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

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BACKGROUND

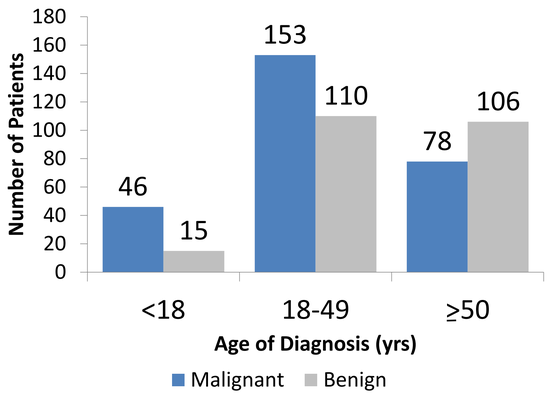
- As genetic testing technology has evolved, the landscape of hereditary brain tumors is expanding
- Malignant brain tumors were previously thought to have a stronger germline component than benign brain tumors
- This study examines whether there are differences in germline contribution to benign and malignant brain tumors

METHODS

- All sequential cases with ≥1 diagnosis of a primary brain tumor (PBT) submitted to Ambry Genetics for any hereditary cancer multigene panel (6-49 genes) between 03/2012 to 12/2016
- Cases were grouped as malignant/malignant potential or benign based on the reported pathology
- 660 patients with a PBT were identified; 610 were analyzed (294 malignant, 316 benign) and 50 were excluded due to insufficient pathology

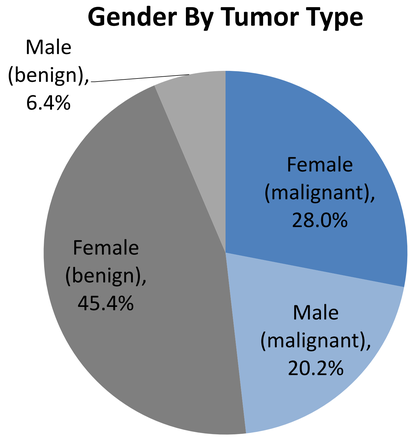
COHORT CHARACTERISTICS

Age of Diagnosis* by Tumor Type

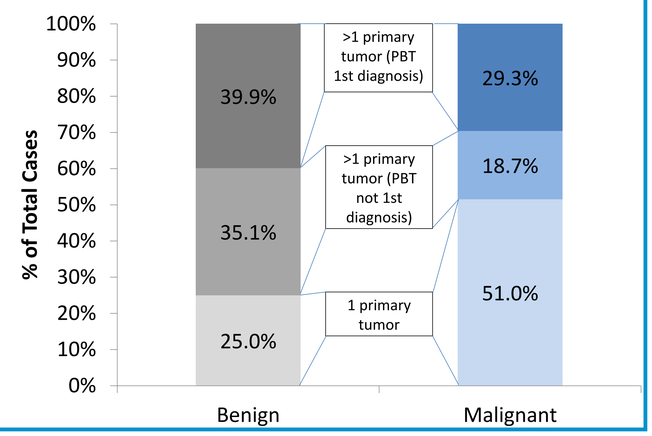


*Ages were excluded if exact number not known

Gender By Tumor Type

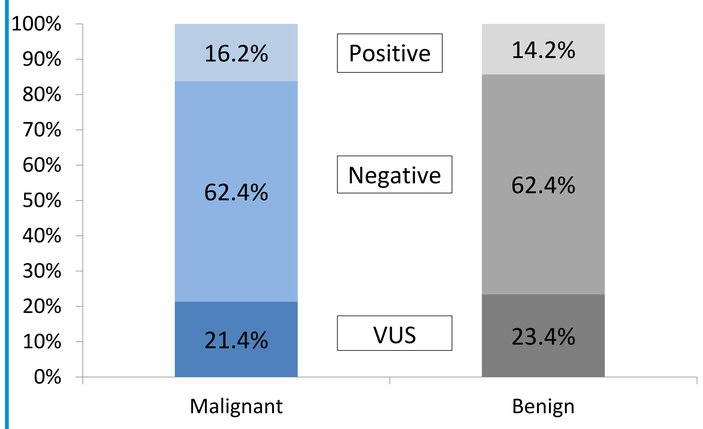


Number of Primary Tumors Diagnosed

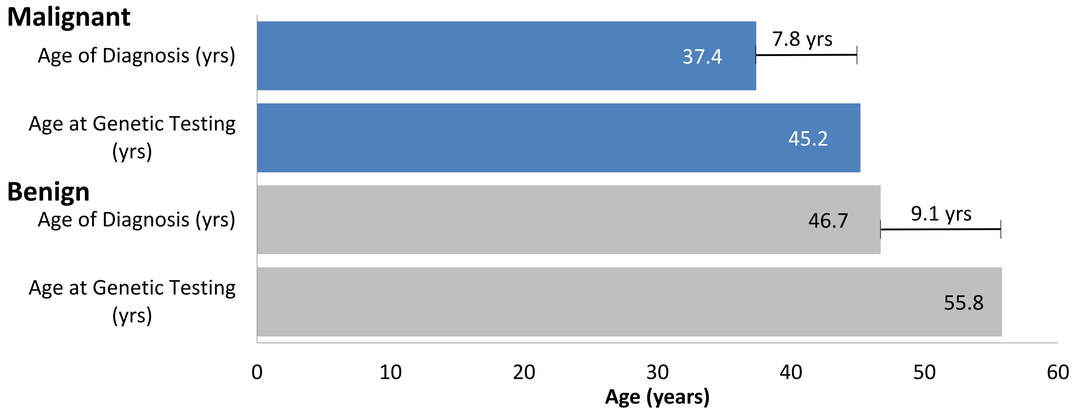


RESULTS

Multigene Panel Mutation Detection Rate for Patients with PBTs



Delayed Timing Between Average Age of Diagnosis and Genetic Testing



Gene Mutations Identified By Pathology Type

Malignant Pathology	Germline Gene Mutations Identified (Number of Cases)	Total Cases (% of Total)
Astrocytoma (anaplastic, NOS)	*APC*(1), *ATM*(1), *CHEK2*(5), *NF1*(1), *PMS2*(3), *POLE*(1), *RET*(1), *SDHB*(2), *TP53*(1), *TSC2*(1)	17 (20%)
Choroid plexus carcinoma	*TP53*(1)	1 (1.2%)
Glioma	*BRCA2*(1), *TP53*(1)	2 (2.4%)
Glioblastoma (NOS)	*ATM*(1), *BRCA1*(1), *BRCA2*(1), *BRIP1*(1), *CHEK2*(1), *MLH1*(1), *NF1*(1), *POLE*(1), *TP53*(1)	9 (10.6%)
Gliobalstoma multiforme	*BRCA1*(1), *CHEK2*(1), *EPCAM*(1), *NF1*(1), *TP53*(1)	5 (5.9%)
Oligodendroglioma	*BRCA2*(1), *CHEK2*(1), *PMS2*(2), *TP53*(1)	5 (5.9%)
Malignant (NOS)	*PMS2*(1)	1 (1.2%)
Medulloblastoma/PNET (all subtypes)	*APC*(1), *PMS2*(1), *TP53*(1)	3 (2.5%)
Benign Pathology		
Astrocytoma (pilocytic)	*BRCA1*(1), *BRCA2*(1), *PMS2*(1),	3 (2.5%)
Benign (NOS)	*BAP1*(1), *BRCA2*(1), *MLH1*(2), *NF1*(2),	6 (7.1%)
Craniopharyngioma	*CHEK2*(1)	1 (1.2%)
Ganglioneuroma	*PTEN*(1)	1 (1.2%)
Germinoma	*BRCA2*(1)	1 (1.2%)
Hemangioblastoma	*CHEK2*(1), *RAD51C*(1), *VHL*(1)	3 (2.5%)
Meningioma	*ATM*(2), *BARD1*(1), *BRCA2*(5), *BRIP1*(1), *CDKN2A*(1), *CHEK2*(5), *MSH6*(2), *PALB2*(1), *PMS2*(1), *PTEN*(2), *SDHB*(1), *SDHD*(1), *SMARCB1*(1), *VHL*(1)	25 (29.4%)
Optic glioma	*NF1*(1)	1 (1.2%)
Pineal (benign)	*BRCA2*(1)	1 (1.2%)

TAKE-HOME POINTS

- Germline mutations were frequent among both benign (14.2%) and malignant (16.2%) subgroups
- This cohort was enriched for patients with multiple primary cancer diagnoses, particularly in the benign subgroup (75%)
- Genetic testing was delayed for close to a decade in both groups which could be due to lack of knowledge of genetic testing for patients diagnosed with a PBT
- 29.3% with a malignant PBT who had >1 primary cancer were diagnosed with their brain tumor first or concurrently with other cancers. This may suggest that some malignant brain tumor patients are surviving their brain tumor and could benefit from knowing if they have an increased risk for other, possibly preventable cancers
- Research is needed to understand mutation prevalence among PBT patients without history of other primary cancer diagnoses and/or families suggestive of inherited cancer predisposition
- Increasing clinician awareness and utilization of germline genetic findings, among both benign and malignant PBT cases, to assist with appropriate and comprehensive screening are important for the patients and their family members

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