Meningiomas are the most common primary intracranial tumors, but the molecular drivers of meningioma tumorigenesis are poorly understood. We hypothesized that investigating intratumor heterogeneity in meningiomas would elucidate biologic drivers and reveal new targets for molecular therapy. To test this hypothesis, we performed multiplatform molecular profiling of 86 spatially-distinct samples from 13 human meningiomas. Our data reveal that regional alterations in chromosome structure underlie clonal transcriptional, epigenetic and histopathologic signatures in meningioma. Stereotactic co-registration of sample coordinates to preoperative magnetic resonance images further demonstrated that high apparent diffusion coefficient (ADC) distinguished meningioma regions with proliferating cells that were enriched in developmental gene expression programs. To understand the function of these genes in meningioma, we developed a human cerebral organoid model of meningioma and validated the high ADC marker genes CH2D and PTPRZ1 as potential targets for meningioma therapy using live imaging, single cell RNA sequencing, CRISPR interference and pharmacologic inhibitors.

Abstract

Methods & Tumor Characteristics

Transcriptomic, CNV & Radiologic Heterogeneity