INTRODUCTION: Glioblastoma multiforme (GBM) is the most malignant and most common primary brain tumor. There is no curative chemotherapeutic regimen for GBM, and its invasiveness greatly limits efficacy of surgery and radiation therapy. Molecular drivers of GBM growth, maintenance, and invasion need to be identified to develop effective therapies. METHODS: We selected 50 genes found to be overexpressed in a high proportion of GBM in comprehensive sequencing and gene expression analysis studies by The Cancer Genome Atlas (TCGA) Research Network and the Howard Hughes Medical Institute (Parsons et al 2008). We hypothesized a common subset of these genes directly promote tumor initiation or maintenance downstream of initiating genetic alterations, and screened them in vivo. A cDNA for each of these genes and SV40 large T antigen (TAg) was cloned into a separate Sleeping Beauty (SB) transposon plasmid. The cDNA delivery plasmids were stereotactically injected into the lateral ventricles of neonatal mice in batches of 9, along with the TAg vector to facilitate tumor formation and a SB transposase expression plasmid containing a firefly luciferase transposon. We monitored tumor development by luciferase imaging. RESULTS: Tumors developed in a subset of mice, the majority of which were highly infiltrative with vascular proliferation and histologically resembled grade 3 glioma. Injection of the HIF1α cDNA was associated with infiltrative tumors in our model and has been implicated in glioma infiltration previously. UBE2C, CCNE2, and EZH2 cDNAs were associated with reduced tumor latency and may drive glioma cell proliferation. We are testing these cDNAs individually in vivo and in vitro to confirm their roles in driving infiltration and proliferation. CONCLUSIONS: We used a SB transposon-based reverse genetic mouse model to screen for common GBM drivers. Of the 50 genes screened, we identified 4 strong candidates which may drive tumor cell proliferation and infiltration.