Abstract 2082

Unraveling the Immunologic Vulnerabilities of Diffuse Hemispheric Glioma, H3 G34 Mutant (DHG-G34)

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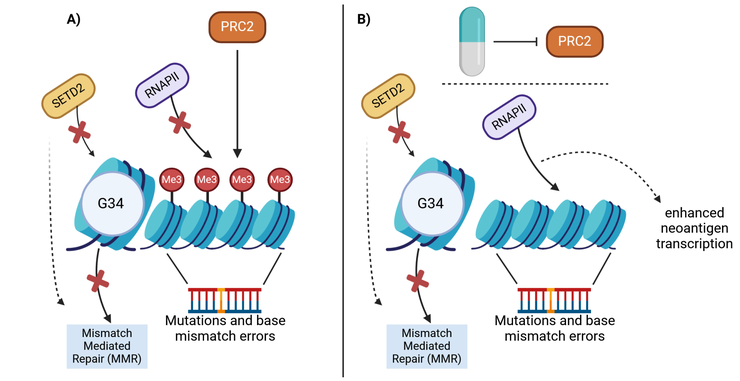
Background/Methods:

- DHG-G34 is an incurable brain cancer of adolescents and young adults, with no targeted treatment
- DHG-G34 is susceptible to localized genome instability near mutated nucleosomes (A)
- Uncovering mechanisms of immune escape may lead to a shift in treatment approach
- Caris Life Sciences has accumulated a large cohort of DHG-G34 omics, permitting an exploration of the molecular and immune landscapes

Proposed Model of Epigenetic Dysregulation: DHG-G34

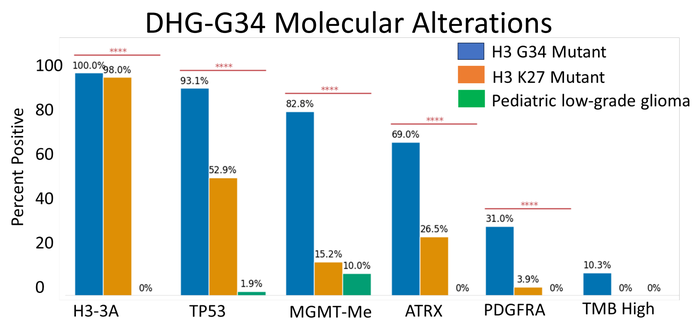


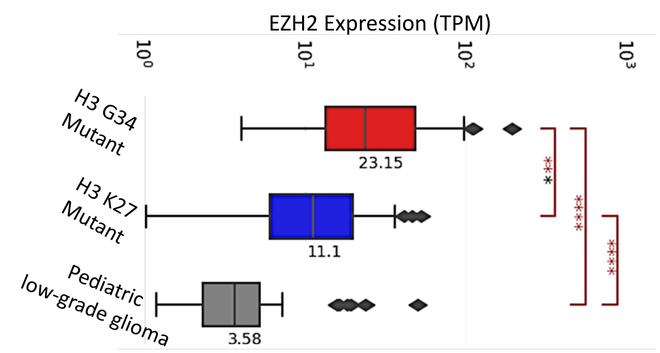
Methods:

- Whole exome and transcriptome patient-derived data is used to characterize DHG-G34 (N = 29) (Caris Life Sciences
- DHG-G34 cell line KNS-42 is used for a pilot experiment to translate findings with the aim to enhance DHG-G34 immunogenicity (B)

Conclusion

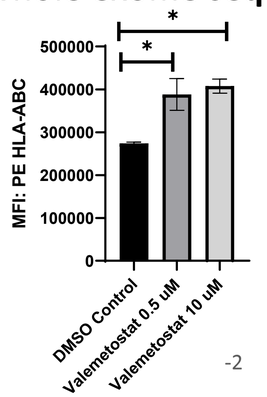
DHG-G34 confers dismal survival. Inhibiting PRC2's unique role in DHG-G34 may enhance its immunogenicity, enabling new treatment strategies

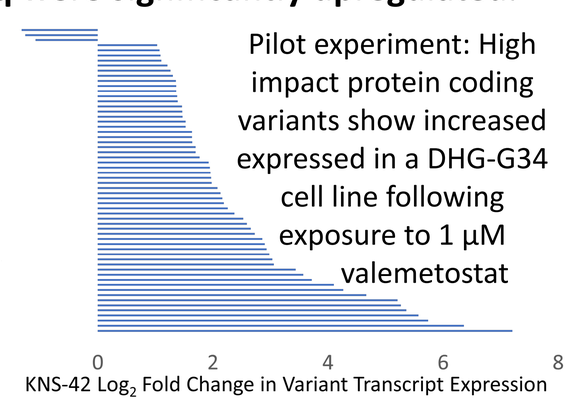




Results:

- DHG-G34 survival is as poor as diffuse midline glioma in the Caris Life Sciences cohort (median OS 15.4 months)
- DHG-G34 patient samples are immunologically cold, with low MHC expression (RNA), low T-cell infiltration (Deconvolution) and low interferon score
- Among Immunosuppressive genes examined, **EZH2** (PRC2's catalytic core) is most highly expressed in DHG-G34 relative to H3K27 glioma and low-grade glioma
- **In KNS-42, EZH2 Inhibition induces readthrough of MHC Class 1 (flow cytometry) and high-impact KNS-42 protein coding variants. 11% of variants on whole exome seq were significantly upregulated.**





Pilot experiment: High impact protein coding variants show increased expressed in a DHG-G34 cell line following exposure to 1 µM valemetostat

Future Directions:

- Further characterization of DHG-G34 neoantigen expression patterns in patient samples
- Explore the immunologic potential of EZH2 inhibition in additional in vitro and in vivo models

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