBS42). In addition, four tumors with >10 median attributable SBS42 variants but without a variant considered significantly mutated have a COSMIC tier 1-curated variant highlighted, (orange text, with the median probability [across 1000 bootstrap samplings] that each variant is attributable to SBS42). COSMIC indicates the Catalogue of Somatic Mutational Signatures in Cancer; SBS42, single-base substitution signature 42.

Thirteen of the 35 samples had a median number of variants attributable to SBS42 greater than zero (Figure 1). Among firefighters, there were two individuals with a high median number of variants attributable to SBS42 and a low number of firefighting years; however, these individuals had additional self-described occupations that possibly exposed them to haloalkanes, such as farming, pesticide use, and petroleum transport[23] (Figure 1A). Removing these two individuals, there was a positive correlation among firefighters between the median number of variants in the samples attributable to SBS42 and firefighting years ($p = .04$; $R^2 = 0.29$). Among nonfirefighters, the individuals with the highest number of median variants attributable to SBS42 also had occupations that possibly exposed them to haloalkanes, such as painting and being a mechanic (Figure 1A).

The SBS42 signature is the likely source of many variants within several samples and also is the most likely source of specific variants that are possible drivers of the cancer phenotype within these samples (Figure 1B). Among the 13 samples with a median SBS42 variant attribution greater than zero, six had at least one significantly mutated gene, of which five had a >50% median likelihood of SBS42 being the signature driving the variant. In addition, samples with >10 median variants attributable to SBS42 also contain variants in *NOTCH1*, *ROS1*, *ETV1*, and *NCOA2*—genes curated within the COSMIC tier 1 list of genes with documented activity relevant to cancer—with a >60% median likelihood of being attributable to SBS42.

CONCLUSIONS

Glioma is largely associated with aging and mutational signatures relating to endogenous mutational processes that correlate with age, such as spontaneous or enzymatic deamination of 5-methylcytosine. However, some gliomas have detectable signatures associated with exogenous mutational processes, such as SBS42 haloalkanes. In these data, we confirm detection of this signature in a cohort of individuals likely highly exposed to haloalkanes, i.e., long-term firefighters. Identifying exogenous mutational processes in cancers is extremely important because they may inform public health intervention strategies to reduce mutagenesis and prevent cancer inception. Identifying occupational correlates with SBS42, associated with occupational exposure to haloalkanes, will pinpoint occupational hazards that may be avoidable. This is especially important for cancers in which exogenous mutagenesis is not well established.

AUTHOR CONTRIBUTIONS

Vincent L. Cannataro: Software; formal analysis; data curation; writing—review and editing; methodology. **Paige M. Bracci**: Funding acquisition; writing—review and editing. **Jennie W. Taylor**: Funding acquisition; writing—review and editing. **Lucie McCoy**: Project administration; data curation; writing—review and editing. **Terri Rice**: Project administration; data curation; writing—review and editing. **Helen M. Hansen**: Data curation; project administration. **Anne E. Heffernan**: Formal analysis; writing—review and editing. **Joseph Wiemels**: Writing—review and editing. **John Wiencke**: Funding acquisition. **Margaret Wrensch**: Funding acquisition; writing—review and editing; project administration; supervision; resources. **Elizabeth B. Claus**: Conceptualization; investigation; funding acquisition; writing—original draft; project administration; supervision; resources; methodology.

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CONFLICT OF INTEREST STATEMENT

Paige M. Bracci reports stock ownership in Neuvivo Inc. outside the submitted work. C -advisory board Servier Pharmaceuticals Jennie W. Taylor reports grant funding from Servier Pharmaceuticals and Bristol-Meyers Squibb; advisory board fees from Servier Pharmaceuticals; consulting fees from Mount Sinai Health Systems and the

University of Colorado; and royalties from UpToDate outside the submitted work. Elizabeth B. Claus reports advisory board fees from Servier Pharmaceuticals outside the submitted work. John Wiencke is cofounder of Cellintec, which played no role in the current work. The remaining authors disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

Code is available at https://github.com/Cannataro-Lab/glioma_FF_haloalkane. The data that support the findings of this study are available upon reasonable request from the University of California, San Francisco authors at margaret.wrensch@ucsf.edu or lucie.mccoy@ucsf.edu. The data are not publicly available because of privacy or ethical restrictions.

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