Comprehensive molecular characterization of pediatric treatment-induced glioblastoma: germline DNA repair defects as a potential etiology

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BACKGROUND: Pediatric treatment-induced high grade glioma (TIGs) are an incurable late complication of cranial radiation therapy or combined radiation/chemotherapy. Previously, we showed that TIG gene expression profiles differ substantially from spontaneous pediatric high grade glioma, and identified two TIG groups (A & B) defined by differential expression profiles. We now evaluate copy-number, sequence and epigenetic alterations in an expanded TIG cohort.

METHODS: Illumina Infinium 450/850K methylation analysis was performed on 34 TIG samples from a multi-institutional cohort and the Childhood Cancer Survivors Study Group. WGS was performed on tumor and matched germline DNA from 15 TIGs.

RESULTS: On methylation profiling, 19/27 TIGs clustered into a subclass of IDH-wild type midline GBM, including all expression group A and B cases (4 each). Recurrent copy number alterations included 1p loss (13/34), 1q gain (13/34), Ch.13 loss (13/34), PDGFRA gain/amplification (17/34), and CDKN2A loss (14/34). WGS identified a mean germline mutation load of 1.50 mut/Mb. Mean somatic mutation load, was 0.12 and 1.08 mut/Mb for TIG expression groups A and B, respectively ($p<0.002$). All four TIG group B cases had pathogenic germline alterations in homologous recombination repair genes, including BARD1 and BRCA1. TIG expression group A samples lacked pathogenic germline variants in DNA repair genes.

CONCLUSIONS: TIGs are enriched for distinctive chromosomal aberrations and cluster into a well-defined epigenetic subgroup. A subset of TIGs have a high somatic mutational load likely due to germline defects in homologous recombination.

Treatment related pediatric radiation-induced glioblastoma: whole genome sequencing of primary patient samples reveals germline susceptibilities to DNA damage in mesenchymal subgroup tumors

Comprehensive Molecular Characterization of Treatment-Related High Grade Gliomas: Contribution of Germline Susceptibilities to DNA Damage and Tumor Development

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BACKGROUND: Treatment related gliomas are a rare consequence of combined modality therapy with radiation and chemotherapy and often have a poor prognosis given limited treatment options. We previously reported that RIG's gene expression profile differs from spontaneous pediatric GBM and that RIGs cluster into proneural and mesenchymal subgroups based upon RNA-Seq analysis. We report on the results of whole genome sequencing (WGS) and methylation analysis in a RIG cohort.

METHODS: WGS was performed on tumor and matched germline DNA of 8 RIG patients undergoing resection from 1995-2015. [ADD Methylation].

RESULTS: WGS: Germline samples have a total mean mutation load of 4,821 variants per sample, with a non-statistically significant trend toward a greater mutation load in the mesenchymal vs. proneural subgroup (5,428 vs. 4,214, p=0.17). The mean somatic mutation load, following subtraction of the germline mutations, is 383 for the proneural and 3,489 for the mesenchymal samples, a 9-fold difference (p<0.002). One proneural sample in a patient with a germline DNA repair defect involving the ATR and BRCA2 genes (and having a somatic mutation load of 5,990) was omitted from the sample group prior to calculation of the mean. Three germline samples from the mesenchymal subgroup had homozygous, likely inactivating variants in BARD1, a gene necessary for homology-directed repair (HDR) of double-stranded (ds) DNA breaks, and the fourth had heterozygous variants in BARD1 and its binding partner in HDR, BRCA1. The remaining three proneural samples had no BARD1 or other germline variants known to cause DNA repair defects.

CONCLUSIONS: WGS revealed that mesenchymal RIGs have a much higher mutational load versus proneural, correlating with germline inactivation of BARD1, which is necessary for HDR of dsDNA breaks induced by ionizing radiation. These results raise the possibility that pre-RT genetic testing could suggest RIG risk, leading to consideration of alternative therapy.

Commented [1]: Suggest using the methylation defined subgroup designation

Commented [2]: I think we need to see how the two designations fit together, which won't likely be possible before the abstract deadline -- we can discuss in our meeting.

Commented [3]: Suggested alternative title. Many of our patients were treated with combined modality therapy and there is a known synergism between the chemo agents and RT to treatment related gliomas in these patients.

Commented [4]: This is reasonable -- we may tweak slightly but definitely agree with the overall concept.

Commented [5]: Will need to rectify RNA seq based clustering and 450K based clustering. Since most of the literature has moved toward methylation as a means of subgrouping peds HGG.

Commented [6]: Can we report in terms of Mut/Mb as this is commonly used in the literature and will be a good frame of reference for the abstract reviewers.

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