Title: Frequency of pathogenic germline variants in pediatric medulloblastoma survivors

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Background: Medulloblastoma is the most common malignant brain tumor in children. Most cases are sporadic, but well characterized germline alterations in *APC*, *ELP1*, *GPR161*, *PTCH1*, *PTCH2*, *SUFU*, and *TP53* predispose to medulloblastoma. However, knowledge about pathogenic/likely pathogenic (P/LP) variants in medulloblastoma cases vary based on genes evaluated, patient demographics, and pathogenicity pipelines.

Objective: To quantify the frequency of germline P/LP variants in cancer susceptibility genes (CSGs) in medulloblastoma patients and available parents compared to controls to better understand germline genetic susceptibility.

Design/Method: Our study included 160 survivors of medulloblastoma diagnosed at <18 years of age. 134 cases were from the Childhood Cancer Survivor Study, a cohort of five-year survivors of childhood cancer. Twenty-six additional cases were from Children's National Medical Center (CNMC). Germline exome sequencing was conducted on all cases plus 40 unaffected parents of CNMC cases. Analyses focused on rare variants in 237 known CSGs – 183 autosomal dominant (AD) and 54 autosomal recessive (AR) genes. P/LP variants were identified using ClinVar and InterVar. Variants of unknown significance (VUS) in the seven medulloblastoma predisposing genes were further analyzed as VUS-damaging (and added to P/LP counts) if predicted as loss of function by snpEff or deleterious in three of four in-silico predictors. We compared the frequency of P/LP variants in cases to that in 1657 in-house cancer-free controls using Fisher's exact tests. A Bonferroni correction threshold of p-value<0.002 was considered significant.

Results: Of the 160 cases, 33 (21%) had a germline P/LP variant in one of the 237 CSGs versus 2.6% in controls ($p<0.001$). Twenty-two individuals (14%) had an AD P/LP variant versus 0.4% in controls ($p<0.0001$), 11 (7%) had a P/LP variant in a known medulloblastoma predisposition gene (*APC*, *ELP1*, *GPR161*, *PTCH2*, *SUFU*) versus zero in controls ($p<0.0001$), and 15 (9.4%) had a heterozygous AR P/LP variant versus 2.2% in controls ($p<0.001$). The CSGs with the most P/LP variants in cases and significantly higher than controls were *ELP1*, *SUFU*, and *PTCH2* (all $p<0.0001$). *BRIP1* and *CHEK2* (AD), and *AGL* and *MRE11A* (AR) genes, had P/LP variants enriched in cases, were nominally significant (all $p<0.02$), and had not been previously associated with medulloblastoma.

Conclusion: One-fifth of pediatric medulloblastoma survivors had a P/LP CSG variant, some in genes which had not previously been associated with medulloblastoma, and therefore need to be replicated. These findings suggest that routine germline testing for children with medulloblastoma at diagnosis should be considered.