HHS Public Access

Author manuscript

Clin Neurol Neurosurg. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Clin Neurol Neurosurg. 2019 February ; 177: 63–67. doi:10.1016/j.clineuro.2018.12.021.

Allergy may confer better survival on patients with gliomas

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Abstract

Objectives: Glioma susceptibility is inversely related to a history of allergies and atopy. Lung allergies are associated with 30% lower glioma susceptibility, compared to no lung allergies. Asthma and eczema also reduce the chance of glioma. However, the effect of allergy on glioma survival is not well characterized. Because of the allergy-glioma inverse relationship we examined the association of allergy with glioma survival in The Cancer Genome Atlas (TCGA).

Patients and methods: We evaluated the association between allergy and overall survival in TCGA Glioma (LGG) dataset. In order to have a sample of sufficient size to analyze, we classified as allergic any patient who answered yes to any of the manifestations of allergy that were queried.

Results: We analyzed data from 526 patients with glioma. History of allergy conferred a survival advantage on glioma patients, when stratified by tumor histologic grade ($p = 0.049$). Because allergy confers a favorable prognosis, we performed Cox regression. The effect of allergy on survival was significant ($p = 0.025$, HR 0.525, 95% CI 0.299–0.924), independent of the effect of chromosome 1p ($p < 0.001$, HR 93.4, 95% CI 16–546) and 19q ($p = 0.801$, HR 1.2, 95% CI 0.23–6.9) codeletion or TP53 mutation ($p = 0.015$, HR 2.7, 95% CI 1.2–5.9), unrelated to TERT expression ($p = 0.365$, HR 1.1, 95% CI 0.89–1.4) or ATRX mutation ($p = 0.904$, HR 1.04, 95% CI 0.51–2.14), independent of tumor grade (grade 2 versus grade 3, $p = 0.004$, HR 2.2, 95% CI 1.3–3.8), not independent of histology (oligodendroglioma and oligoastrocytoma, NOS versus astrocytoma, $p = 0.08$, HR 0.62, 95% CI 0.36–1.1). Diminished RNA expression of three loci, having reproducible genetic associations with allergic disease risk, are significantly associated with increased survival in glioma: FOSL2, APOBR, and NCF4. Diminished NCF4 copy number is significantly associated with reduced survival (D).

Conclusion: Our finding of the improved prognosis that allergy confers on glioma increases the potential importance of understanding the allergy-glioma inverse association. If the mechanism could be more clearly elucidated, new, more effective treatments and preventive measures may be developed. Further studies are warranted.

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Compliance with ethical standards

Full.

Conflict of interest

None.

Keywords

Glioma; Glioblastoma; Survival; Allergy; Atopy; The cancer genome atlas

1. Introduction

Glioma is a lethal malady of young adults with death occurring after approximately 7 years. Although glioma patients do better than patients with high grade (WHO grade III/IV) glioma, a majority of gliomas become fatal high grade gliomas. The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute indicates that glioma patients' grim prognosis has not improved in the past thirty years [1].

Glioma susceptibility is inversely related to a history of allergies and atopy. Lung allergies are associated with 30% lower glioma susceptibility, compared to no lung allergies. Asthma and eczema also reduce the chance of glioma [2].

The effect of allergy on glioma survival is not as well characterized. Glioblastoma patients with elevated IgE to four herpesviruses had 9 months longer survival than those with normal or borderline IgE levels [3].

Because of the allergy-glioma inverse relationship we examined the association of allergy with glioma survival in The Cancer Genome Atlas (TCGA). We also evaluated RNA expression, mutations, and copy number segments of genes related to both glioma and allergy.

2. Patients and methods

We examined the association between allergy and overall survival in the TCGA Glioma (LGG) dataset. TCGA contains the analysis of over 11,000 tumors from 33 of the most prevalent forms of cancer [4]. TCGA molecular profiling has already revealed biologically discrete subsets and pathways of progression in diffuse glioma [5]. We have changed the TCGA designation *oligoastrocytoma* to *oligoastrocytoma*, NOS in conformity with the 2016 WHO classifications [6].

To access and analyze the data we used:

- Genomic Data Commons Data Portal (https://portal.gdc.cancer.gov)
- UCSC Xena browser (https://xenabrowser.net). UCSC Xena is a web-based visual integration and exploration tool for TCGA data, including clinical and phenotypic annotations [7].
- Oncomine (https://oncomine.org)

Survival data of the glioma subgroup were extracted for analysis and generation of Kaplan–Meier curves for overall survival. Survival time was defined as the period from date of surgery to date of death. If unavailable, date of last follow-up was used for KM right censoring. The significance of prognostic factors was determined with a multivariate

analysis using Cox regression. Differences between Kaplan-Meier survival curves were calculated by the log-rank (Mantel-Cox) test.

Six manifestations of allergy (yes or no) are recorded in the TCGA dataset:

- Animal or insect allergy history
- Asthma history
- Eczema history
- Food allergy history
- Hay fever history
- Mold or dust allergy history

In order to have a sample of sufficient size to analyze, we classified as allergic any patient who answered yes to any of the six manifestations of allergy that were queried. Amirian et al note that having two allergies is more protective than having one, but The Cancer Genome Atlas does not have a large enough sample to confirm or refute this conclusion [2]. Cases with missing data were excluded.

Genetic loci examined were chosen if they were associated with glioma (1p, 19q, TERT, ATRX) or allergy (FOSL2, APOBR and NCF4) [8].

3. Results

We analyzed data from 526 patients with gliomas. The patients' mean age was 43 ± 14 (mean ± SD). 55% of the patients were male, 45% female. 92.1% were white, 4.1% African-American, 1.6% Asian, 0.2% American Indian or Alaska native, 1.9% unclassified. Mean survival was 7.8 years.

Glioma prognosis is related to tumor histologic grade. Patients with Grade 3 tumors had significantly worse survival than patients with grade 2 tumors ($p < 0.001$).

Amirian et al report that the relationship of respiratory allergies and glioma risk is restricted to high-histologic grade gliomas, whereas the effect was not apparent in lower-grade gliomas [2]. Therefore, we stratified our survival analysis by glioma histologic grade. History of allergy conferred a survival advantage on glioma patients, when stratified by tumor histologic grade (Fig. 1). History of allergy improved cumulative survival of glioma, but only in patients with high histologic grade (grade 3) tumors. The overall effect of allergy was significant ($p = 0.049$, log rank test).

Gliomas may be genetically separated into two disease entities, one with better prognosis characterized by loss of chromosome arms 1p and 19q and TERT over-expression, the other with worse prognosis characterized by TP53 and ATRX mutations (Fig. 2).

Because allergy confers a favorable prognosis, we performed Cox regression. The effect of allergy on survival was significant ($p = 0.025$, HR 0.525, 95% CI 0.299–0.924), independent of the effect of chromo-some 1p ($p < 0.001$, HR 93.4, 95% CI 16–546) and 19q ($p = 0.801$,

HR 1.2, 95% CI 0.23–6.9) codeletion or TP53 mutation (p = 0.015, HR 2.7, 95% CI 1.2–5.9), unrelated to TERT expression (p = 0.365, HR 1.1, 95% CI 0.89–1.4) or ATRX mutation (p = 0.904, HR 1.04, 95% CI 0.51–2.14), independent of tumor grade (grade 2 versus grade 3, p = 0.004, HR 2.2, 95% CI 1.3–3.8), not independent of histology (oligodendroglioma and oligoastrocytoma, NOS, versus astrocytoma, p = 0.08, HR 0.62, 95% CI 0.36–1.1). We combined patients with oli-godendroglioma and oligoastrocytoma, NOS, in the analysis versus astrocytoma because survival of patients with oligodendroglioma or oli-goastrocytoma, NOS is approximately equivalent and better than the survival of patients with astrocytoma (Fig. 3). P values represent the statistics of allergy on survival after adjustment of the given prognosticator.

Ferreira et al report eleven loci having new reproducible genetic associations with allergic disease risk [8]. Of these, diminished FOSL2, APOBR and NCF4 RNA expression are significantly associated with increased glioma survival. Diminished NCF4 copy number is associated with reduced glioma survival (Fig. 4).

4. Discussion

The underlying biological mechanism of the association of allergy, reduced glioma risk and favorable prognosis is not entirely clear. Allergies and atopy might represent increased immune sensitivity, the underlying pathophysiology of which is unclear [9]. Why allergic sensitivity could inhibit cancer proliferation is a mystery. Allergies diminish frequency of some malignancies, such as glioma and pancreatic cancer, yet augment the chance for others, bladder cancer for example [10]. Apparently, IgE antibodies against specific allergens show cross-reactivity to glioma antigens [11]. Those patients with glioma who do have allergy and who have the highest levels of immunoglobulin E may have significantly longer survival, implying a potential role for immune system activation [12].

Allergies and IgE may have evolved as protection against macro parasites [13]. Moreover, the Th2-IgE mediated allergic response could play an important role in protecting against toxins and other harmful biologic substances. Perhaps people with stronger allergic responses are better able to rid themselves of and/or inactivate noxious substances that otherwise might predispose to glioma [14]. The protective effect is mainly associated with macro-parasites.

As Palm et al note, macro-parasites are the parasites most commonly associated with eosinophilia [14]. Allergy is also associated with eosinophilia. It would be interesting to know if the percentage of eosinophils in the peripheral smear also predicts (inversely correlates with) survival in malignant glioma, which is generally associated with neutrophilia and lymphopenia [15,16].

Our finding of the improved prognosis that allergy confers on glioma increases the potential importance of understanding the allergy-glioma inverse association. If the mechanism could be clearly elucidated, new, more effective treatments and preventive measures might be developed. Further studies are warranted.

Acknowledgments

Funding

None.

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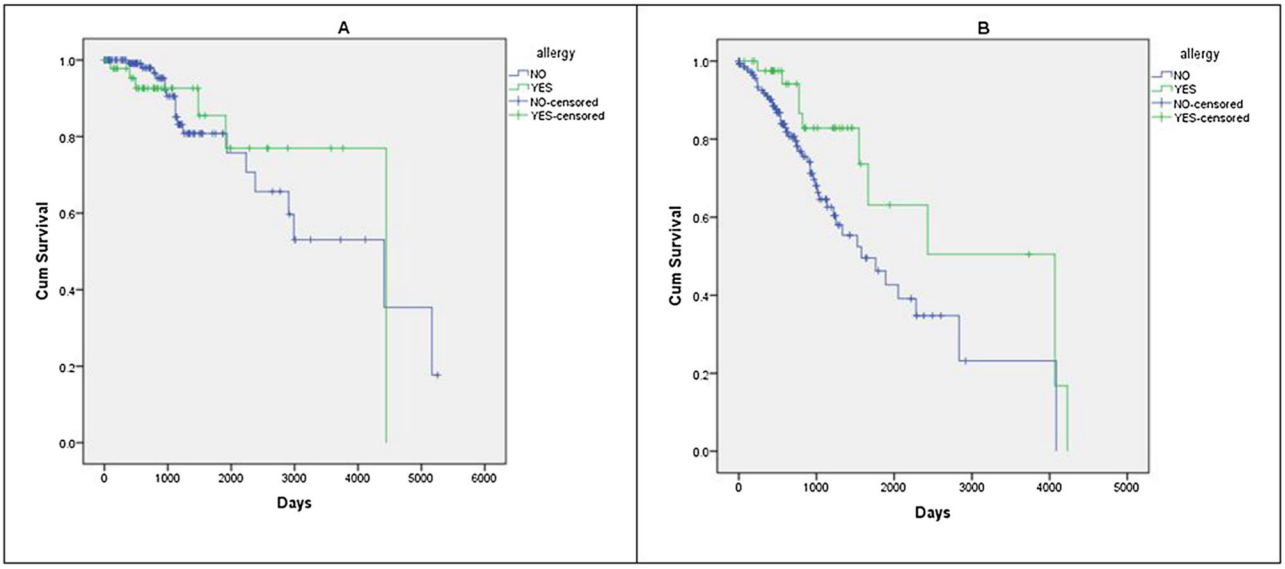

Fig. 1.

History of allergy improves cumulative survival of glioma patients. A (left) patients with histologic grade 2 tumor. B (right) patients with histologic grade 3 tumor. The overall effect of allergy was significant (p = 0.049, log rank test).

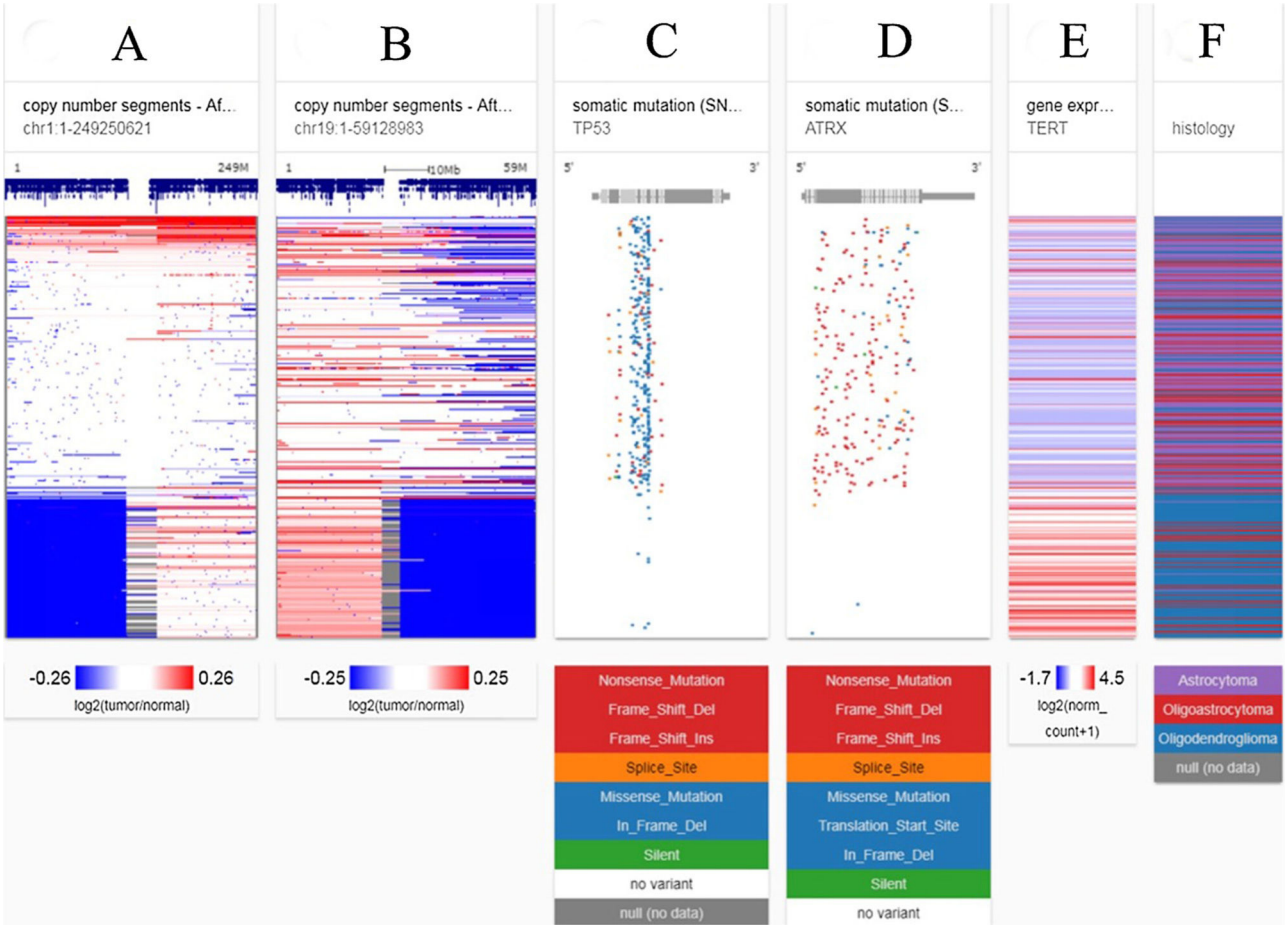

Fig. 2.

Genetic separation of gliomas into two disease groups in 526 patients studied. Group 1 is characterized by loss of chromosome arms 1p and 19q (blue blocks, columns A and B) and TERT over-expression (column E); group 2 by TP53 and ATRX mutations (columns C and D). Astrocytoma (column F) falls into the second, poorer prognosis, group. Each row contains data from a single sample. Row order is determined by sorting the rows by their column values (UCSC Xena http://xena.ucsc.edu). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

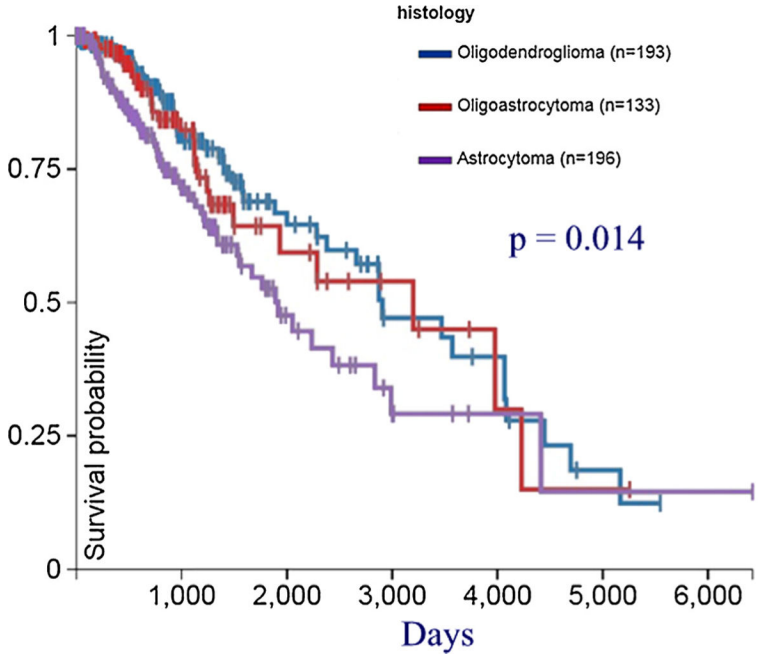

Fig. 3.

Survival of 522 patients stratified by histology. Astrocytoma patients had the poorest survival. The TCGA designation *oligoastrocytoma* is now oli-goastrocytoma, NOS in conformity with the 2016 WHO classifications.

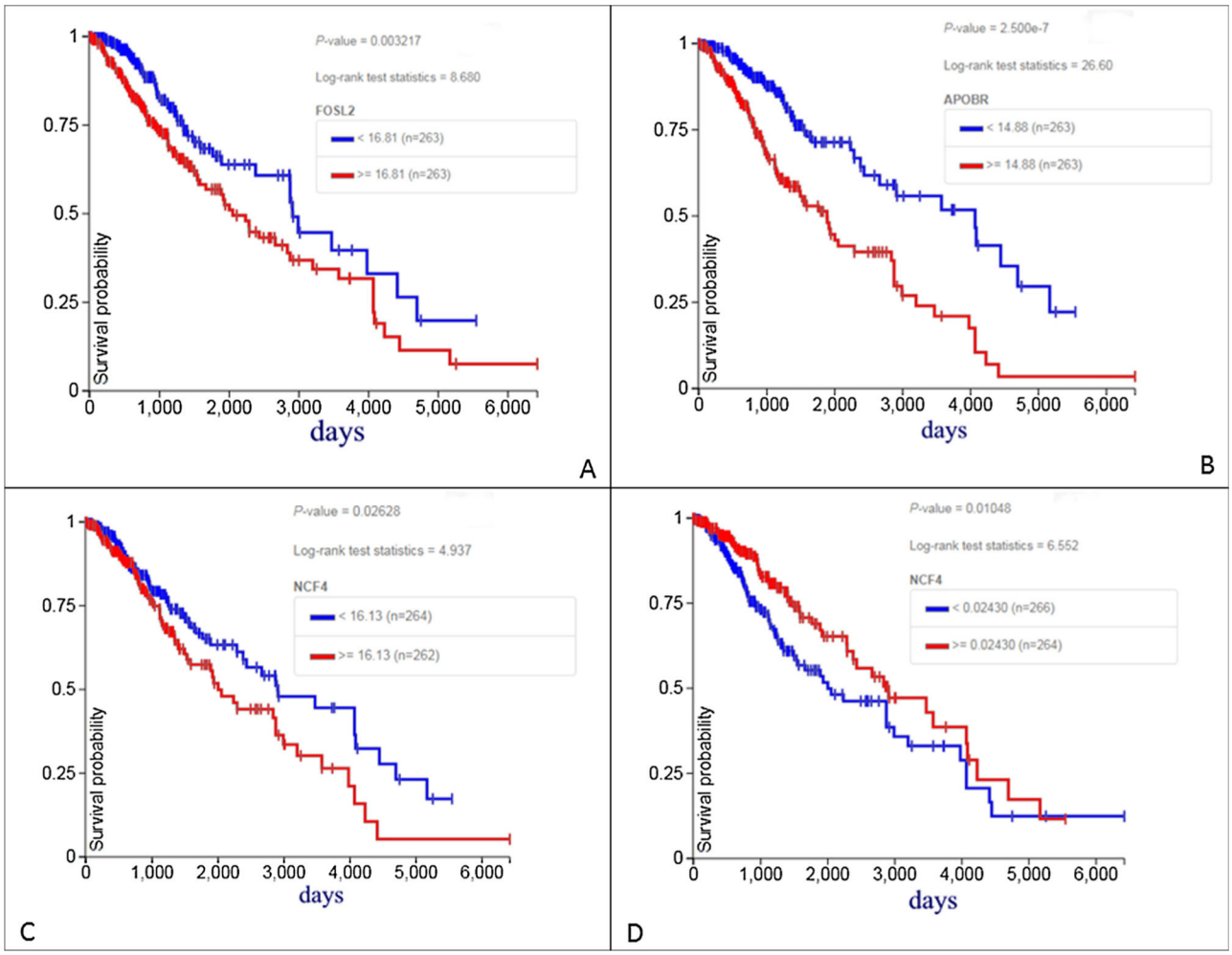

Fig. 4.

Four loci having reproducible genetic associations with allergic disease risk. Diminished FOSL2 (A), APOBR (B) and NCF4 (C) RNA expression (blue) are significantly associated with increased survival in glioma. Diminished NCF4 copy number (masked copy number segment) expression is significantly associated with reduced survival (D) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).