Hotspot Mutations in *H3F3A* and *IDH1* Define Distinct Epigenetic and Biological Subgroups of Glioblastoma

We identified six distinct GBM subgroups based on global DNA methylation patterns. Three epigenetic GBM subgroups correlate strictly with mutations in *H3F3A* and *IDH1*. *H3F3A* K27- and G34 mutant GBMs clearly arise in different anatomic compartments. One GBM subgroup (G34) lacks important markers of neural lineage commitment.

Summary

Glioblastoma (GBM) is a brain tumor that carries a dismal prognosis and displays considerable heterogeneity. We have recently identified recurrent *H3F3A* mutations affecting two critical amino acids (K27 and G34) of histone H3.3 in one-third of pediatric GBM. Here, we show that each *H3F3A* mutation defines an epigenetic subgroup of GBM with a distinct global methylation pattern, and that they are mutually exclusive with *IDH1* mutations, which characterize a third mutation-defined subgroup. Three further epigenetic subgroups were enriched for hallmark genetic events of adult GBM and/or established transcriptomic signatures. We also demonstrate that the two *H3F3A* mutations give rise to GBMs in separate anatomic compartments, with differential regulation of transcription factors *OLIG1*, *OLIG2*, and *FOXG1*, possibly reflecting different cellular origins.