Early truncating mutations in *ASXL1* drive reduced H3K27me3 across various central nervous system tumors

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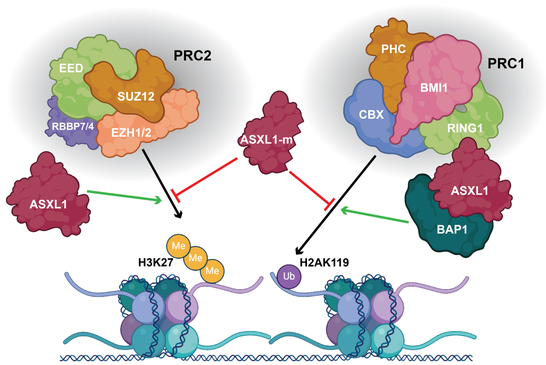
Background

- *ASXL1* encodes an epigenetic modifier and is one of the most frequently mutated genes in a variety of myeloid malignancies.[1]
- ASXL1 interacts with PRC2 to repress target genes by trimethylation at target H3K27 sites, and ASXL1 depletion leads to global reduction of H3K27me3 in myeloid malignancies.[2]
- Mutant ASXL1 also interferes with the catalytic function of BAP1, leading to decreased H2AK119ub.[3]
- The C-terminal PHD domain is a putative histone-interacting module.[4]

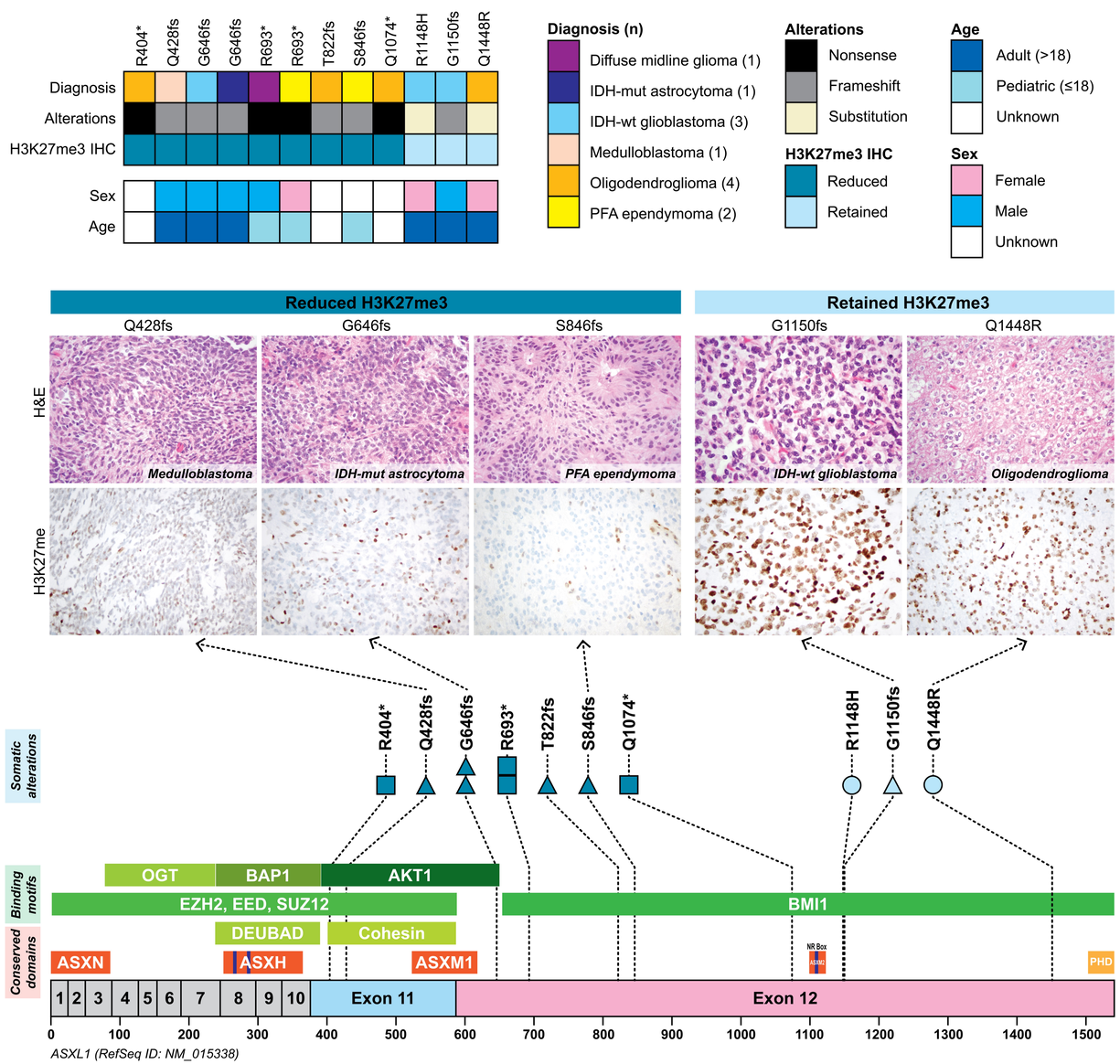


- The function of *ASXL1* in central nervous system tumors is poorly characterized to date.
- We hypothesize that central nervous system tumors harboring *ASXL1* mutations will demonstrate aberrant H3K27me3.

Design

- Clinically sequenced cases of central nervous system tumors at JHH and MSKCC were retrospectively queried for *ASXL1* alterations.
- Tumors harboring *ASXL1* alterations were immunohistochemically analyzed for H3K27me3.

Results



Results

- 9 cases harbored truncating *ASXL1* mutations localizing to either exon 11 (p.R404*, p.Q428fs) or the 5' region of exon 12 (p.G646fs x2, p.R693* x2, p.T822fs, p.S846fs, p.Q1074*).
  - These cases demonstrated reduced H3K27me3 by immunohistochemistry.
- The 3 cases harboring alterations localizing to the 3' region of exon 12 (p.R1148H, p.G1150fs, p.Q1448R) demonstrated retained H3K27me.
- Of note, the single diffuse midline glioma case exhibited an oncogenic *H3F3A* p.K27M mutation.

Conclusions

- Early truncation of *ASXL1* is an uncommon mechanism for reduced H3K27me3 across various CNS tumors.
- Cases harboring *ASXL1* alterations leading to reduced H3K27me3 may present diagnostic challenges, with differential considerations including other H3K27me3-altered entities.
- While *ASXL1* has been reported in a small subset of these tumors, how *ASXL1* mutations may synergize with either H3 p.K27M mutations in diffuse midline glioma or EZHIP overexpression in PFA ependymoma to modulate H3K27me3 remains to be explored.

References

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