

Title: Hereditary Brain Tumors Are More Common Than You Think: Germline Mutations in Benign and Malignant Primary Brain Tumors

Authors: Michelle Jackson, Holly LaDuca, Amanda Bergner

As genetic testing technology has evolved, the landscape of hereditary brain tumors is expanding beyond syndromes such as Li-Fraumeni, von-Hippel-Lindau, neurofibromatosis, and tuberous sclerosis. Anecdotally, many consider benign brain tumors to have less of a germline component than malignant tumors. Based on published literature, it is unclear if there are differences between benign and malignant tumors in terms of the germline contribution to causation and this study examines that gap. All sequential cases with at least one diagnosis of a primary brain tumor (PBT) submitted to a single laboratory for hereditary cancer multigene panels between March 2012 and December 2016 were retrospectively reviewed. Cases were grouped as benign or malignant/malignant potential based on the reported pathology. Age at diagnosis and genetic testing, and mutation distribution were analyzed. Of 610 PBT cases, about half (51.8%) were benign. Germline mutations were identified in 14.2% (n=316) of benign cases and 17.4% (n=294) of malignant cases. Overall, 62.1% had multiple primary tumors; 75.3% in the benign subgroup had >1 primary cancer diagnosis compared to 48.0% in the malignant group. In the benign subgroup, 53.3% had their PBT as the initial or concurrent diagnosis compared to 61.0% in the malignant subgroup. The average length of time from PBT diagnosis to genetic testing was similar for benign and malignant subgroups (9y and 8y, respectively). Though this cohort was enriched for patients with multiple primary cancer diagnoses, germline mutations were frequent among both benign and malignant subgroups. In the malignant subgroup, over half presented with a PBT as their first diagnosis, however, genetic testing was delayed for close to a decade on average. Clinician awareness of germline genetic findings among both benign and malignant PBT cases, and the utilization of genetic testing to assist with appropriate and comprehensive screening are important.