Combined risk stratification models were designed based on clinical and cytogenetic biomarkers identified by multivariate Cox proportional-hazards analyses. Identified biomarkers were tested using FISH on a non-overlapping medulloblastoma tissue microarray (n=453), with subsequent validation of the risk stratification models. Results: Subgroup information improves the predictive accuracy of a multivariate survival model compared to clinical biomarkers alone. Most previously published cytogenetic biomarkers are only prognostic within a single medulloblastoma subgroup. Profiling a six-pack of FISH biomarkers (GLI2, MYC, 11, 14, 17p, and 17q) on FFPE tissues, we can reliably and reproducibly identify very low-risk and very high-risk patients within each of SHH, Group3 and Group4 medulloblastomas. Conclusions: Combining subgroup and cytogenetic biomarkers with established clinical biomarkers substantially improves patient prognostication, even in the context of heterogeneous clinical therapies. The prognostic significance of most molecular biomarkers is restricted to a specific subgroup. We have identified a small panel of cytogenetic biomarkers that reliably identifies very high-risk, and very low-risk groups of patients, and which will make an excellent tool for selecting patients for therapy intensification and therapy de-escalation in future clinical trials.

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Abstract withdrawn.

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An *in vitro* mouse model of GBM with abrupt and predictable onset

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Glioblastoma (GBM) is a fatal cancer which harbors multiple genetic alterations, many of which are thought to be passenger mutations. Those that involve receptor tyrosine kinase signaling and the p53 and RB pathways are found in most newly diagnosed GBMs and are thought to be 'drivers' of this cancer. Here we report a PDGF-A-linked *in vitro* mouse model of GBM in which malignant transformation appears to occur abruptly, and the responsible genetic events can be studied. Cells from the subventricular zone (SVZ) of p53-null, adult mice were dissected and cultured as spheres in serum-free media supplemented with either EGF/FGF or PDGF-A. p53-null SVZ cells cultured continuously in EGF/FGF proliferated rapidly but remained growth factor dependent and non-tumorigenic. In contrast, PDGF-A cultured SVZ cells grew poorly over 3-4 months until passage 8, whereupon sphere formation and size accelerated abruptly in multiple independent cultures. These transformed cells proliferated rapidly in the absence of PDGF-A, and unfailingly, generated tumors with a striking resemblance to GBMs when implanted into the striatum of immunocompetent, p53 wild-type mice. EGFR, PDGFRα, Olig2 and NG2 were expressed in EGF/FGF and PDGF-A cultures in early to late passages (≤P1-P15). Increased nestin expression was observed in PDGF-A transformed cultures only, whereas GFAP expression decreased in both. This model recapitulates other systems in which PDGF-A-driven glioma formation has been achieved *in vivo* in p53-null mice, but may have these advantages: low cost, easy accessibility to sequential molecular interrogation, and suitability for screening of libraries of potential inhibitors of gliomagenesis.

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Targeting oncofetal high mobility group A2 (HMGA2) to increase sensitivity to temozolomide (TMZ) in glioblastoma (GB) cells

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The Base Excision Repair (BER) pathway facilitates the removal of temozolomide (TMZ) induced alkylated DNA bases. We previously identified the non-histone chromatin binding protein and DNA minor groove binder HMGA2 as a novel member of BER that directly interacts with APE1, a key BER member. We showed that the AP/ dRP lyase activity, located within the AT-hook DNA binding domains of HMGA2, protects stem cells and cancer cells against alkylating drugs. The in-vivo interactions of HMGA2 with Ataxia telangiectasia and Rad3-related kinase (ATR) and checkpoint kinase 1 (CHK1) result in sustained activation of the ATR-CHK1 signaling pathway, prolonged G2/M