Antibody Reactivity to Varicella Zoster Virus Improves Glioma Survival and is Modified by Germline HLA Polymorphisms

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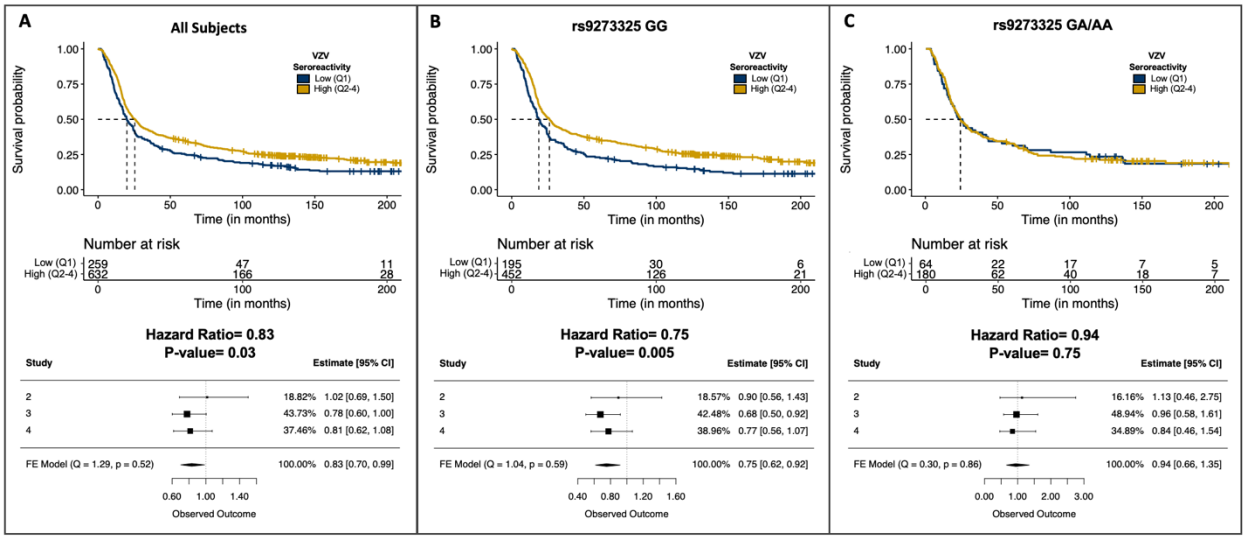
Etiologic studies of glioma have shown inconsistent risk estimates associated with viral infections. Antigenic reactivity towards varicella zoster virus (VZV) has shown a consistent reduction in glioma risk across multiple studies on multiple continents. Using the UK BioBank we have previously shown that germline polymorphism, primarily in the HLA, significantly effect reactivity to a variety of viral infections. In this study we investigate this association in the context of germline HLA polymorphisms known to influence reactivity to herpesviruses.

We measured quantitative IgG reactivity towards VZV in 1378 adults with glioma. Associations of patient IgG levels with overall survival were estimated using Cox models adjusted for age, sex, self-reported race, surgery type, dexamethasone usage at blood draw, and tumor grade. Stratified analyses in 906 patients with whole genome array data were conducted based on a previously discovered HLA polymorphism that is associated with VZV antigen reactivity.

Overall, VZV antibody seropositivity was associated with improved survival outcomes in adults with glioma (HR = 0.70, 95% CI 0.54–0.90, *p*= .006). **Figure A)** In the subset of patients with germline genetic data, the association remains (HR = 0.80 (0.68-0.94) p=0.0055). **B)** In patients with the VZV associated HLA polymorphism the survival benefit of high VZV reactivity is strengthened (HR = 0.73 (0.61-0.88) p=0.00097). **C)** In patients with the VZV associated HLA polymorphism (n=257) no prognostic effect of VZV reactivity is observed (HR = 0.97 (0.70-1.34) p=0.847).



A strong antibody response to VZV is associated with improved glioma prognosis. We observed evidence that the effect of VZV reactivity on glioma survival is modified by a specific HLA polymorphism that points towards an MHC mediated mechanism. However, the complex linkage surrounding this polymorphism clouds SNP based analysis of this prognostic gene x virus association. Accounting for the HLA is critical for understanding the underlying mechanism. Investigating the effect of VZV vaccination on glioma risk and prognosis is warranted.