Molecular Characterization of Radiation Induced Gliomas (RIG) in Survivors of Childhood Cancer

A report from the Childhood Cancer Survivor Study

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Childhood Cancer Survivor Study

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Multi-institutional Review & Rigorous Molecular Characterization

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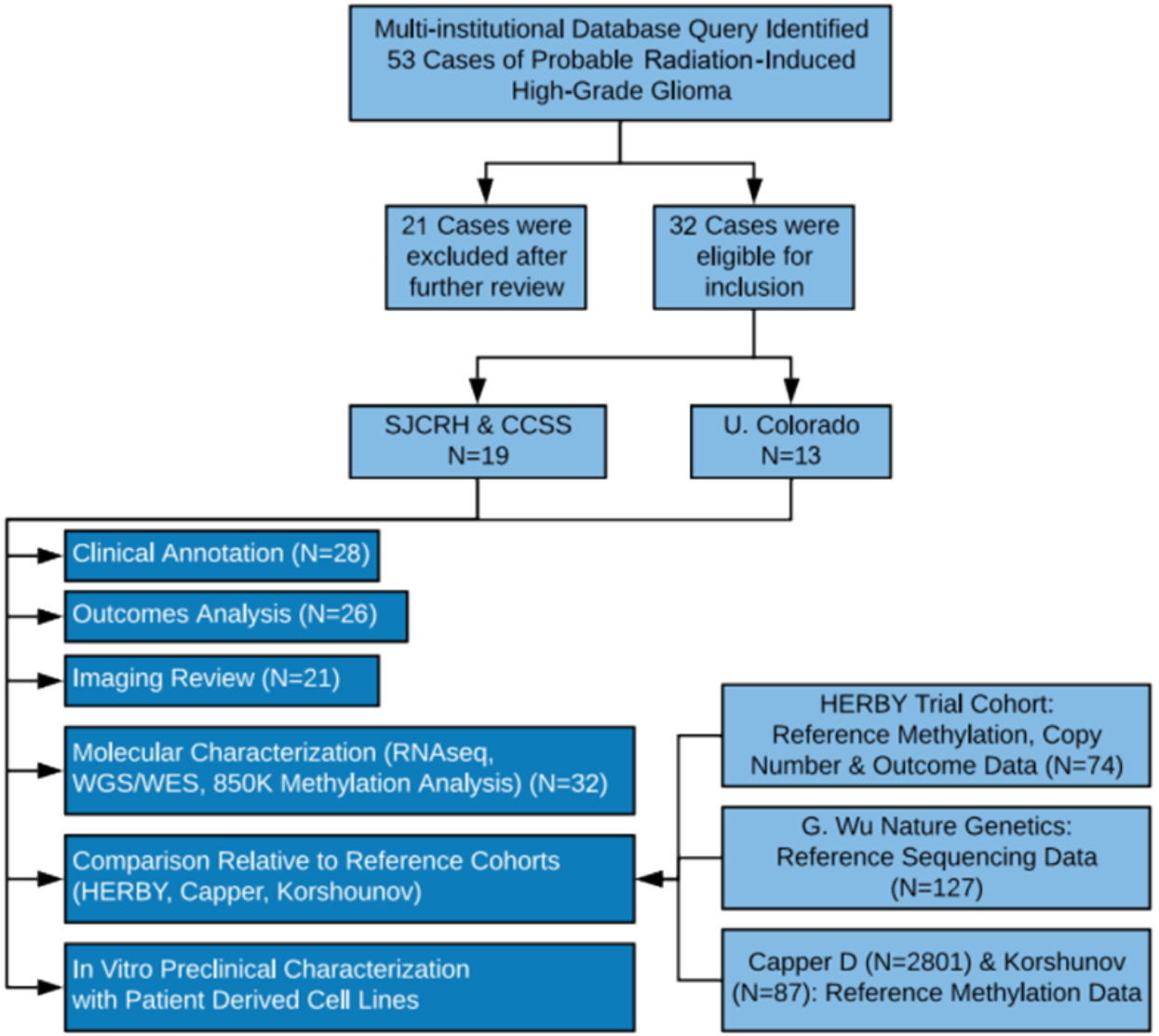
RIG is the ***deadliest late consequence*** of CNS radiation in childhood cancer survivors.

RIGs were collected from ***multiple institutions*** and selected according to compliance with ***Cahan's criteria***.

32 RIG cases were eligible for inclusion.

RIG were characterized with regard to ***clinical, imaging, & molecular features*** using chart review & WES/WGS/RNAseq/850K and were ***compared*** to reference ***de novo pediatric high-grade gliomas***.



RIG clinical origins were varied

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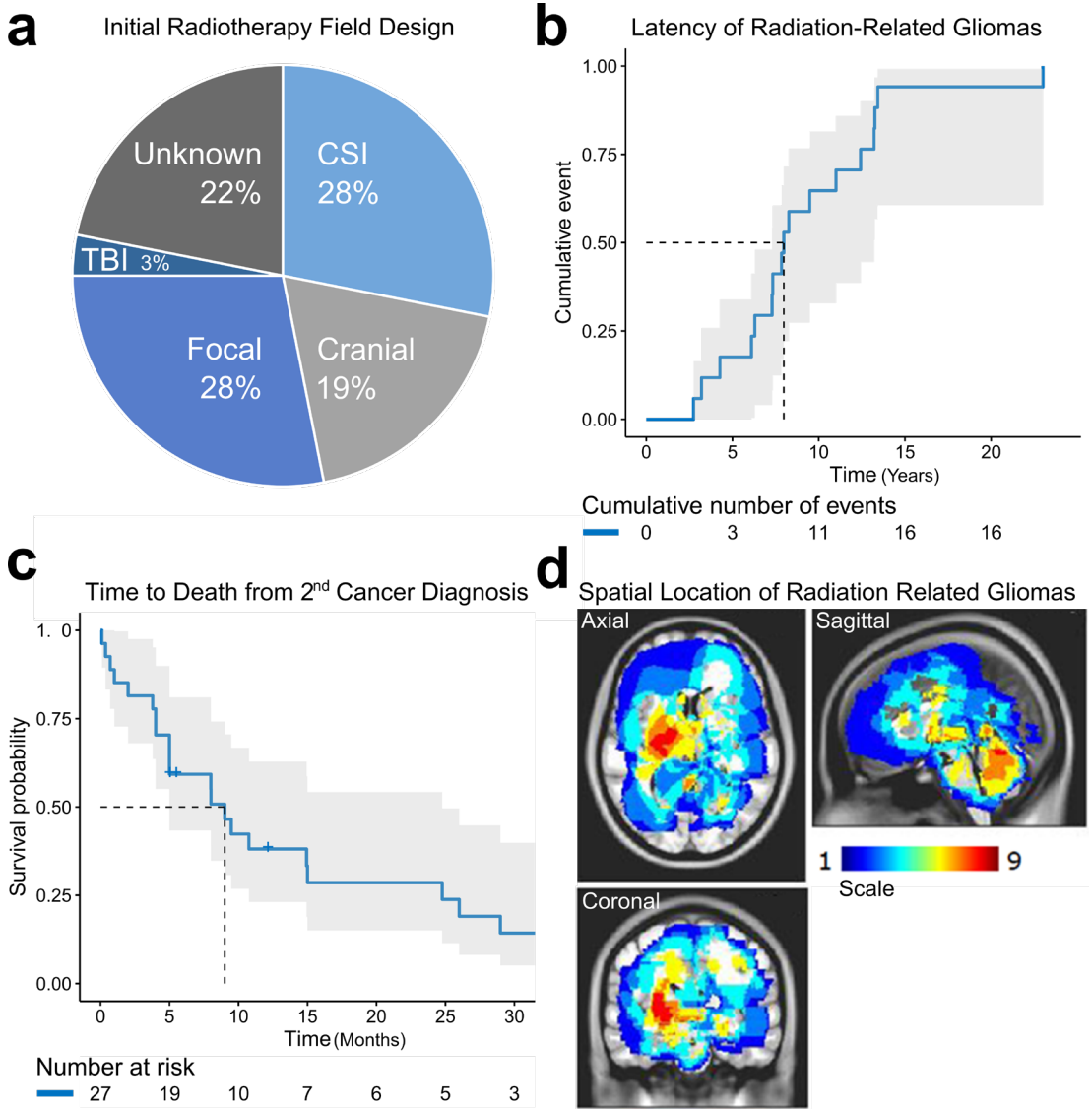

RIG were exhaustively clinically characterized according to ***radiation exposure timing, field design, dose, location & antecedent malignancy***.

RIG are more frequently localized within the ***frontotemporal & posterior fossa*** region.

RIG are **epigenetically distinct** ***despite*** their **disparate clinical origins**

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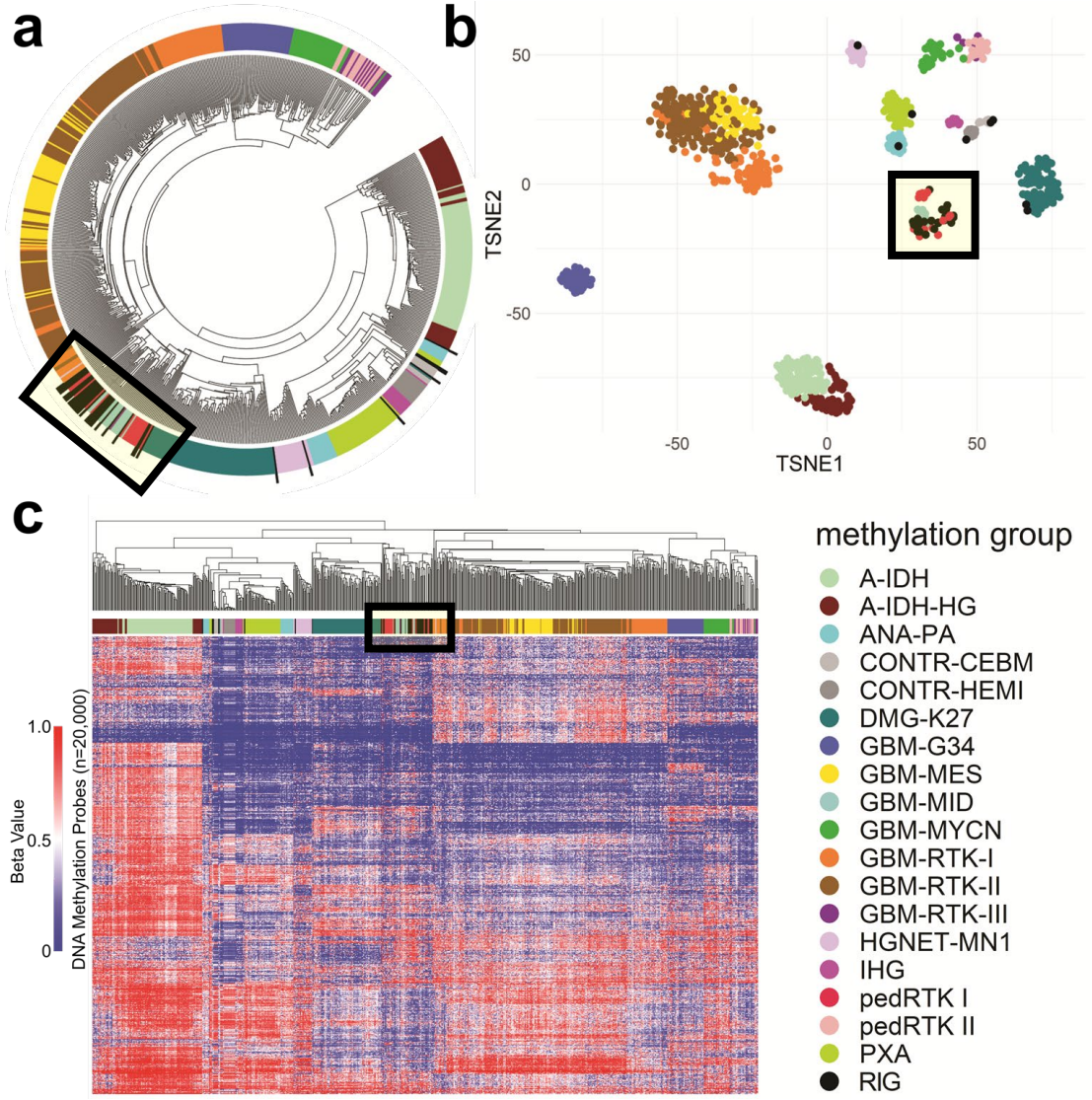

RIG are ***epigenetically similar*** to one another.

RIG share ***strong similarity*** with the *de novo* ***pedRTK1*** group of gliomas.

De novo *pedRTK1* gliomas are a subset with a "***pro-neural***" like expression signature & frequent CDKN2A del, EGFR & PDGFRamp.

RIG have **distinct *somatic*** alterations relative to *de novo* pediatric gliomas

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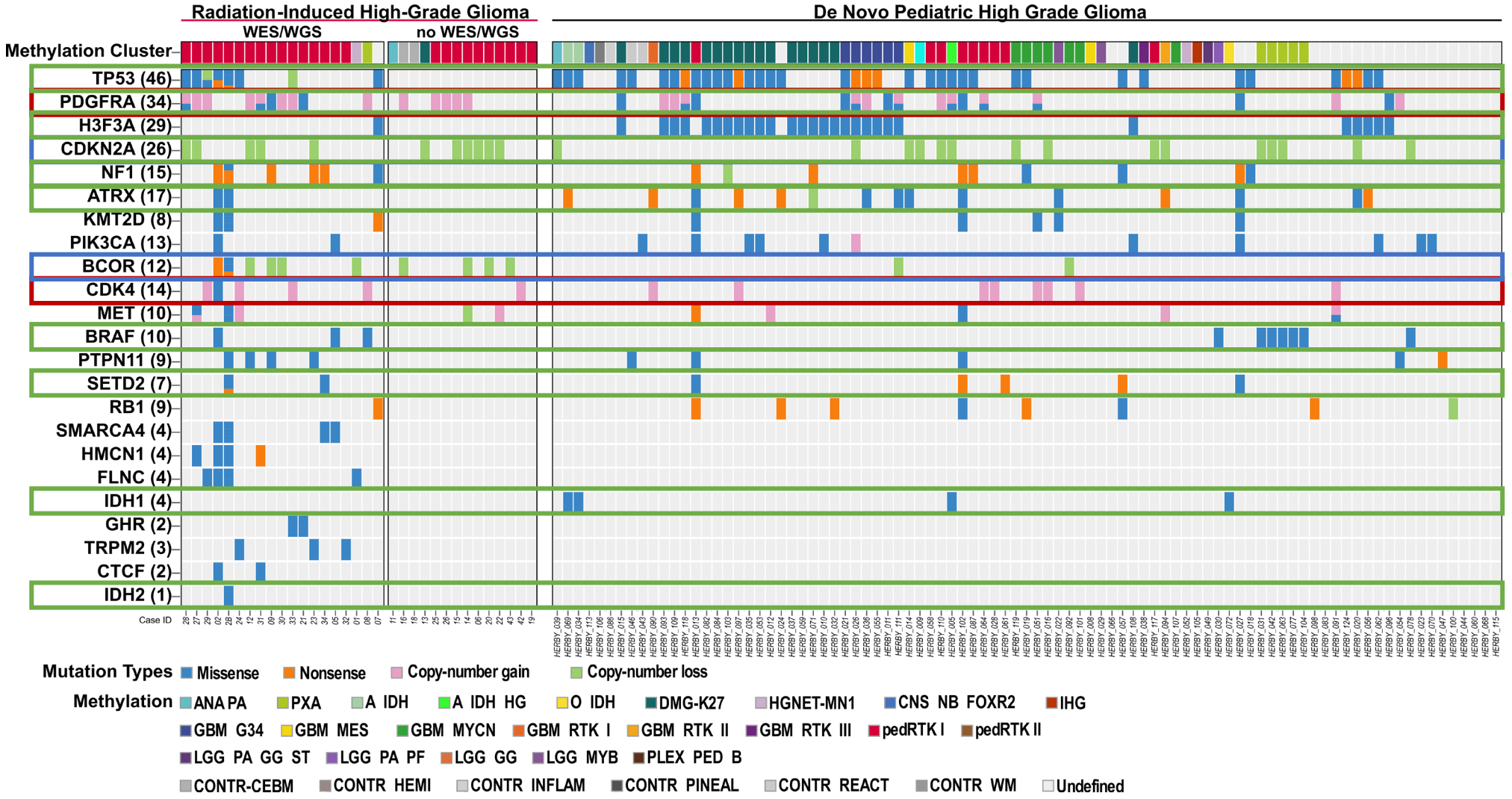

Amplification of **PDGFR** & **CDK4**, and ***loss*** of **CDKNA** & **BCOR** were common in RIG

Mutations characteristic of ***de novo*** gliomas were ***low frequency*** *(TP53, NF, H3F3A)*

RIG are **DNA Repair Deficient** & Enriched in **Pro-inflammatory** mediators

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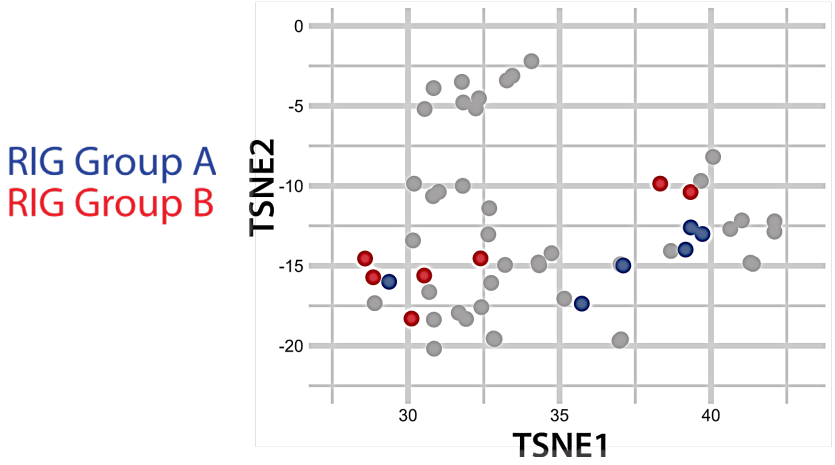

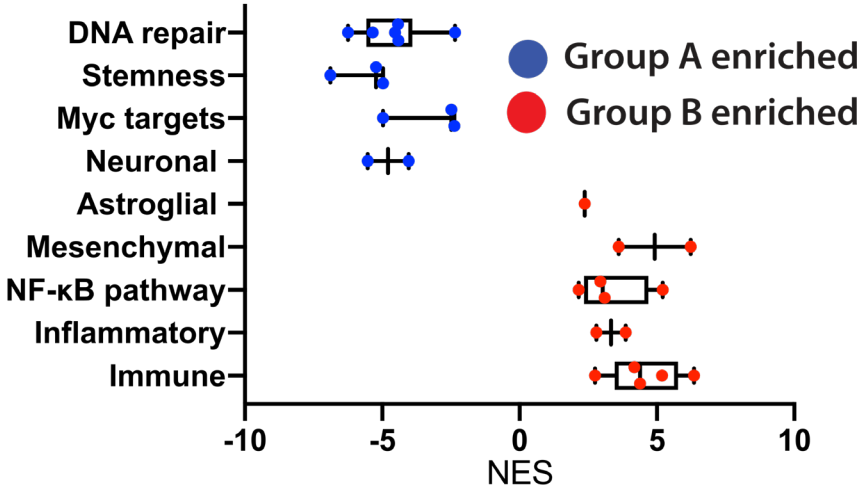

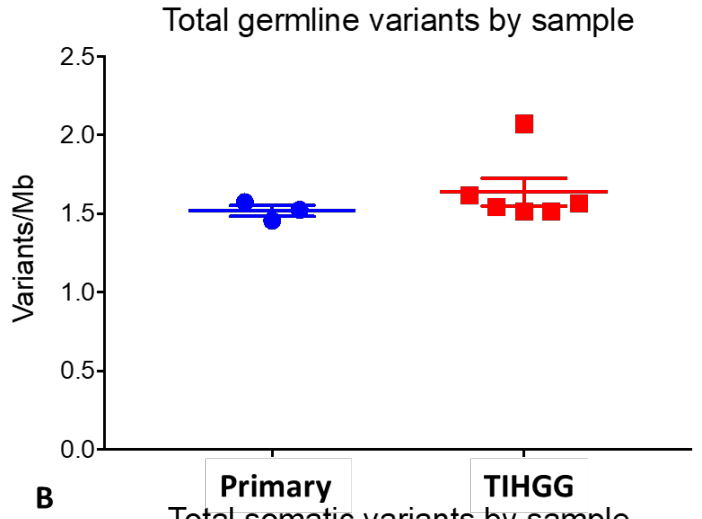

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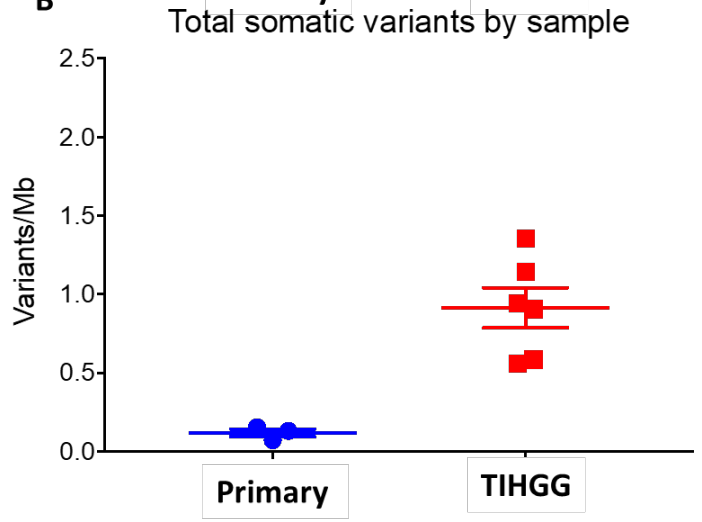

Two ***expression-based*** subgroups were identified.

Group A – Enrichment in ***DNA damage machinery***, Stem-like

Group B – Enrichment of ***inflammatory-response*** elements.

Variants per Mb

-***No difference in germline*** variant frequency

-***Increased somatic*** variant frequency

Among the DNA repair deficient cases, we noted a high frequency of homozygous germline mutations in homologous repair genes like BARD1, however the findings were classified as a “variant of unknown significance” thus had unclear meaning.

RIG *Mutational Signature Analysis* suggests a *common path* to ***increased somatic variation***

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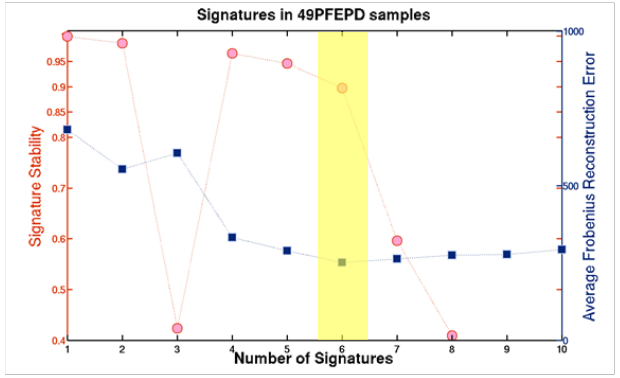

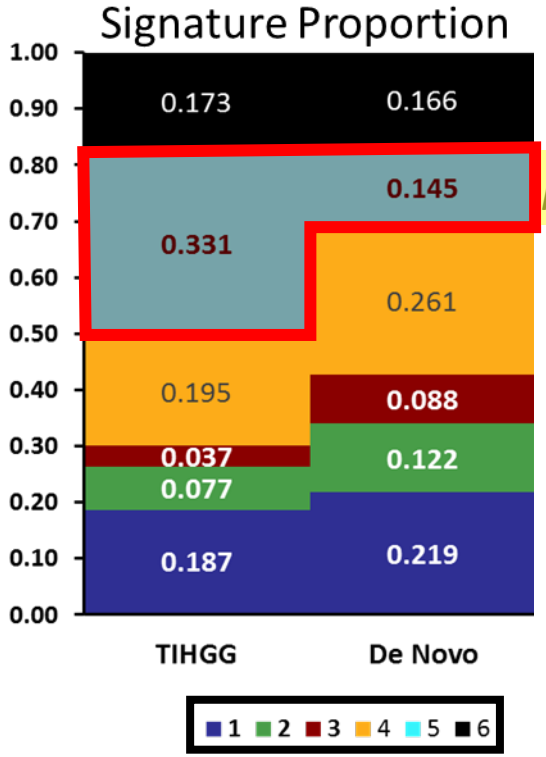

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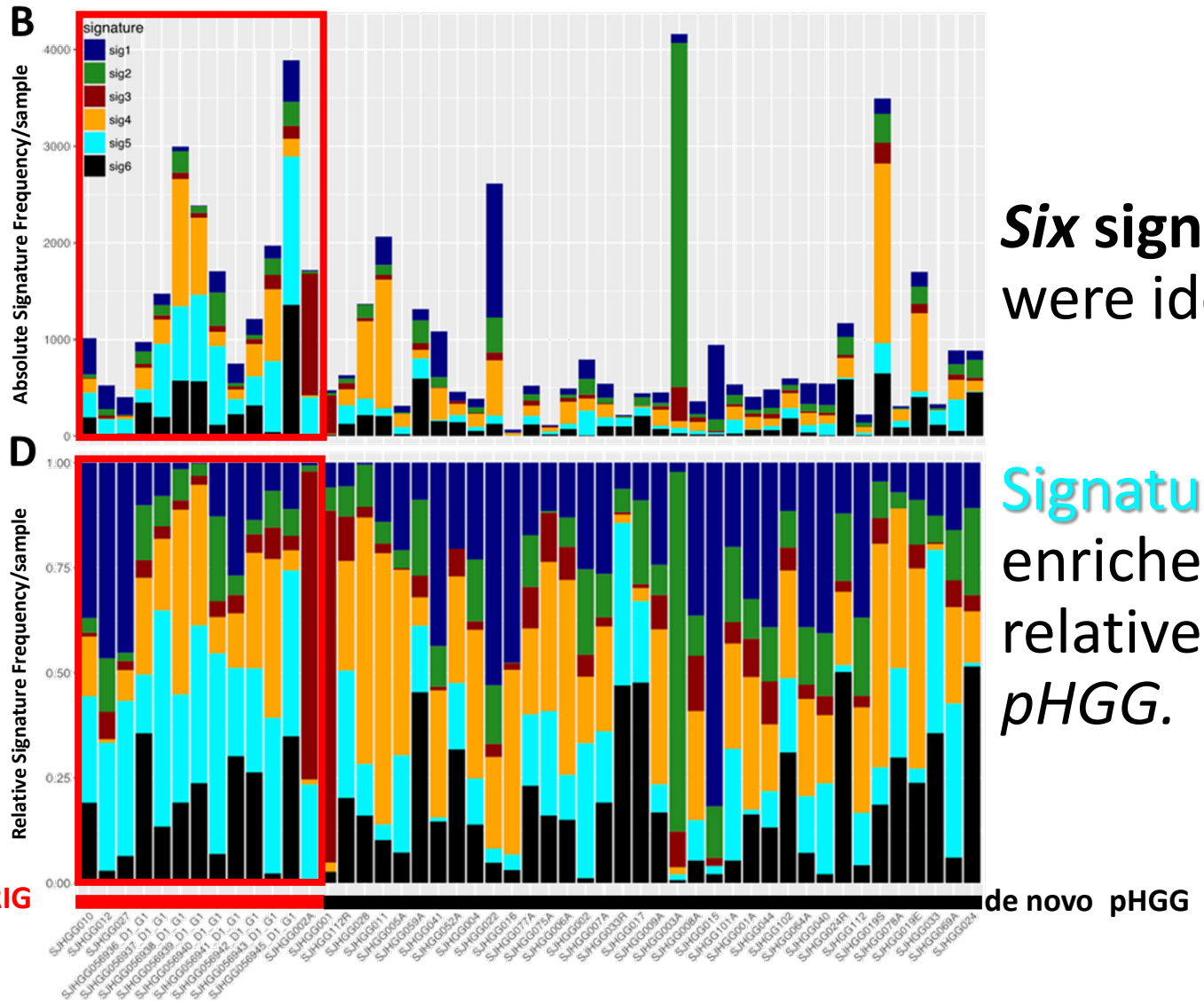

***Six* signatures** were identified.

Signature #5 was enriched in **RIG** relative to *de novo pHGG.*

Conclusions

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RIG are ***epigenetically distinct*** and have ***characteristic mutations*** which may inform future targeted therapeutic approaches.

The ***increased proportion of somatic variants*** relative to de novo HGG and ***distinct mutational signature*** suggest a *potential common underlying etiology*.

While our analysis suggested a ***potential contribution*** of *germline DNA repair deficient genes*, our sample size and the allele frequency of the variant in the population **precluded definitive assessment**.

Two recent large scale epidemiological studies have now confirmed its role as a cancer predisposition gene suggesting that **some high frequency "low penetrance" alleles may be *unmasked* by further insult *(ionizing radiation)*** to increase the risk for subsequent malignancies.

Future large-scale studies should ***re-evaluate molecular contributions to subsequent neoplasm risk*** in the context of ***relevant DNA-damaging treatment exposures***.

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