Title: *BRCA2* mutation carriers may present with primary brain tumors: a review of a multigene panel testing cohort

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Background Primary brain tumors (PBTs) include both benign and malignant tumors occurring within the central nervous system that are not the result of metastasis. The contribution of germline mutations to the development of PBTs is not well understood. Given the increasing opportunity to effectively treat certain types of brain tumors based on underlying genetic mutations, and the potential impact of heritability within the family, exploring the contribution of germline genetic mutations to the development of PBTs is important for appropriate medical management and genetic counseling.

Methods All sequential cases submitted to our laboratory for hereditary cancer panels between March 2012 and December 2015 were retrospectively reviewed. Test request forms indicating at least one PBT for the proband were selected and the detection rate for this cohort was calculated. Analysis of the type of brain tumor, age of diagnosis, genetic test results, and positive gene distribution was conducted.

Results 364 probands were identified with a PBT, including glial tumors (47.8%), meningiomas (34.3%), medulloblastomas/PNET (3.0%), hemangioblastomas (2.5%), other rare types (1.1%), and unknown (11.3%). Of these cases, 52 (14.3%) harbored a germline mutation. While mutations were identified in 18 genes, *BRCA2* was seen in 21.2% of positives. Mean age of the PBT for *BRCA2* cases was 34.1 years (1-66). In more than half, the PBT was the first primary tumor and there was no history of breast, ovarian, or colon cancer at the time of testing. No biallelic *BRCA2* mutations, associated with Fanconi anemia, were found.

Discussion To our knowledge, this is the largest cohort of individuals with PBTs who have undergone germline genetic testing and the first report of heterozygous *BRCA2* germline mutations identified in a cohort of individuals with PBTs. This data suggests that *BRCA2* mutation carriers may present with PBTs, which could have important implications for the provision of genetic counseling and test selection. Further studies are needed to clarify this association.