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Meningioma Driver Mutations Determine Their Anatomical Site of Origin

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Introduction

Meningiomas comprise over 35% of all primary intracranial tumors, arising from the membranes surrounding the brain and spinal cord. Until recently, the genomic landscape of these tumors were poorly understood.

Methods

We used next-generation genomic approaches to identify driver mutations in over 500 meningiomas, correlating our findings with clinical data, including their intracranial origin.

Results

We identified driver mutations in 5 genes including NF2, TRAF7, which co-occurred with either the known oncogenic AKT1E17K mutation or with a recurrent mutation, K409Q, in the KLF4 gene and SMO activating mutations, which resulted in constitutive Sonic Hedgehog (SHH) signaling. NF2 mutant meningiomas were of fibrous or transitional histology and originated along the posterior cerebral hemispheres, the posterior and lateral part of the skull base, and along the spinal cord. In contrast, meningiomas bearing mutations in the other 4 driver genes grew almost exclusively along the midline of the skull base and anterior cerebral hemispheres. Interestingly, the growth of SMO mutant meningiomas was restricted to the midline of the anterior skull base, where Sonic Hedgehog (SHH) signaling plays a critical role in cranio-facial patterning during embryonic development.

Conclusions

Mutually exclusive mutations in these 5 driver genes classify meningiomas into mutually-exclusive groups with distinctive clinical correlations, identifying therapeutically relevant pathways with clear implications for targeted therapies, such as AKT1 or SHH inhibition.

Learning Objectives

Clinical correlation of the molecular landscape of meningiomas

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